Single Technology Appraisal

Nemolizumab for treating prurigo nodularis [ID6451]

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Nemolizumab for treating prurigo nodularis [ID6451]

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The following documents are made available to stakeholders:

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

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2. **Clarification questions and company responses**
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3. **Patient group, professional group, and NHS organisation submissions** from:
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4. **Expert personal perspectives** from:
   a. Dr Andrew Pink, Consultant Dermatologist – clinical expert, nominated by Galderma
   b. Sailaja Maganti – patient expert, nominated by Prurigo Nodularis International
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5. **External Assessment Report** prepared by Aberdeen HTA Group

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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

Nemolizumab for adults with moderate to severe prurigo nodularis [ID6451]

Document B
Company evidence submission

October 2024

File name	Version	Contains confidential information	Date
[ID6451] Nemolizumab Document B 110325 [Redacted]	V3.0	Yes	11/03/25

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Abbreviations

Abbreviation	Definition
A&E	Accident and Emergency
AD	atopic dermatitis
AE	adverse event
AESI	adverse event of special interest
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
AP NRS	average pruritis numerical rating scale
AST	aspartate aminotransferase
BMI	body mass index
BNF	British National Formulary
BSC	best supportive care
CC	complexity and comorbidity
CE	Conformité Européenne
CI	confidence interval
CLA	cutaneous lymphocyte-associated antigen
CMH	Cochran-Mantel-Haenszel
COVID	coronavirus-19 disease
CPRD	Clinical Practice Research Datalink
CSR	clinical study report
DSA	deterministic sensitivity analysis
DCS	dual chamber syringe
DLQI	Dermatology Life Quality Index
EAG	external assessment group
ECG	electrocardiogram
eCRF	electronic case reporting form
EQ-5D	EuroQol 5-dimensions
EU	European Union
FDA	US Food and Drug Administration
GARD	Genetic and Rare Diseases Information Center
GBP	Great British Pound
GI	gastrointestinal
GP	general practitioner
HADS	Hospital Anxiety and Depression Scale
HCRU	healthcare resource use
HES	hospital episode statistic
HIV	human immunodeficiency virus
HRQoL	health-related quality of life
ICD	International Classification of Diseases 10th Revision
ICER	Incremental cost-effectiveness ratio
ICF	Informed consent form

Abbreviation	Definition
IFSI	International Forum for the Study of Itch
IGA	Investigator's global assessment
IGA-PN-S	Investigator's global assessment for Prurigo nodularis scale
IL	interleukin
IRR	incidence rate ratio
ITC	indirect treatment comparison
ITT	intent-to-treat
JAK	Janus kinase
KLF16	Krüppel-like factor 16
LS mean	least squares mean
LTE	long-term extension
MAR	missing at random
MHRA	Medicines and Healthcare products Regulatory Agency
MI	multiple imputation
MMRM	mixed effect model for repeated measure
NA	not applicable
NHS	National Health Service
NICE	National Institute for Health and Clinical Excellence
NK1	neurokinin-1
NK1R	neurokinin-1 receptor
NMA	network meta-analysis
NRS	Numerical Rating Scale
NORD	National Organisation for Rare Diseases
OPD	outpatient dermatology
PAS	Patient access scheme
PDE-4	phosphodiesterase-4
PK	pharmacokinetics
PLD	patient level data
PN	prurigo nodularis
PP NRS	peak pruritus numerical rating scale
PSA	probabilistic sensitivity analysis
PSS	personal social services
PSSRU	personal social services research unit
PT	preferred term
Q4W	every four weeks
QALY	quality-adjusted life years
QALYG	quality-adjusted life years gained
QoL	quality of life
RCT	randomised controlled trial
RWE	real world evidence
SAE	serious adverse event
SAP	statistical analysis plan

Abbreviation	Definition
SC	subcutaneous
SD	standard deviation
SD NDS	sleep disturbance numerical rating scale
SE	standard error
SLR	systematic literature review
SNRI	serotonin and norepinephrine reuptake inhibitors
SOC	standard of care
SSRI	selective serotonin reuptake inhibitor
TCI	topical calcineurin inhibitor
TCS	topical corticosteroid
TEAE	treatment emergent adverse event
Th2	T-helper 2 cell
TRAE	treatment-related adverse events
UK	United Kingdom
ULN	upper limits of normal
US	United States
UV	ultraviolet
VAS	visual analogue scale
VBA	visual basics for applications
WI NRS	worst itch numerical rating scale
WPAI	Work Productivity and Activity Impairment
WTP	willingness to pay

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

B.1.1. Decision problem

The submission covers part of the anticipated marketing authorisation for nemolizumab considering the treatment of adult patients with moderate to severe prurigo nodularis (PN). This represents the patient population with the greatest unmet clinical need for new safe and effective therapeutic options and is aligned to the clinical evidence available for nemolizumab. The decision problem addressed is consistent with the final NICE scope and the NICE reference case outlined 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 PN	Adults with moderate to severe PN	Adults with moderate to severe PN are those with the greatest unmet need for new safe and effective therapeutic options. Furthermore, this population aligns with the patient population included in the clinical evidence,[1-3] the economic analysis and is considered the population most likely to receive nemolizumab by UK clinical experts.[4,5]
Intervention	Nemolizumab	Nemolizumab with BSC	It is anticipated that nemolizumab will be used with existing BSC, which can include topical emollients, TCSs, and TCIs, in patients with moderate to severe PN. This is aligned with the anticipated use of nemolizumab in clinical practice and has been validated by UK clinical experts.[5]
Comparator(s)	Established clinical management, including: • Topical emollients • TCS • TCI • Antihistamines • Oral corticosteroids • Phototherapy	Established clinical management, including: • Topical emollients • TCS • TCI • Antihistamines • Systemic corticosteroids	Treatment options for patients with PN are limited, as there are currently no guidelines published nor any treatments recommended by NICE for the treatment of PN. During a Delphi panel conducted by Galderma, UK clinicians agreed that the BSC landscape for treating patients with PN includes emollients, TCSs, and TCIs. The UK

	• Immunosuppressive therapies (azathioprine, ciclosporin, methotrexate, or thalidomide) • Antidepressants including selective serotonin reuptake inhibitors (SSRIs) and serotonin norepinephrine reuptake inhibitors (SNRIs)	• Immunosuppressive therapies (azathioprine, ciclosporin, methotrexate, or thalidomide)	clinicians stated that there is significant variation in the subsequent systemic treatments provided. While not considered BSC, antihistamines, systemic corticosteroids and immunosuppressants were treatments used on occasion to manage the symptoms experienced by patients with PN.[4] Therefore, this submission considers topical emollients, TCSs, and TCIs as BSC and the most relevant comparators for nemolizumab.
Outcomes	The outcome measures to be considered include: • Measures of disease severity • Measures of symptom control including improvement in itch • Time to relapse/prevention of relapse • Adverse effects of treatment • HRQoL • Disease-free period/maintenance of remission	The outcome measures to be considered include: • Measures of disease severity • Measures of symptom control including improvement in itch • Adverse effects of treatment • HRQoL	During TA955, disease-free period/maintenance of remission and time to relapse/prevention of relapse were not considered relevant in PN.[7] Furthermore, the OLYMPIA 1[1] and OLYMPIA 2[2] clinical trials include a placebo-controlled 24-week and 16-week treatment duration, respectively; while the subsequent LTE study is no longer placebo controlled. Therefore, there is limited long-term comparative data that would allow for a meaningful comparative analysis of disease-free period/maintenance of remission or time to relapse/prevention of relapse in patients with PN.

Subgroups	If evidence allows the following subgroups will be considered: • Skin colour subgroups	Subgroups of interest for nemolizumab in moderate to severe PN include: • Skin colour subgroups • Patients weighing < 90kg and ≥ 90kg	The dose of nemolizumab in PN is dependent on the patient's weight. Patients weighing ≥ 90 kg receive 60 mg Q4W, while patients < 90 kg to receive a 60 mg loading dose at Week 0, followed by 30 mg Q4W thereafter.[6]
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 treatment technologies will be considered. The availability and cost of biosimilar and generic products should be considered.	As per NICE scope	N/A

Abbreviations: BSC, best supportive care; HRQoL, health-related quality of life; PN, prurigo nodularis; SNRI, serotonin norepinephrine reuptake inhibitors; SSRI, selective serotonin reuptake inhibitor; TCI, topical calcineurin inhibitor; TCS, topical corticosteroid

B.1.2. Description of the technology being evaluated

The submission addresses the clinical efficacy, safety, comparative effectiveness, and cost-effectiveness of nemolizumab in adult (≥ 18 years) patients with moderate to severe PN. Details of the technology being appraised in this submission are summarised in Table 2 and detailed in the following subsections. Additionally, the draft Summary of Product Characteristics for nemolizumab is presented in Appendix C.

Table 2. Technology being evaluated

UK approved name and brand name	Nemolizumab (Nemluvio©)
Mechanism of action	Nemolizumab is a humanised monoclonal antibody that targets the interleukin-31 receptor alpha (IL-31RA). Interleukin-31 (IL-31) is a key mediator of itch, known as a pruritogen, in PN. Nemolizumab inhibits IL-31 signalling and suppresses pruritus by competitively preventing IL-31 from binding to IL-31RA.[8] Nemolizumab treatment has been shown to suppress T-helper 2 cell (Th2) and IL-4/IL-13 responses in PN skin and decrease the expression of factors such as KLF16, which have been shown to inhibit neurite growth. In addition, nerve growth factor, which has been confirmed to be increased in PN skin, is also normalised by nemolizumab.[9]
Marketing authorisation/CE mark status	UK MAA submission via Access Consortium NASWSI was performed [redacted] The anticipated UK marketing authorisation date is [redacted]
Indications and any restriction(s) as described in the summary of product characteristics (SmPC)	Nemolizumab is indicated for the treatment of PN. Nemolizumab is also indicated for the treatment of moderate to severe atopic dermatitis (AD) in patients aged 12 years and older who are candidates for systemic therapy; however, this is not the focus of this submission.
Method of administration and dosage	Subcutaneous injection, with dosage dependant on patient's weight: patients weighing ≥ 90 kg receive 60 mg Q4W, while patients < 90 kg receive 60 mg loading dose at Week 0, followed by 30 mg Q4W thereafter. Treatment continues for as long as patients are responding to treatment.
Additional tests or investigations	No additional tests beyond those already recommended for patients with PN are required.
List price	[redacted]/SKU
Patient access scheme (if applicable)	Simple discount

Abbreviations: CE, Conformité Européenne; IL, interleukin; KLF16, Krüppel-like factor 16; MHRA, Medicines and Health Product Regulatory Agency; PN, prurigo nodularis; Q4W, every 4 weeks; SKU, stock keeping unit; Th2, T-helper 2

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

Summary

Disease pathophysiology, epidemiology, and burden

- PN is a rare, chronic, debilitating neuroimmune dermatological disease that imposes physical, emotional and psychosocial burden on patients, resulting in significant disruption to patients' daily activities, including sleep.[10]
- The primary symptom of PN is severe, intractable, relentless itch accompanied by a constant urge to scratch, which is often painful and can lead to psychiatric impacts that include depression.[11]
- The pathophysiology of PN is associated with IL-31–driven neuroimmune responses, which promote intense itch and the development of the 'itch-scratch' cycle that perpetuates PN.[9]
- The estimated prevalence of PN in England is 3.27 per 10,000 people.[12]
- PN has a significant impact on patients' sleep,[13] mental health and quality of life (QoL),[14] with one study reporting that 18.5% of patients with PN experience suicidal ideations.[15]

Clinical pathway and treatment landscape

- Treatment goals are to reduce pruritus, interrupt the itch-scratch cycle, and completely heal PN lesions. Adequate treatment of PN must address both the neurologic and immunologic components of pruritus.
- Treatment options are limited; currently there are no guidelines published by NICE for the treatment of PN, nor are any treatments approved by NICE for the indication of PN, with all treatments included in the decision problem currently being used off label.
- Treatment is based on clinical judgment rather than a strict stepwise approach. The International Forum for the Study of Itch (IFSI) have published a treatment cascade that forms the basis of most clinical decisions in the management of PN.[16]

- Current treatment options for PN aim to address symptoms. Therefore, there is a significant unmet need for a targeted treatment that addresses the underlying pathophysiology of PN.

Nemolizumab

- Nemolizumab is safe and effective treatment for patients with moderate to severe PN, which is a patient population with very limited therapeutic options.[1,2]
- Nemolizumab addresses the significant unmet need in patients with moderate to severe PN by offering a novel mechanism of action to other treatments utilised in the management of PN by targeting IL-31, a known major pruritogen in the disease.[17]

B.1.3.1. Disease overview

PN is a rare, chronic, debilitating neuroimmune dermatological disease that imposes a physical, emotional and psychosocial burden on patients, resulting in significant disruption to patients' daily activities, including sleep.[10] PN is characterised by multiple hyperkeratotic nodules and papules that are extremely pruritic and typically distributed symmetrically along a patient's trunk and extremities.[10,11]

The most prominent and burdensome symptom of PN is an intractable itch, followed by visibility and bleeding of lesions. Patients regularly experience intense and ongoing itching that severely impacts both the quality and quantity of sleep, which in turn precipitates higher scores for depression and impaired QoL; one third of patients with PN have reported to scratch automatically, even in the absence of itch.[18]

B.1.3.1.1. Pathophysiology

While the exact cause of PN is unknown, altered function of the immune system and nerves in the skin are believed to be associated with the relentless pruritus that leads to frequent scratching.[19] The pathophysiology of PN is associated with IL-31-driven neuroimmune responses, which promote intense itch and the development of the 'itch-scratch' cycle that perpetuates this dermatological disease.[9] The condition is thought to present because of immunological dysregulation and neural amplification, driven by the immune system.[20]

Available data shows that IL-31 is strongly linked with pruritic skin disorders, in part due to its role in the regulation of immune responses, as well as cell proliferation and differentiation.[21] The role of IL-31 in the development of pruritis is believed to present as a result of crosstalk between sensory nerve fibres, epidermal keratinocytes, fibroblasts, and immune cells together with eosinophils (Figure 1).[22]

An analysis of skin samples from patients with different chronic inflammatory skin diseases revealed that patients with PN had the highest levels of IL-31 located in lesional skin, with expression of IL-31 messenger ribonucleic acid (mRNA) almost 50-fold higher than in that of skin from healthy individuals.[11]

In the skin, cutaneous lymphocyte antigen (CLA^+) T-helper 2 (Th2) cells secrete IL-31, which in turn activate cutaneous sensory nerves and innate immune cells as well as keratinocytes. Cutaneous IL-31 signalling results in peripheral pruritus, (neuro)-inflammation, and an impaired barrier function through IL-31-mediated suppression of terminally differentiated genes such as filaggrin and a reduced lipid envelope.[17] Activated keratinocytes secrete chemo-attractants that trigger additional recruitment of IL-31-expressing CLA^+ Th2 cells to the site of inflammation, promoting a positive feedback loop of skin inflammation and pruritus.[17]

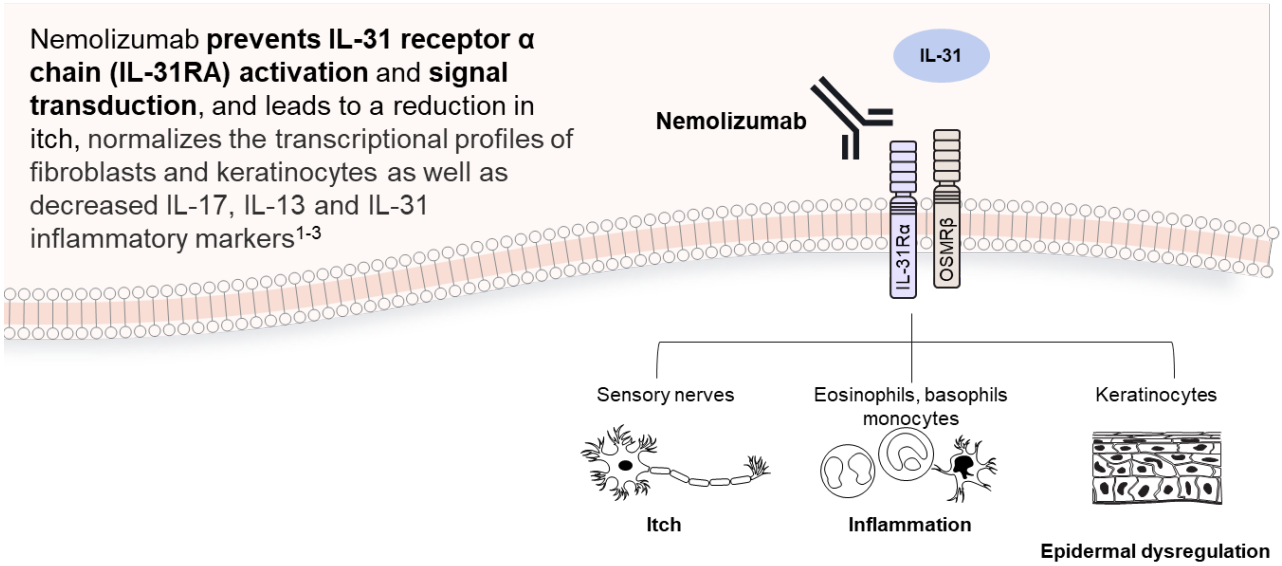

Figure 1. Nemolizumab mechanism of action
Abbreviations: IL-31, interleukin-31;

PN is classified as a rare disease by the National Institute of Health Genetic and Rare Diseases Information Center (GARD) and National Organisation for Rare Diseases (NORD),[19] with limited information on its epidemiology across the world.[12,22] A code to designate the disease was introduced in the International Classification of Diseases, Tenth Revision (ICD-10) in 2015 and there are still geographic differences on its terminology.[22-25]

The estimated prevalence of PN in England was found to be 3.27 per 10,000 people.[12] Of which, 26.8% of patients with moderate to severe PN are believed to be inadequately controlled with current treatments.[7] Although PN can affect patients of all ages, it most commonly develops in middle-aged adults, with approximately 70% of patients presenting at the age of 50 years or older. PN has a slightly higher prevalence in women and disproportionately affects patients with African descent in the US.[26-28]

B.1.3.1.2. Clinical presentation

The primary symptom of PN is severe, intractable, relentless itch accompanied by a constant urge to scratch, which is often painful and can lead to sleep disturbances as well as psychological impacts that include depression.[11] The clinical presentation of PN is often heterogeneous, resulting in lesions that vary in quantity, severity, size (from a few millimetres to a few centimetres) and colour (from the natural skin colour to pink, red, brown and black).[29]

Chronic, intractable itch is the hallmark of PN. Its intensity and frequency are greater than other dermatological conditions and it is perceived by patients as the most frequent, burdensome and debilitating symptom.[13,23,30,31] As confirmed in several European studies that conducted Delphi panels, cross-sectional studies, retrospective studies or surveys, patients with PN experience severe itch, as defined by the mean numerical rating scale (NRS), which ranges from 6.5 to 8.7 out of 10 (where 0 represents no itch and 10 the worst imaginable itch). This surpasses the itch experienced with other dermatological conditions, including psoriasis (mean NRS: 7.5 vs 8.7 for PN in the same study) (Figure 2).[13,23,31-33]

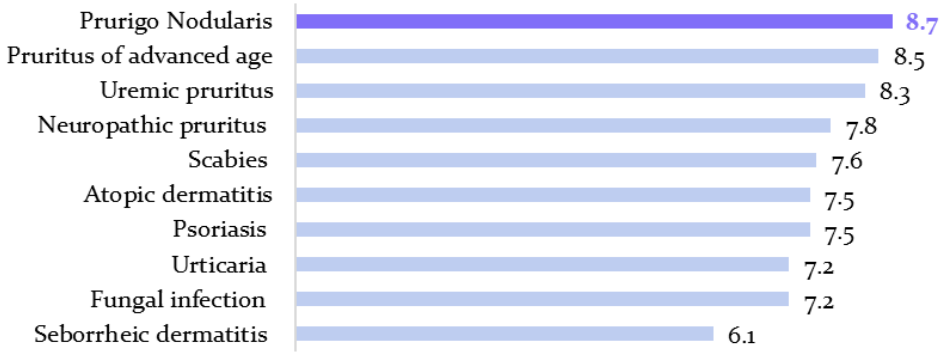

Figure 2. Mean NRS for itch for different pruritic skin conditions

Data are extracted from Mollanazar (2016)[33] providing the mean NRS at the first visit for each diagnosis of PN. The sample was disease specific. A group of 35 patients were analysed for PN.

As per a visual analogue scale (VAS) scale, patients with PN (n = 52) taking part in a survey-based study conducted in Denmark, all reported moderate to severe pruritis (mean ± standard deviation [SD] VAS 6.6 ± 2.4), with 65.4% of patients itching at least several times a day, with the evening and night being reported as the most intense hours of pruritis (66.7% and 41.1%, respectively).[34] In the same study, 75.0% of patients reported that pruritis had a negative effect on their QoL (mean ± SD Dermatology Life Quality Index [DLQI] was 7.0 ± 5.6); 26.9% avoided social activities and were more prone to absenteeism at work due to their disease, and 19.2% relied on sleep medication at least once a month to counteract the impact of their PN symptoms.[34]

A study where patients with PN (n = 21) were interviewed using the patient reported Sleep Disturbance Numerical Rating Scale (SD NRS) found that 19 participants (90.5%) had problems falling asleep, with six of these participants (31.6%) reportedly taking more than an hour to get to sleep. A total of 19 participants (90.5%) also discussed experiences with nighttime awakening, 18 of whom (94.7%) tended to wake up at least once per night. When these 19 participants commented on the effect of PN on the quality of their sleep, 16 participants (84.2%) stated their sleep was negatively affected by PN.[35]

Pruriginous lesions in PN are defined as elevated lesions (papules, nodules, or plaques) that can range in number from 1 to > 100 (≥ 20 in moderate to severe PN). Papule size is up to 0.5 cm, while nodules are firm and dome-shaped lesions with a

diameter of up to 1 cm. Plaques are flat with a diameter > 1 cm, often present on the lower leg, and often show a whitish or pink centre with a hyperpigmented border.[16,24,36] Papules and nodules are highly pruritic and can result in bleeding due to chronic scratching; the nodules are persistent and generally symmetrically distributed on the extensor surfaces of the extremities and trunk which are accessible to scratching,[23,28,36] sparing the palms, soles, scalp, and genitals.[28,36] Most patients with PN present the "butterfly" sign, which is the absence of PN lesions at the centre of their back caused by the inability to scratch that area.[23,28,36]

B.1.3.1.3. Diagnosis and assessment of severity

PN diagnoses are based upon clinical evaluations, with patients commonly presenting a history of chronic severe pruritus and flesh-coloured nodular lesions on exterior surfaces and/or the trunk.[37]

The primary signs of PN are represented by pruriginous lesions distributed symmetrically on areas of the skin generally accessible to scratching, normal or lichenified skin between lesions, excoriations, and scars (scratch-induced lesions).[23] PN symptoms are characterised by itch, which precedes development of skin lesions and may be accompanied by burning, stinging, pain and other sensations.[23]

PN can be classified as mild, moderate or severe. Severity can be assessed in different ways using the Prurigo Activity Score, the number of nodules (as estimated by the Investigator's Global Assessment [IGA]), itch severity, as measured by the NRS or VAS, or QoL impact (as assessed using the DLQI).[16,24]

While few studies have been published on disease staging in PN, one established method of staging uses the IGA scale, in which investigators assess disease severity and classify patients on a five-point scale ranging from 0 (clear) to 4 (severe):[38]

- **Grade 0 (clear):** no nodules (zero nodules)
- **Grade 1 (almost clear):** rare, palpable pruriginous nodules (approximately 1–5 nodules)
- **Grade 2 (mild):** few, palpable pruriginous nodules (approximately 6–19 nodules)
- **Grade 3 (moderate):** many palpable pruriginous nodules (approximately 20–100 nodules)
- **Grade 4 (severe):** abundant palpable pruriginous nodules (> 100 nodules)

The Prurigo Activity Score 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. 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 < 3), moderate pruritus (≥ 3 to < 7), severe pruritus (≥ 7 to < 9) or very severe pruritus (≥ 9).[16]

B.1.3.1.4. Burden of disease

B.1.3.1.4.1. Clinical Burden

It has been previously reported that 71% of patients with PN experience ‘‘intractable’’ itch all or most of the time, with moderate to severe intensity. Regarding the emotional experience of their itch, patients reported their itch as being disturbing (55.2%), burdensome (50.7%), agonising (46.6%), and intractable (35.0%). It was also found that 53.1% of patients reported a negative impact on their everyday life due to itch, with 42.5% experiencing sleep impairment and 37.6% reporting that itch affected their social interactions.[13] A study in patients with PN reported that 100% of patients had sleep disturbance as a result of their disease, with 29% of patients reporting disturbance to their daily life or work as a result of the sleep disturbance.[30] Sleep disorders carry numerous personal and societal consequences, with research documenting that poor sleep is linked to development of depression, suicide, anxiety and disability.[39]

Moderate to severe pain is also common in patients with PN; in a cross-sectional study of pain in patients with dermatologic conditions in 13 European countries, 80.0% of patients with PN reported moderate or severe pain/discomfort using the EuroQol 5-dimensions (EQ-5D) for pain/discomfort, compared with 66.4% of patients with psoriasis and 64.7% of patients with atopic dermatitis (AD).[40]

PN is often associated with other dermatological, systemic, neurologic, psychiatric/psychosomatic malignancies and some infectious diseases, such as AD, cardiometabolic diseases, chronic kidney disease, depression and/or anxiety, and human immunodeficiency virus (HIV). Although the relationship between these comorbidities and PN is difficult to establish, the increased prevalence of these

comorbidities in PN is of clinical relevance to guide decision-making at diagnostic work-up and patient management.[12,36,41,42]

A study in patients with PN reported that 57% of patients experienced depression due to the disease.[30] Patients with PN have been shown to be almost three-times more likely to have concomitant depression when compared with patients with AD and 2.5 times more likely to have depression when compared with patients with psoriasis.[43] Approximately 51.0% of patients with PN reportedly use antidepressants, compared with 28.0% for the control population.[44] These findings suggest a significant psychologic component to PN, and are consistent with previous reports describing a relationship between chronic itch and mood disorders.[43]

Overall, PN has a significant negative impact on QoL and mental health,[14] with one study reporting 18.5% of patients with PN experienced suicidal ideations.[15]

B.1.3.1.4.2. Humanistic burden

A European study of 27 patients with PN found a mean DLQI score of 12.4, with a very large or extreme impact on QoL.[45] PN was associated with similar DLQI scores to hidradenitis suppurativa and greater scores than AD, pruritus, and other skin disorders. Among the dermatological diseases studied, patients with PN had the third worst self-reported health, with an EQ-5D-3L VAS score of 57.4, behind leg ulcers (56.0) and hidradenitis suppurativa (56.9).[45]

An observational, cross-sectional study, conducted across 17 European countries showed that patients with PN (n = 5487) are six-times more likely to experience symptoms of body dysmorphic disorder (aOR > 6) compared with those with no dermatological disorders.[46] A qualitative study that enrolled 21 patients with PN found that over half (59%) of participants wore specific clothes to hide their skin due to embarrassment, with one participant specifying a fear that people would think that their condition is contagious.[30] Furthermore, 67% of participants indicated that their PN-associated lesions impacted their love life, family life or interactions with friends and acquaintances, with 43% of these having lost the desire to go out with others due to shame or embarrassment. Others stated the condition left them unable to go on vacation, and their partner being disgusted by the appearance of the PN lesions.[30]

PN impacts all aspects of a patient's life, with a patient cohort (n = 70) from France finding that 21.4% missed at least one day of work, learning, training, school or university, 72.9% gave up a leisure or sport activity, and 62.9% refused an invitation to a dinner or a party within the three months prior to data collection as a result of their PN (Table 3).[47]

Table 3. Association between QoL and stigma, general health status, impact on daily life, and sleep

Impact on activities	Mild disease (DLQI < 7)		Moderate to severe disease (DLQI ≥ 7)		p-value
	n	%	n	%	
Absenteeism	0	0	15	28.85	0.01
Refusing an activity	3	16.67	48	92.31	< 0.0001
Refusing an invitation	1	5.56	43	82.69	< 0.0001

Source: Misery et al. (2023)[47]

Abbreviations: DLQI, Dermatology Life Quality Index

An observational study conducted in Japan found that the severity of PN experienced by patients has a significant impact on presenteeism and work productivity loss, with median Work Productivity and Activity Impairment (WPAI) scores of 40% for patients with moderate to severe PN for presenteeism versus 10% in patients with mild disease (p = 0.0205). The same results were observed for patients' WPAI work productivity loss scores (40% vs. 10%; p = 0.0176).[48] WPAI scores are self-reported by patients and expressed as a percentage, with higher scores indicating increased impairment. They cover aspects of working life such as current employment status, number of work hours missed due to condition, and the degree to which the disease affects productivity while working.

B.1.3.1.4.3. Economic burden

A UK study comparing the healthcare utilisation in patients with PN versus a matched control population (patients without PN) found higher healthcare usage in patients with PN, with

- an increase in primary care contacts of 14.8 per year versus 8.9 in the control group (incident rate ratio [IRR]: 1.48 [95% CI 1.47–1.49]),
- an increase of 80% in the inpatient setting with 1.3 annual visits versus 0.5, respectively (IRR: 1.80 [95% CI 1.75–1.85]),
- 2.2 times higher usage for the outpatient setting with 7.6 annual visits versus 3.0, respectively (IRR: 2.15 [95% CI 2.13–2.18]),
- 32% increased visitations to Accident & Emergency (A&E) departments with 0.6 annual visits versus 0.4, respectively (IRR: 1.32 [95% CI 1.27-1.36]).[49]

This increase in contact was reflected in higher mean costs per annum for all healthcare contacts for patients with PN versus the control population (patients without PN): £371 versus £218 for primary care, £1,326 versus £731 for inpatient contacts, £737 versus £331 for outpatient contacts, and £97 versus £53 for accident and emergency contacts.[49]

A significant economic burden has been established regarding patients with PN due to considerable healthcare resource utilisation. A retrospective study utilising the Clinical Practice Research Datalink (CPRD) Aurum and Gold databases linked to Hospital Episode Statistics assessed the healthcare resource use (HCRU) in England.[50] This study showed that HCRU in England, while generally higher in the first-year post-diagnosis, will persist beyond this and in some instances rise, exemplifying the ongoing costs associated with this chronic dermatological disease.

In the first year following a diagnosis of PN, 96.7% of patients visit a GP regarding their condition, with this figure remaining consistent through 2 to 5 years post diagnosis (95.3%). Overall, from years 0 to 5 following their diagnosis, nearly all patients will visit their GP (99.4%). Outpatient dermatology wards (OPD) are visited by nearly half of all overall patients in their first year following diagnosis (49.6%), which only falls slightly through years 2 to 5 (32.7%). When looking specifically at those patients who attended OPD services, just over half continue to attend through years 2 to 5 (51.3%). Nearly 4 out of 5 patients diagnosed with PN visit an outpatient service in their first year following diagnosis (79.5%), with the percentage increasing

through years 2 to 5 (82.9%); more than 9 out of 10 patients will access outpatient services in the first 5 years following their PN diagnosis (93.1%). A&E services were used by 30.2% of patients in the first year following a diagnosis with PN, rising to over half of patients with PN between years 2 and 5 post-diagnosis (53.3%); in total, nearly 7 in 10 patients access A&E in the first five years following diagnosis with PN (68.1%).[50]

Patients with PN also experience considerable out-of-pocket expenses. A survey-based study conducted in France reported that median annual out-of-pocket expenses per patient were €605.[51,52] This amount increased with pruritus severity from a median value of €202 for the least severe cases, to a median value of €922 for the most severe.[51,52] These costs include health products (cosmetics, keratolytic hydration, bandages), precautionary devices (clothing, shoes and gloves), alternative and complementary medicines and psycho-corporeal practices (hypnosis, magnetism and meditation) and other medical practitioners, mainly psychologists.[51,52]

B.1.3.2. Clinical pathway and positioning of nemolizumab

B.1.3.2.1. Current treatment of PN

Treatment goals in the management of PN are to reduce pruritus, interrupt the itch-scratch cycle, and completely heal PN lesions. Adequate treatment of PN must address both the neural and immunologic components of pruritus. Treatment options for patients with PN are limited, as there are currently no guidelines published by NICE for the treatment of PN, nor are there any treatments approved by NICE for PN. With the exception of dupilumab, which was not recommended by NICE for PN,[7] all treatments used in the management of PN are used off-label and aim to provide symptomatic relief to patients rather than address the underlying pathophysiology of the disease.

While a definitive guideline for the treatment of patients with PN in the UK is currently unavailable, management requires a multifaceted approach.

- The treatment of PN presents a challenge to the clinician as there are few randomised controlled trials (RCTs) delineating therapy options. Therapies

should be tailored to the patient's age, comorbidities, severity of PN, QoL and expected side effects. Discussions with the patient should include the advantages and disadvantages of the therapy, side effects, and possible use of off-label medications.[10]

- Identifying an underlying cause, if present, is essential to properly treating a patient with PN to prevent any recurrent pruritus that may lead to recurrence, as well as to avoid any treatments that may be contraindicated.[10]

Current treatments used in the management of PN only target its symptoms and include emollients, topical corticosteroids (TCSs), topical calcineurin inhibitors (TCIs), topical capsaicin, antihistamines, systemic corticosteroids, intralesional corticosteroids, neuromodulators (e.g., gabapentinoids, cannabinoids, or anaesthetics), antidepressants, phototherapy, and immunosuppressants, which tend to be more commonly used for moderate to severe disease.[53]

Treatment of PN is currently based on clinical judgment rather than on a strict stepwise approach. The International Forum for the Study of Itch (IFSI) have published a stepwise treatment cascade that forms the basis of most clinical decisions in the management of PN (Figure 3).

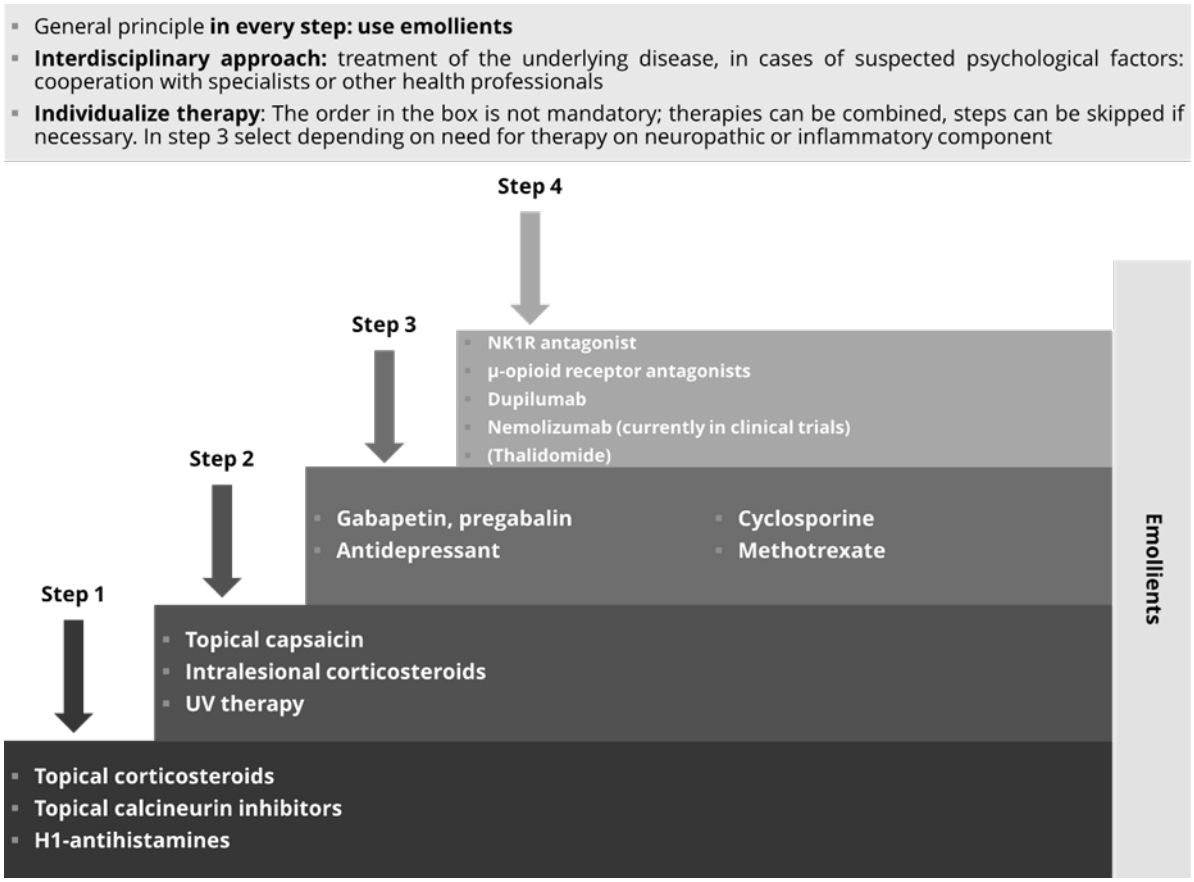

Figure 3. IFSI stepwise treatment recommendations

Source: Ständer et al. (2020)[24]

Abbreviations: IFSI, International Forum for the Study of Itch; NK1R, neurokinin-1 receptor; UV, ultraviolet.

B.1.3.2.2. Current clinical practice in the UK

During a Delphi panel conducted by Galderma, clinicians specialising in the treatment of PN, including clinicians from the UK, described utilising treatment pathways that generally followed the pathway outlined by the IFSI guidelines, albeit with some differences owing to the current lack of definitive guidelines published in the UK.[4] It was also found that the limited number of treatment guidelines available for PN are now 'out of date' and 'limited by the evidence base,' leading to observed variations in reported management practises.[4]

Based on the limited treatments currently available, UK clinicians involved in the Delphi panel exercise agreed that the best supportive care (BSC) landscape for treating patients with PN include emollients, TCSs, and TCIs. The UK clinicians stated that there is significant variation in the off-label treatments offered in the subsequent lines of therapy. While not considered BSC, antihistamines, systemic corticosteroids, and immunosuppressants (e.g. methotrexate and ciclosporin) are

used on occasion to manage the symptoms experienced by patients with PN; however, these do not treat the disease itself.[4]

The clinical experts went on to identify TCSs as the most frequently used first-line (1L) treatment prescribed to patients with moderate to severe PN.[4] In addition to TCSs, emollients have been found to be almost universally used as BSC for pruritus in patients with PN (92.1% of patients with mild or moderate pruritus and 91.3% of those with severe pruritus); sedatives to help improve sleep were the second choice therapy (38.9% and 50.0%).[54]

Phototherapy, while recognised as a potential treatment option for patients with PN, is rarely recommended by UK clinicians, as confirmed by a Delphi panel exercise.[4] This is likely due to its limited effectiveness, inconvenience to patients who have to regularly access clinics incurring out-of-pocket costs, and the concern patients have regarding the increased risk of melanoma from exposure to ultraviolet light.[55]

B.1.3.2.3. Limitations of current treatment

Currently, there are no therapies recommended by NICE specific for the treatment of patients with PN. With the exception of dupilumab, which was not recommended by NICE for the treatment of PN,[7] current treatment options are prescribed off-label and aim to relieve symptoms, rather than address the underlying disease pathophysiology. This lack of effective treatment options that effectively control the disease in patients with PN results in greater HCRU resulting from increased visitation to both GPs and emergency services.[50] Left unmanaged, the itch-scratch cycle that perpetuates this disease results in increased disease severity,[9] which impacts patient QoL, as well as their ability to perform everyday activities including paid work.[48]

A questionnaire study conducted across 15 European dermatological centres (N = 406) found that a substantial number of patients with PN (28.7%) consider none of the therapeutic options offered to them as effective. Despite chronic PN being a severe disease, most patients did not receive potent systemic drugs, which may contribute to the high levels of dissatisfaction and disbelief in the effectiveness of currently available therapies.[56]

Most patients rely on topical therapies which are labour intensive and require frequent applications. Patients value having a choice in their treatment decisions; however, with no recommended therapies available and no definitive treatment guidelines, patients with PN are not offered this. As such, a novel targeted therapy that addresses the pathophysiology of PN would be of substantial benefit to patients, especially regarding symptomatic relief and reduced disease burden, which would prevent disease progression if it successfully broke the itch-scratch cycle. Likewise, nemolizumab is offered as a convenient and simple injection, once every four weeks (Q4W), which would relieve patients of their current daily treatment regimens.

Despite their widespread use in the management of PN, topical and other dermatological therapies can themselves add to the burden of the disease, as their application may be time consuming, messy, intervene with clothing choice, lead to side effects such as skin atrophy,[57] and impact HRQoL in ways that are unique to the skin. Furthermore, even systemic dermatological medications, such as cytotoxic drugs, corticosteroids, and retinoids have an associated burden. Systemic treatment options for patients with PN include methotrexate, thalidomide, and cyclosporin, which carry notable risks and issues with their usage. Even at low dosage, methotrexate may cause significant side effects; gastrointestinal (GI) manifestations are the most common, such as nausea, vomiting, mucosal ulcers, and loss of appetite.[58] Severe AEs may also occur, such as hepatotoxicity, pulmonary toxicity, myelosuppression, and nephrotoxicity, which perquisite regular blood monitoring.[58] Thalidomide and lenalidomide have a dose-limiting toxicity profile and significant side effects, such as peripheral neuropathy, teratogenicity, fatigue and hypercoagulability.[10,59,60] In the largest study to date investigating thalidomide use in patients with PN (n = 42), 59% of patients discontinued treatment due to peripheral neuropathy.[10,59,61]

B.1.3.2.4. Unmet need

A significant unmet need exists for an efficacious systemic treatment for moderate to severe PN, especially as there are currently no systemic treatments reimbursed by NICE for this patient population.

Improvements in itch, clearance of skin lesions, and reduction in sleep disturbance are seen as the most important goals for successful treatment. Most patients with PN were not satisfied with their previous therapy (56.8%), while 9.8% did not receive any therapy despite having active disease.[56] All currently prescribed off-label treatments are associated with AEs, including local site reactions (burning, itching, irritation, and dryness),[13,16,34,62,63] peripheral oedema,[16] renal dysfunction[16] and increased risk of malignancy (Section B.1.3.2.3).[20]

Nemolizumab, a targeted systemic therapy, presents a new mechanism of action to other treatments utilised in the management of PN that targets IL-31, a major pruritogen, suppressing pruritus by competitively preventing IL-31 from binding to IL-31RA.[8] Nemolizumab treatment has also been shown to suppress Th2 and IL-4/IL-13 responses in skin and decrease expression of factors such as KLF16, which has been shown to inhibit neurite growth.[9] Nemolizumab has been demonstrated to be safe and efficacious in the treatment of patients with PN (Section B.2), demonstrating positive efficacy outcomes in a patient population with very limited therapeutic options in both the Phase 3 OLYMPIA 1 and OLYMPIA 2 clinical trials.[1,2] Patients experienced rapid response times after initiating nemolizumab, experiencing relief of itch, which has been described as the most burdensome symptom of this disease, in as little as two days (Section B.2.6 and B.2.10).[1,2]

Nemolizumab benefits patients with a convenient Q4W dosing regimen,[6] which can be self-administered following a short training consultation with a healthcare professional; this should replace the need for a daily systemic therapy to be taken orally and limit the number of daily applications required of topical dermatological therapies, which can become burdensome. Unlike some systemic treatments used to manage PN, there is no requirement for regular blood tests or monitoring, as is the case with immunosuppressive therapies, such as methotrexate and thalidomide.[58,64]

B.1.3.2.5. Positioning of nemolizumab

There are currently no recommended systemic treatments for patients with PN. It is anticipated that nemolizumab will be used alongside existing topical treatments, which can include topical emollients, TCSs, and TCIs, in patients with moderate to severe PN who have had an inadequate response to existing topical treatments, or

where these treatments are contraindicated or not tolerated (Figure 4). Any use of TCSs or TCIs should aim to be tapered and subsequently discontinued when the disease has sufficiently improved. This positioning is considered appropriate by UK clinical experts.[5]

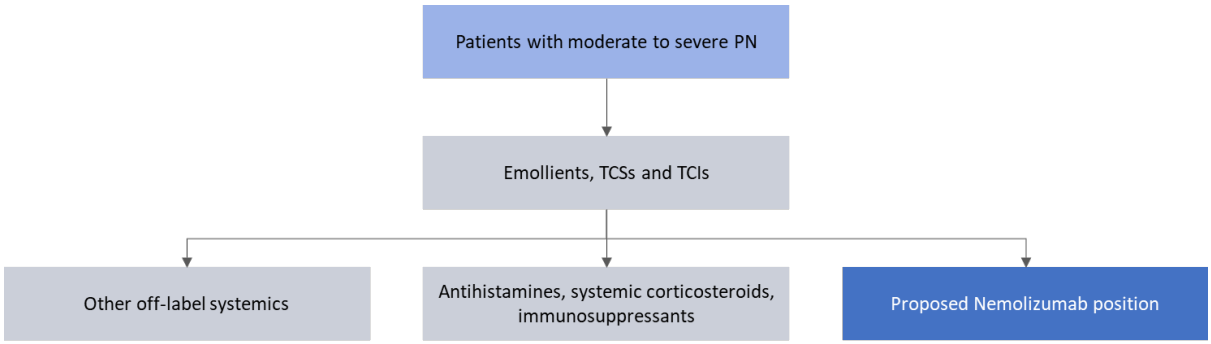

Figure 4. Anticipated positioning of nemolizumab

Abbreviations: PN: prurigo nodularis; TCIs: topical calcineurin inhibitors; TCSs: topical corticosteroids.

B.1.4. Equality considerations

The use of nemolizumab is not anticipated to raise any specific equality issues or result in a recommendation that has a differential impact on individuals protected by equality legislation or those with disabilities, compared with the wider population.

However, we are aware of the documented challenges in assessing skin disorders in patients with skin of colour.[65,66] These patients have a greater propensity for papulation, lichenification, PN, pigmentary changes, and extensor surface involvement than patients with white skin.[65,66] Erythema is more difficult to detect in highly pigmented patients, and can lead to an underestimation of disease severity.[65] Accordingly, certain patient populations may be more likely to receive sub-optimal treatment.

B.2. Clinical effectiveness

Summary of clinical evidence

Trial overview

- The nemolizumab clinical development programme comprised two Phase 3, multicentre, double-blind, placebo-controlled, randomised, parallel-group studies (OLYMPIA 1 and OLYPMIA 2),[1,2] and one long term extension (LTE) study (OLYMPIA LTE),[3] which followed on from these trials. These studies will be used as the basis to inform the clinical efficacy and safety of nemolizumab in patients with moderate to severe PN within this submission.
- The primary endpoints of the OLYMPIA 1 and OLYMPIA 2 randomised controlled trials (RCTs) were an improvement of ≥ 4 in peak pruritus numerical rating scale (PP NRS), and IGA success (score of 0/1) with a change of > 2 points at Week 16.[1,2]
- The pooled analysis results from the OLYMPIA 1 and OLYMPIA 2 trials have informed the economic analysis.

Efficacy results

- A statistically significantly higher proportion of patients (strata adjusted p < 0.0001) in the nemolizumab arms demonstrated a ≥ 4-point improvement in PP NRS from baseline to Week 16 in both trials (OLYMPIA 1: 58.4% nemolizumab, 16.7% placebo; OLYMPIA 2: nemolizumab 56.3%, placebo, 20.9%).[1,2]
- A statistically significantly higher proportion of patients in the nemolizumab arms demonstrated IGA success at Week 16 in both trials (OLYMPIA 1: nemolizumab 26.3%, placebo 7.3%, strata adjusted p = 0.0025; OLYMPIA 2: nemolizumab 37.7%, placebo 11.0%, strata adjusted p < 0.0001).[1,2]
- In the single arm LTE study, these positive efficacy outcomes were demonstrated up to Week 52, both in patients who previously received nemolizumab in prior RCTs and in nemolizumab-naïve patients. Efficacy outcomes in patients who were nemolizumab-naïve coincided with those of patients who had previously received nemolizumab in as little as four weeks.[3]

- In subgroup analyses undertaken as part of this clinical programme, results were directionally consistent with those of the primary analysis in all subgroups of interest, including race and weight.[1,2]

Safety results

- Treatment with nemolizumab was well tolerated by patients in both the OLYMPIA 1 and OLYMPIA 2 trials, with an adverse event (AE) profile comparable to that of placebo.[1,2]
- This tolerability persisted to Week 52 in the LTE study in patients who had previously received nemolizumab, and was comparable with the AEs recorded in nemolizumab-naïve patients upon enrolment into the LTE study.[3]

Conclusion

- Nemolizumab is a targeted systemic therapy that has demonstrated significant efficacy across all trials compared with placebo and was well-tolerated with a similar safety profile to placebo over 52 weeks. Therefore, nemolizumab has the potential to address the significant unmet need in patients with moderate to severe PN, who currently have limited therapeutic options.

B.2.1. Identification and selection of relevant studies

A systematic literature review (SLR) was conducted to identify all the relevant clinical effectiveness evidence (efficacy and safety) of interventions for the treatment of PN. Database searches were initially conducted on 25 September 2023 and subsequently updated on 17 May 2024. In total 19 studies from 59 publications met the eligibility criteria and were included in this review. Full details of the process and methods to identify and select the relevant clinical evidence are summarised in Appendix D.

B.2.2. List of relevant clinical effectiveness evidence

The nemolizumab clinical development programme was designed to demonstrate the efficacy and safety of nemolizumab for the treatment of patients with moderate to severe PN.

Two key Phase 3 clinical trials (OLYMPIA 1: NCT04501666, OLYMPIA 2: NCT04501679) and a long-term extension (LTE) study (OLYMPIA LTE: NCT04204616) that followed on from these Phase 3 trials are used inform the clinical efficacy and safety of nemolizumab in patients with moderate to severe PN within this submission (Table 4).

The pivotal OLYMPIA 1 and 2 trials are of similar design; both were conducted as Phase 3, multicentre, double-blind, randomised, placebo-controlled, parallel-group studies, and both include primary outcomes that assess efficacy after 16 weeks. These studies were conducted in multiple locations, with OLYMPIA 1 enrolling patients in Austria, Canada, Denmark, Germany, Hungary, Italy, Poland, Sweden, the UK, and the US, and OLYMPIA 2 enrolling patients in Belgium, Canada, France, Netherlands, Poland, South Korea, Spain, Switzerland and the US (N = 560 overall; OLYMPIA 1: n = 286; UK: n = 17; OLYMPIA 2: n = 274).

The LTE study recruited patients (n = 508) who were previously enrolled in either the OLYMPIA 1 or OLYMPIA 2 trials and was conducted as a Phase 3 prospective, multicentre, long-term study.

Table 4. Clinical effectiveness evidence

Study	OLYMPIA 1 (NCT04501666)	OLYMPIA 2 (NCT04501679)	LTE study (NCT04204616)
Study design	Phase 3, multicentre, double-blind, placebo-controlled, randomised, parallel-group study		Phase 3 prospective, multicentre, long-term study
Duration	24 Weeks	16 Weeks	196 Weeks
Population	Adult patients with a clinical diagnosis of PN for at least six months with pruriginous nodular lesions on upper limbs, trunk, and/or lower limbs with at least 20 nodules on the entire body with a bilateral distribution, Investigator's Global Assessment score ≥ 3 (based on the IGA scale ranging from 0 to 4, in which 3 was moderate and 4 was severe) at both the screening and baseline visits		Adult patients who had been enrolled in prior nemolizumab PN Phase 2a or Phase 3 studies
Intervention(s)	Nemolizumab: • if patient weighs < 90 kg; 60 mg loading dose followed by 30 mg administered SC Q4W at weeks 4, 8, 12 and 16 (and 20 for OLYMPIA 1) • if patient weighs ≥ 90kg; 60 mg loading dose followed 60 mg (2 x 30 mg injections) administered SC Q4W at weeks 4, 8, 12 and 16 (and 20 for OLYMPIA 1)		Nemolizumab: • Patients weighing < 90 kg at baseline received open-label 30 mg nemolizumab every 4 weeks (Q4W), with 60 mg loading dose at baseline • Patients weighing ≥ 90 kg at baseline received 60 mg nemolizumab Q4W via two 30 mg injections • Beginning at Week 56, nemolizumab dosage will be adjusted every 6 months for patients with a documented weight change above or below the 90 kg threshold at 2 consecutive designated visits
Comparator(s)	Placebo administered SC Q4W at weeks 4, 8, 12 and 16 (and 20 for OLYMPIA 1)		N/A
Indicate if trial supports application for marketing authorisation	Yes		Yes

Study	OLYMPIA 1 (NCT04501666)	OLYMPIA 2 (NCT04501679)	LTE study (NCT04204616)
Indicate if trial used in the economic model	Yes		Yes
Rationale for use in the model	Relevant patient population (adult patients with moderate to severe PN) and outcomes, as described below were reported in the trials, as aligned with the decision problem.		
Primary outcomes	• The proportion of patients with an improvement of ≥ 4 from baseline in PP NRS at Week 16 • The proportion of patients with an IGA success (defined as an IGA of 0 [clear] or 1 [almost clear] and a ≥ 2-grade improvement from baseline) at Week 16		• Incidence and severity of adverse events (AEs), including AEs of special interest, treatment-emergent AEs, and serious AEs
Secondary outcomes	• The proportion of patients with an improvement of ≥ 4 from baseline in PP NRS at Week 4 • The proportion of patients with a PP NRS < 2 at Week 4 • The proportion of patients with IGA success and an improvement of ≥ 4 from baseline in PP NRS at Week 16 (and Weeks 20 and 24 in OLYMPIA 1) • The proportion of patients with ≥ 4-point improvement from baseline in weekly average SD NRS at Week 4 and 16 • The proportion of patients with an improvement of ≥ 4-points from baseline in DLQI total score at Week 4, 16 (and Week 24 in OLYMPIA 1) • Change from baseline in EQ-5D total score at Week 4, 16 (and Week 24 in OLYMPIA 1) • Change from baseline in HADs score at Week 4, 16 (and Week 24 in OLYMPIA 1)		• The proportion of patients with an IGA success at Week 52 • The proportion of patients with an improvement of ≥ 4 from baseline in PP NRS at Week 52 • The proportion of patients with a PP NRS < 2 at Week 52 • The proportion of patients with ≥ 4-point improvement from baseline in weekly average SD NRS at Week 52 • The proportion of patients with an improvement of ≥ 4-points from baseline in DLQI total score at Week 52
All other reported outcomes	• Safety		• Safety

Abbreviations: AE, adverse event; IGA, Investigator's Global Assessment Score; DLQI, Dermatology Life Quality Index; EQ-5D, EuroQol five dimension; kg, kilogram; LTE, long term extension; mg, milligram; N/A, not applicable; PN, prurigo nodularis; PP NRS, Peak Pruritis Numerical Rating Scale; Q4W, every four weeks; SD NRS, Sleep Disturbance Numerical Rating Scale; TBC, to be confirmed.

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

B.2.3.1. OLYMPIA 1 and OLYMPIA 2

The OLYMPIA 1 and 2 studies were both Phase 3, multicentre, double-blind, randomised, placebo-controlled, parallel-group trials designed to evaluate the efficacy and safety of nemolizumab in patients with moderate to severe PN.

In total, 560 patients across 16 countries were randomised 2:1 and received either nemolizumab or placebo for up to 24 weeks in OLYMPIA 1, or up to 16 weeks in OLYMPIA 2, with patients being stratified by study site location and baseline body weight (< 90 kg, ≥ 90 kg) (Table 5). Both studies consisted of a screening period (up to 4 weeks), a 24- or 16-week treatment period, and an 8-week follow-up period (12 weeks after the last study drug injection) (Figure 5 and Figure 6). Treatment summaries for the OLYMPIA 1 and 2 trials can be found in Table 6; in both studies, patients were permitted to use certain concomitant medications throughout the duration of the trials; a summary of these permitted treatments can be found in Table 7.

The co-primary efficacy outcomes for both clinical trials were PP NRS (a change of ≥ 4-points from baseline) and IGA success (a change of ≥ 2-points from baseline and a score of 0/1) at Week 16.

Itch has been reported to be the first and the most debilitating symptom of PN as reported by patients.[13,23,30,31] Furthermore, itch in patients with PN has been identified as a key component in the impact in both quantity and quality of sleep, which, in turn, has been shown to impact the mental health of patients.[11] The PP NRS scale is a clinically validated single-item patient reported measure of itch severity over the previous 24-hour period based on a single question, being, ‘On a scale of 0 to 10, with 0 being “no itch” and 10 being “worst itch imaginable”, how would you rate your itch at the worst moment during the previous 24 hours?’[67] Treatment with nemolizumab was deemed clinically effective if patients reported a change in PP NRS of ≥ 4 points following treatment (Table 5).

The IGA scale is used to determine the severity of PN in patients based on the number of pruriginous lesions present on the skin of a patient with PN, ranging from zero (clear; no pruriginous lesions) to four (severe; abundant palpable pruriginous lesions [> 100]).[16,24] The presence of pruriginous lesions is linked to the psychological burden of PN in patients and has been identified as a factor relating to issues of self-esteem, suicidal ideation and humanistic burden in patients with PN.[39] Treatment with nemolizumab was deemed effective if patients presented with an IGA score of zero (clear) or one (almost clear), and a change of at least 2-points from baseline to Week 16 following treatment with nemolizumab (Table 5).

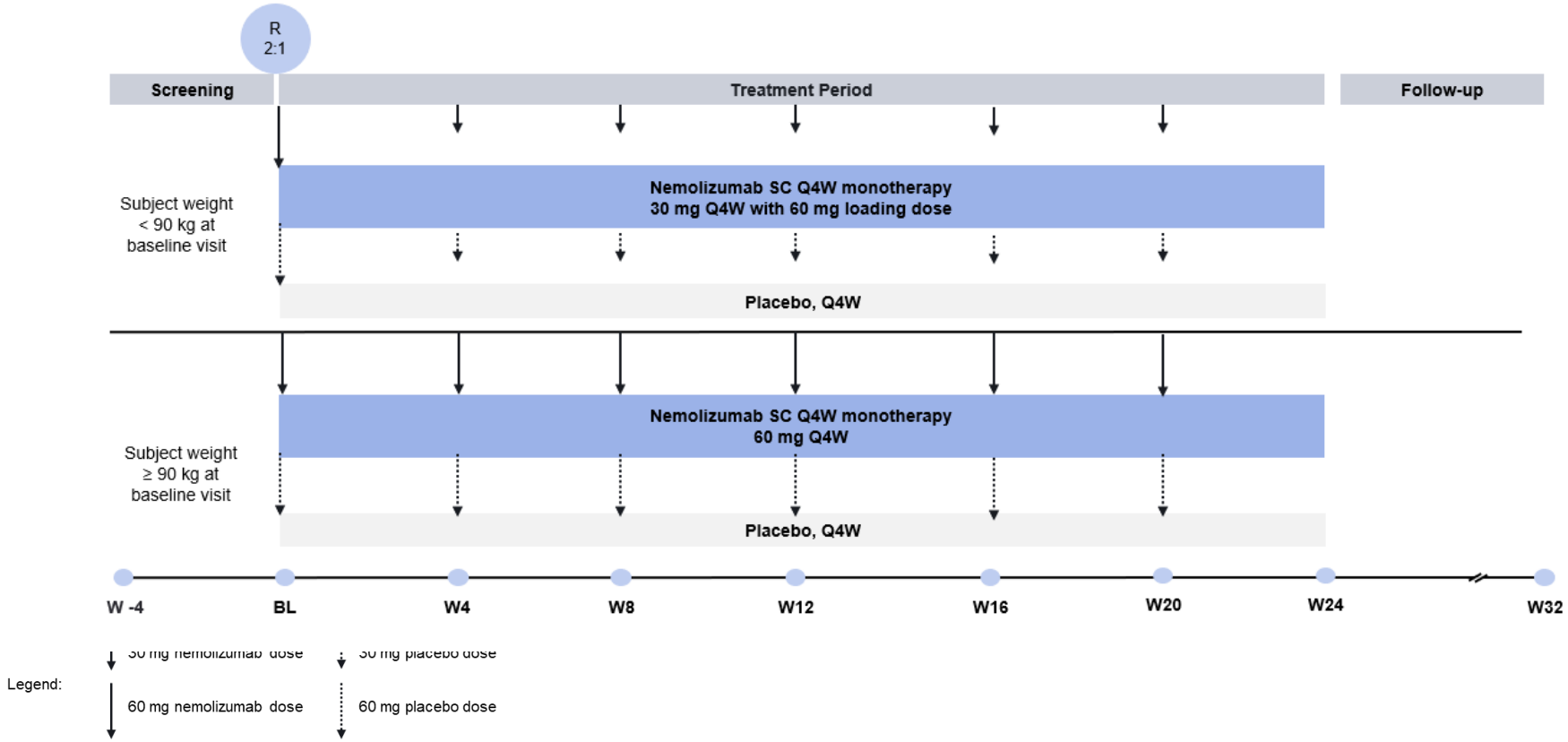

Figure 5. OLYMPIA 1 study design

Schematic representation of the OLYMPIA 1 study, reporting the initial screening phase, followed by the treatment period and follow-up period. The schematic was organised into two treatment groups with patients weighing < 90 kg or ≥ 90 kg.

Abbreviations: BL, baseline; kg, kilogram; mg, milligram; Q4W, every four weeks; R, randomisation; SC, subcutaneously; W, week.

Source: Galderma. OLYMPIA 1 CSR[1]

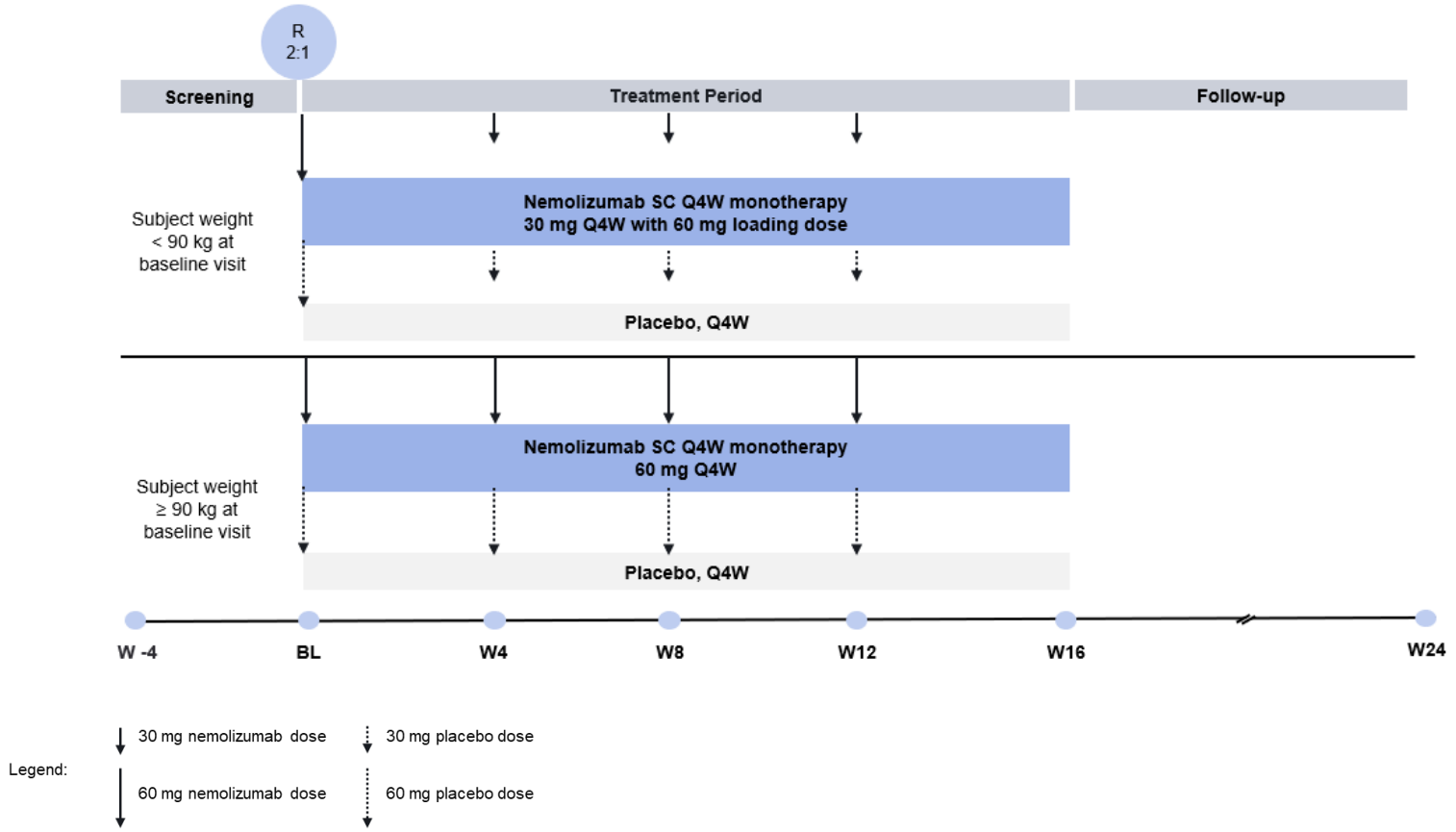

Figure 6. OLYMPIA 2 study design

Schematic representation of the OLYMPIA 2 study, reporting the initial screening phase, followed by the treatment period and follow-up period. The schematic was organised into two treatment groups with patients weighing < 90 kg or ≥ 90 kg.

Abbreviations: BL, baseline; kg, kilogram; mg, milligram; Q4W, every four weeks; R, randomisation; SC, subcutaneously; W, week.

Source: Galderma. OLYMPIA 2 CSR[2]

Table 5. Study design for OLYMPIA 1 and OLYMPIA 2

Trial name	OLYMPIA 1 (NCT04501666)[1]	OLYMPIA 2 (NCT04501679)[2]
Location	77 investigational sites across 10 countries: Austria, Canada, Denmark, Germany, Hungary, Italy, Poland, Sweden, UK and US	55 study sites across 9 countries: Belgium, Canada, France, Netherlands, Poland, South Korea, Spain, Switzerland and US
Trial design	Phase 3 randomised, placebo-controlled, double-blind, parallel-group, multicentre study	
Eligibility criteria for participants	1. Male or female aged ≥ 18 years at the time of screening 2. Clinical diagnosis of PN for at least six months with: a. Pruriginous nodular lesions on upper limbs, trunk, and/or lower limbs b. At least 20 nodules on the entire body with a bilateral distribution c. IGA score ≥ 3 (based on the IGA scale ranging from 0 to 4, in which 3 was moderate and 4 was severe) at both the screening and baseline visits 3. Severe pruritus, defined as follows on the PP NRS: • At the screening visit (Visit 1): PP NRS score was ≥ 7.0 for the 24-hour period immediately preceding the screening visit. • At the baseline visit (Visit 2): mean daily intensity of the PP NRS score was ≥ 7.0 over the previous week. 4. Female patients of childbearing potential must have agreed to use at least one adequate and approved method of contraception throughout the study and for 12 weeks after the last study drug injection (Full detail can be found in the CSR[1]). 5. Female patients of non-childbearing potential must have met one of the following criteria: • Absence of menstrual bleeding for 1 one year prior to screening without any other medical reason, confirmed with a follicle-stimulating hormone level in the postmenopausal range • Documented hysterectomy, bilateral salpingectomy, or bilateral oophorectomy at least three months before the study 6. Patient was willing and able to comply with all of the time commitments and procedural requirements of the clinical study protocol, including daily diary recordings by the patient using an electronic handheld device provided for this study 7. Read, understood, and signed an ICF before any investigational procedure(s) were performed.	

Trial name	OLYMPIA 1 (NCT04501666)[1]	OLYMPIA 2 (NCT04501679)[2]
Study drugs	Nemolizumab 30 mg/60 mg SC Q4W or placebo	
Concomitant medications	• Drugs/therapies included, but were not limited to, prescription, over the counter, birth control pills/patches/hormonal devices, vitamins, moisturisers, sunscreens, herbal medicines/supplements, and homeopathic preparations • Medical and surgical procedures (e.g., phototherapy, exodontia): procedures whose sole purpose was diagnosis (non-therapeutic) were not included • Where patients received treatments other than the study drug, reassessment of these patients was necessary before the patient could continue in the study. If a patient received a prohibited therapy during the clinical study the Investigator was to notify the medical monitor and discuss whether or not it was acceptable for the subject to continue receiving study drug For more details, see Table 7	
Primary outcome	The primary objective was to assess the efficacy of nemolizumab compared with placebo in patients ≥ 18 years of age with PN after a 16-week treatment period. There were two primary endpoints in this study: • Proportion of patients with ≥ 4-point improvement from baseline in PP NRS at Week 24 • Proportion of patients with an IGA of success at Week 24	The primary objective was to assess the efficacy of nemolizumab compared with placebo in patients ≥ 18 years of age with PN after a 16-week treatment period. There were two primary endpoints in this study: • Proportion of patients with ≥ 4-point improvement from baseline in PP NRS at Week 16 • Proportion of patients with an IGA of success at Week 1
Pre-planned subgroups	• Region (Europe, North America) • Age group (18–-65 and > 65) • Sex (male, female) • Race • Weight at randomisation (< 90 kg, ≥ 90 kg) • Baseline IGA score (moderate [3], severe [4])	

Abbreviations: IGA, Investigator's Global Assessment score; kg, kilogram; mg, milligram; PK, pharmacokinetics; PN, prurigo nodularis; PP NRS, Peak Pruritis Numerical Rating Scale; Q4W, every four weeks; SC, subcutaneously
Source: Galderma. OLYMPIA 1 CSR[1]; Galderma. OLYMPIA 2 CSR[2]

Table 6. Treatment summary for OLYMPIA 1 and OLYMPIA 2

	OLYMPIA 1		OLYMPIA 2	
	Nemolizumab	**Placebo**	**Nemolizumab**	**Placebo**
Pharmaceutical form	Lyophilised powder in a DCS for solution for injection			
Storage conditions	2°C to 8°C (36°F to 46°F); protected from light and freezing			
Dosage	Patients weighing < 90 kg at baseline: 30 mg, with a loading dose of 60 mg at baseline Patients weighing ≥ 90 kg at baseline: 60 mg	Not applicable	Patients weighing < 90 kg at baseline: 30 mg, with a loading dose of 60 mg at baseline Patients weighing ≥ 90 kg at baseline: 60 mg	Not applicable
Route	SC use by patients or clinic staff after reconstitution			
Dose regimen	Patients weighing < 90 kg at baseline: 2 injections at baseline, then one injection Q4W Patients weighing ≥ 90 kg at baseline: 2 injections at baseline, then two injections Q4W			
Treatment duration	24 weeks with last injection at Week 20		16 weeks with last injection at Week 12	

Abbreviations: DCS, dual chamber syringe; kg, kilogram; mg, milligram; Q4W, every four weeks; SC, subcutaneous.
Source: OLYMPIA 1 CSR[1]; Galderma. OLYMPIA 2 CSR[2]

Table 7. Concomitant medications and prohibited treatments – OLYMPIA 1 and OLYMPIA 2

Permitted concomitant therapy	Prohibited therapy	Rescue medication only*
Unless specified as a prohibited therapy, all therapies were authorised including basic skin care, moisturisers, bleach baths and topical anaesthetics.	TCIs and TCSs	TCSs
	Topical vitamin D analogues	TCIs
	Topical or systemic PDE-4 inhibitors	Oral antihistamines
	Any other topical treatment than moisturiser	Systemic or intralesional corticosteroids
	Emollients or moisturisers with menthol, polidocanol or having an anti-itch claim	Biologics (including their biosimilars)
	Systemic or intralesional corticosteroids (corticosteroid inhalers were permitted)	Systemic nonsteroidal immunosuppressants/ immunomodulators
	Oral antihistamines (unless these treatments were taken at a stable dose for 3 months prior to screening or for a seasonal allergy	Phototherapy
	Drugs with sedative effects (such as benzodiazepines, imidazopyridines, barbiturates, sedative antidepressants (e.g., amitriptyline), SSRIs (e.g., paroxetine), or SNRIs)	Gabapentinoids
	Phototherapy	
	Tanning beds	
	Immunosuppressive or immunomodulatory drugs (e.g., ciclosporin A, methotrexate, thalidomide, oral tacrolimus, cyclophosphamide, azathioprine, mycophenolate mofetil, JAK inhibitors)	
	Biologics and their biosimilars (e.g., etanercept, adalimumab, infliximab, omalizumab)	

Permitted concomitant therapy	Prohibited therapy	Rescue medication only*
	Dupilumab	
	Systemic retinoids	
	Systemic roxithromycin or erythromycin	
	Opioid antagonists (e.g., naltrexone, naloxone), opioid partial/mixed agonists (e.g., nalbuphine, butorphanol), or opioid agonists (except when used for short term/acute pain); NK1 receptor antagonists (e.g., aprepitant, serlopitant)	
	Gabapentinoids unless used at a stable dose for at least six months or used for non-prurigo conditions	
	Cannabinoids	
	Investigational topical or systemic medication	
	Alternative medicine (e.g., Traditional Chinese medicine)	
	Live vaccines	
	Non-live vaccines	

*If deemed medically necessary. Rescue therapies must not have been prescribed during the screening period. As a general guideline, rescue therapy was not prescribed in the first 4 weeks after baseline to allow a minimum time for study drug exposure.
Note: patients were allowed to receive non-permitted concomitant therapy if necessary for a condition other than PN provided it was discussed and agreed upon with the Investigator and the medical monitor.
Abbreviations: DCS, dual chamber syringe; JAK, Janus kinase; kg, kilogram; mg, milligram; NK1, neurokinin 1; PDE-4, phosphodiesterase-4; Q4W, every four weeks; SNRI, serotonin and norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor; TCI, topical calcineurin inhibitor; TCS, topical corticosteroid.
Source: Galderma. OLYMPIA 1 CSR[1], Galderma. OLYMPA 2 CSR[2]

B.2.3.2. LTE study

A prospective, multicentre LTE study of patients who were enrolled in OLYMPIA 1 and 2, and a Phase 2a study (NCT03181503) is currently being conducted at 120 sites across Austria, Belgium, Canada, Denmark, France, Germany, Hungary, Italy, Netherlands, Poland, South Korea, Spain, Switzerland, the UK and the US spanning a 196-week period, consisting of a 4-week screening period, up to 184-week treatment period and an 8-week follow up period (Figure 7).

The primary objective of the LTE study is to assess the long-term safety of nemolizumab in the treatment of moderate to severe PN. The secondary objective is to assess the long-term efficacy of nemolizumab in the treatment of PN. Figure 8 illustrates the transition between the OLYMPIA 1, OLYMPIA 2 and Phase 2a trials into the LTE study (Table 8). The treatment summary for interventions used in the OLYMPIA LTE study can be found in Figure 9.

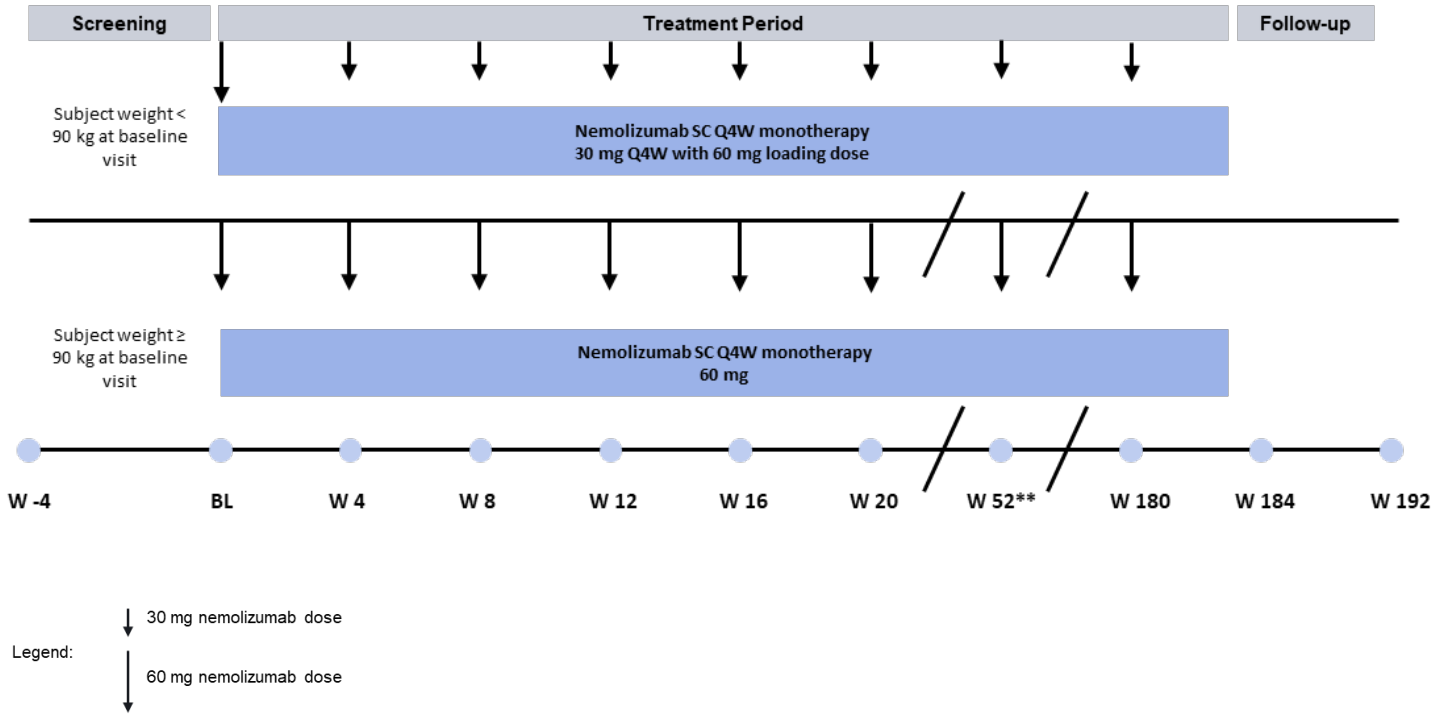

Figure 7. OLYMPIA LTE study design

Abbreviations: BL, baseline; kg, kilograms; mg, milligram; Q4W, every four weeks; SC, subcutaneously; W, week.

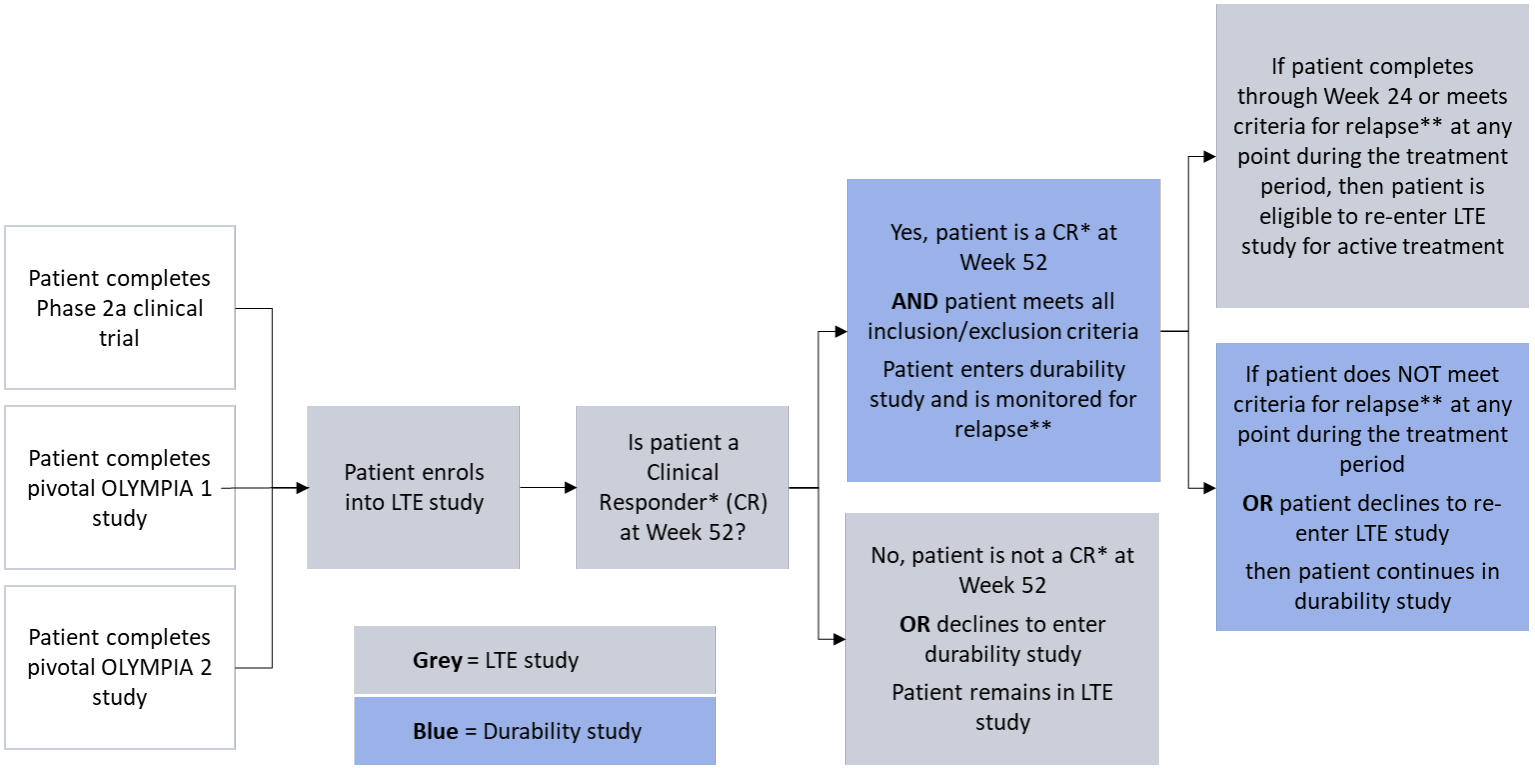

Figure 8. Patient transition between LTE and durability studies

Note: Pivotal studies SPR.202685 and SPR.203065 refer to the OLYMPIA 1 and 2 trials; SPR.115828 refers to the Phase 2a clinical trial assessing the safety and efficacy of nemolizumab in patients with PN.

Abbreviations: BL, baseline; CR, clinical responder; IGA, Investigator's Global Assessment; LTE, long-term extension; PP NRS, Peak Pruritus Numerical Rating Scale; Q4W, every 4 weeks; W, week

* CR was defined as a patient with an IGA score = 0 or 1 and an improvement in the PP NRS score of ≥4 points from baseline at Week 52. Patients who entered the durability study were to complete all scheduled assessments except study drug administration at the Week 52 visit.

** Relapse was defined as an increase in weekly average of PP NRS score ≥4 points from baseline or an increase in IGA score ≥2 from baseline at any point during the study.

Source: Galderma. OLYMPIA LTE CSR[3]

Table 8. Study design of OLYMPIA LTE study

Trial name	OLYMPIA LTE study
Location	Approximately 160 study sites in Austria, Belgium, Canada, Denmark, France, Germany, Hungary, Italy, Netherlands, Poland, South Korea, Spain, Switzerland, the UK and the US
Trial design	Phase 3 prospective, multicentre LTE study
Eligibility criteria for participants	1. Patients who may benefit from study participation in the opinion of the investigator and participated in a prior nemolizumab study for PN, including: a. Patients who completed the treatment period in a phase 3 pivotal study (OLYMPIA 1 or OLYMPIA 2) and enrol within 56 days b. Or patients who were previously randomised in the nemolizumab phase 2a PN study c. Or patients who completed through week 24 of the Phase 3b durability study or who exit the study due to relapse may be eligible to re-enter the LTE study within 28 days of exiting the durability study 2. Female patients of childbearing potential must agree to use an adequate method and approved method of contraception throughout the study and for 12 weeks after the last study drug injection 3. Female patients of non-childbearing potential must meet one of the following criteria: absence of menstrual bleeding for one year prior to screening without any other medical reason, confirmed with follicle stimulating hormone level in the postmenopausal range, or documented hysterectomy, bilateral salpingectomy, or bilateral oophorectomy at least three months before the study 4. Patient is willing and able to comply with all of the time commitments and procedural requirements of the clinical study protocol, including periodic weekly recordings by the patient using an electronic handheld device provided for by the study 5. Understand and sign an informed consent form before any investigational procedure(s) are performed
Study drugs	Nemolizumab 30 mg/60 mg SC Q4W Placebo
Concomitant medications	• Drugs/therapies included, but were not limited to prescription, over the counter, birth control pills/patches/hormonal devices, vitamins, moisturisers, sunscreens, herbal medicines/supplements, and homeopathic preparations

Trial name	OLYMPIA LTE study
	• Medical and surgical procedures (e.g., phototherapy, exodontia): procedures whose sole purpose was diagnosis (non-therapeutic) were not included Concomitant, prohibited and rescue medicines were aligned with OLYMPIA 1 and OLYMPIA 2, see Table 7 for details
Primary outcome	The primary objective is to assess the long-term safety of nemolizumab in patients with PN: • Incidence and severity of AEs, including AEs of special interest, treatment-emergent AEs, and serious AEs
Pre-planned subgroups	Region (Europe, North America, Asia-Pacific) • Age group (18–65 and > 65) • Sex (male, female) • Race (White, Black, or African American, Asian, American Indian or Alaska Native, Native Hawaiian or Pacific Islander, Other [including multiple]) • Weight at randomisation (< 90 kg, ≥ 90 kg) • Baseline IGA score (moderate [3], severe [4])

Abbreviations: AE: adverse event; IGA: Investigator's Global Assessment; kg, kilogram; LTE, long term extension; PN: prurigo nodularis; Q4W, every four weeks; SC: subcutaneous; US< United States.

Source: Galderma. OLYMPIA LTE CSR[3]

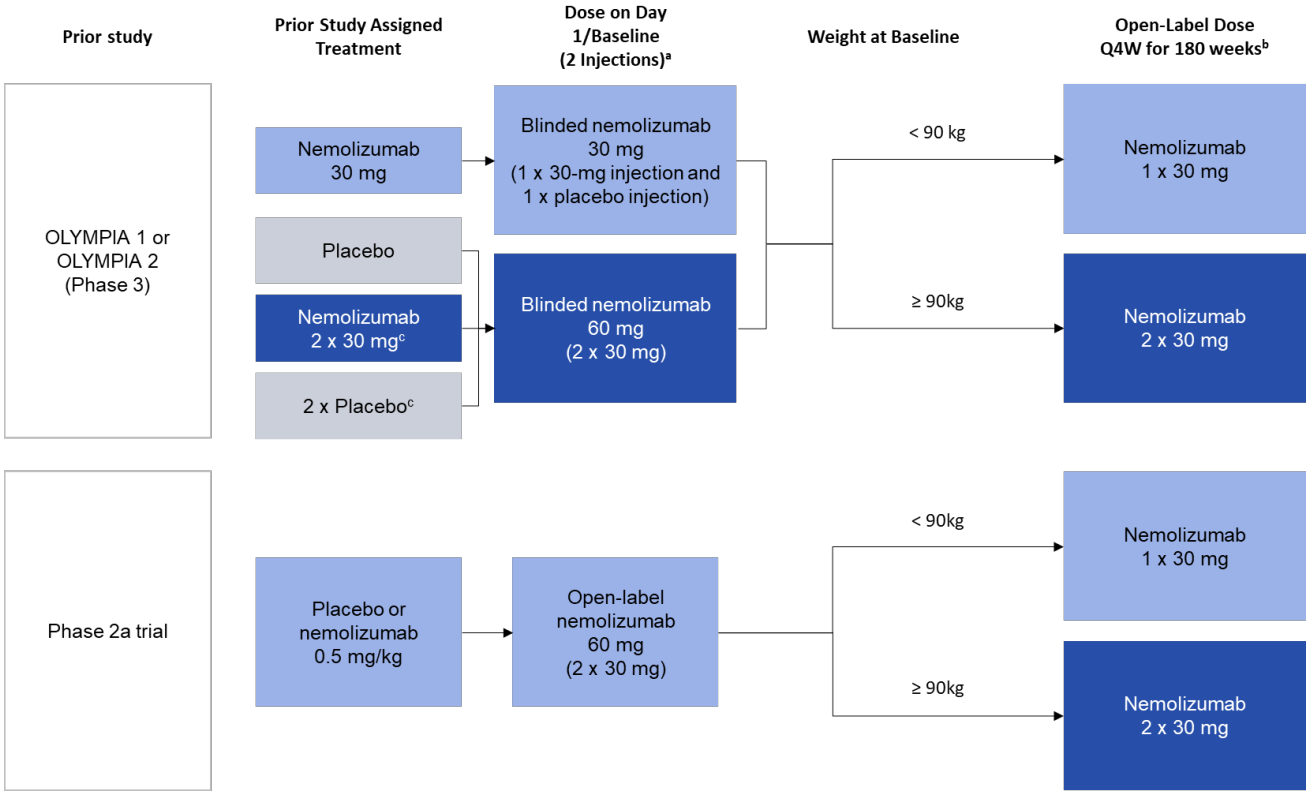

Figure 9. Treatment summary of the LTE study

[a]Any patient with a > 12-week interval since the last dose of study drug received a 60-mg dose of nemolizumab via two 30-mg injections at the Day 1/baseline visit.

[b]Beginning at Week 56, the nemolizumab dosage was adjusted every 6 months for patients with a documented weight change above or below the 90-kg threshold at 2 consecutive designated visits.

[c]In studies OLYMPIA 1 and 2, patients weighing < 90 kg at baseline received either 30 mg nemolizumab or placebo Q4W while patients weighing ≥ 90 kg at baseline received either 60 mg nemolizumab or placebo Q4W. When patients rolled into this LTE from OLYMPIA 1 and 2, patients weighing < 90 kg received 30 mg nemolizumab Q4W while patients weighing ≥ 90 kg received 60 mg nemolizumab Q4W. Initial dosing was based on weight at baseline of the lead-in study.

Abbreviations: kg, kilogram; mg, milligram; NA, not applicable; Q4W, every 4 weeks.

Source: Galderma. OLYMPIA LTE CSR[3]

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

B.2.4.1. OLYMPIA 1 and OLYMPIA 2

A summary of the statistical analyses for the OLYMPIA 1 and 2 studies can be found in Table 9, as informed by the corresponding statistical analysis plans.

Table 9. Statistical analysis and definition of study groups in OLYMPIA 1 and OLYMPIA 2

	OLYMPIA 1 (NCT04501666)	OLYMPIA 2 (NCT04501679)
Analysis populations	The **Intent-to-Treat (ITT) population** consisted of all randomised patients. The ITT population was the primary population for efficacy analyses. In analyses of the ITT population, patients were included in the treatment group to which they were randomised. The **Per-Protocol (PP) population** consisted of all patients in the ITT population and had no major protocol deviations that would have had a significant effect on the efficacy of the study treatment. Only primary, key secondary and selected secondary endpoints were analysed using the PP population, under the treatment group as randomised. The **Safety (SAF) population** consisted of all randomised patients who received at least one administration of study drug. The treatment group assignment in this population was defined by the treatment received. This population was used for the analyses of safety.	The **Intent-to-Treat (ITT) population** consisted of all randomised patients. The ITT population was the primary population for efficacy analyses. In analyses of the ITT population, patients were included in the treatment group to which they were randomised. The **Per-Protocol (PP) population** consisted of all patients in the ITT population who had no major protocol deviations that would have had a significant effect on the efficacy of the study treatment. Only primary and key secondary endpoints were analysed using the PP population under the treatment group as randomised. The **Safety (SAF) population** consisted of all randomised patients who received at least one administration of study drug. The treatment group assignment in this population was defined by the treatment received. This population was used for the analyses of safety. The **PK analysis population** consisted of all patients included in the safety population with at least one measurable post-baseline PK assessment. Similar to the safety population, the treatment group assignment in this population was defined by the treatment received. This population informs the descriptive analyses of PK concentrations.
Statistical analysis of primary endpoints	Both primary endpoints were analysed using a CMH test adjusted for the randomisation strata analysis centre and body weight at randomisation (< 90 kg, ≥ 90 kg), to test the difference between nemolizumab and placebo for the proportion of patients achieving success in each endpoint. The estimate of the treatment difference and corresponding two-sided 95% CI and p values were presented. The CIs were based on Wald statistic controlling for stratification variables. Strata-adjusted proportion differences were obtained using weighted average of stratum-specific proportion using CMH. In addition, an unadjusted CMH test was performed.	

	OLYMPIA 1 (NCT04501666)	OLYMPIA 2 (NCT04501679)
Statistical analysis of secondary endpoints	Continuous secondary endpoints (except EQ-5D, HADS, and PN intensity) were analysed using MI assuming MAR for missing data, including treatment group, analysis centre and body weight at randomisation cut-off (< 90 kg and ≥ 90 kg) as factor and baseline as covariate where applies, and using mixed effect MMRM approach, including visit, treatment group, analysis centre and body weight at randomisation cut-off (< 90 kg and ≥ 90 kg) as factor, baseline, the interaction term between baseline and visit, and the interaction term between treatment group and visit as covariates The estimated treatment difference for each endpoint at each visit was displayed in the summary of statistical analysis together with the 95% CI and associated p-value. EQ-5D and HADS endpoints were analysed using ANCOVA including treatment group, analysis centre and body weight at randomisation cut-off (< 90 kg and ≥ 90 kg) as factor and baseline as covariate. PN intensity was analysed using mixed effect MMRM approach, including visit, treatment group, analysis centre and body weight at randomisation cut-off (< 90 kg and ≥ 90 kg) as factor, baseline, the interaction term between baseline and visit, and the interaction term between treatment group and visit as covariates. All secondary endpoints were presented descriptively using OC. Binary secondary endpoints were analysed as described in the SAP if not specified otherwise. Missing values will be imputed as non-responder except for OC analysis. If a patient is in receipt of rescue medication at any point, continuous data on or after receipt of rescue medication will be set to worst case value, except for OC analysis, and the binary response are derived from the underlying value.	Binary secondary endpoints were analysed as described in the CSR if not specified otherwise. Missing values were imputed as a non-responder except for OC analysis. If a patient was in receipt of rescue medication at any point, data on or after receipt of rescue medication were regarded as non-response/treatment failure. Continuous secondary endpoints (except EQ-5D and HADS) were analysed using MI assuming MAR and using a MMRM approach, including analysis centre and body weight at randomisation cut-off (< 90 kg and ≥ 90 kg) as factors, and baseline as a covariate, where applicable. The estimated treatment difference for each endpoint at each visit was displayed in the summary of statistical analysis together with the 95% CI and associated p-value. EQ-5D and HADS endpoints were analysed using an ANCOVA, including analysis centre and body weight at randomisation cut-off (< 90 kg and ≥ 90 kg) as factors.

	OLYMPIA 1 (NCT04501666)	OLYMPIA 2 (NCT04501679)
Statistical analysis of safety endpoints	Safety assessments were conducted for all patients at the screening visit (upon signing of the ICF) and at every subsequent visit. Safety will be assessed based on AEs (including TEAEs, AESIs, SAEs and adjudicated AEs), physical examination and vital signs, clinical laboratory tests, ECG, respiratory examination, and assessments. Summary of all safety endpoints were presented for each treatment group. AEs were coded using MedDRA Version 25.0. Treatment-emergent AEs (TEAEs), defined as those AEs occurring after the first administration of study treatment until the last study visit, were tabulated in frequency tables SOC and PT based on the Medical Dictionary for Regulatory Activities for treatment and follow-up periods. AEs were summarised using the number and percent of patients reporting each SOC and PT and sorted alphabetically by SOC and by descending frequency of PT within SOC.	All safety data were summarised for the safety population. Safety assessments were conducted for all patients at the screening visit (upon signing of the ICF) and at every subsequent visit. Safety was assessed based on AEs (including TEAEs, AESIs, SAEs, and adjudicated AEs), physical examination, vital signs, clinical laboratory tests, ECGs, and respiratory examination and assessments. A summary of all safety endpoints was presented for each treatment group. All safety data were listed by patients (e.g., AEs/SAEs/AESIs, TEAEs for patients with COVID-19 infection, laboratory assessments, pregnancy test results, virology and TB testing results, vital signs, patients with at least one PCS laboratory or vital sign result). Adverse events were coded using MedDRA Version 25.0. Treatment-emergent adverse events were summarised using the number and percentage of patients reporting each SOC and PT. Patients who experienced multiple events within the same SOC were counted once in the SOC summary. Patients who experienced multiple occurrences of events with the same PT were counted once in the PT summary. When summarising by causality or maximum severity, if a patient experienced >1 occurrence of the same AE, the occurrence with the greatest severity and the closest association with the study drug were used in summary tables. Treatment emergent adverse events related to study drug/study procedure were identified as having a reasonable possibility of relationship to study drug/study procedure. If relationship or severity was missing, the event was considered as an AE related to study drug/study procedure or a severe AE.

	OLYMPIA 1 (NCT04501666)	OLYMPIA 2 (NCT04501679)
Sample size and power calculation	To achieve at least 90% power for both primary endpoints at 5% significance level, 270 (180 nemolizumab, 90 placebo) patients were randomised to detect the following differences in both primary endpoints between treatment groups with 2:1 randomisation, assuming a 15% dropout rate during treatment period: • NRS responders (≥ 4-point reduction from baseline): Based on phase 2a data, it was expected that the NRS response at Week 16 would be 50% in nemolizumab and 20% in placebo • IGA response (0/1): It was expected that the IGA response at Week 16 would be 30% in Nemolizumab and 10% in placebo	To achieve at least 90% power for both primary endpoints at a 5% significance level, 270 (180 nemolizumab, 90 placebo) patients were randomised to detect the following differences in both primary endpoints between treatment groups with 2:1 randomisation, assuming a 15% dropout rate during treatment period: • NRS responders (≥ 4-point reduction from baseline): based on phase 2a data, it was expected that the NRS response at Week 16 would be 50% in nemolizumab and 20% in placebo • IGA response (0/1): it was expected that the IGA response at Week 16 would be 30% in nemolizumab and 10% in placebo The CSR provides the resulting power with 270 patients (180 nemolizumab, 90 placebo) for different responses in the primary endpoints.
Handling of missing data and participant withdrawals	Patient disposition was summarised based on the ITT population by treatment and overall. Summaries included patients randomised, patients randomised but not treated, patients treated, patients completed treatment, patients discontinued treatment, primary reason for discontinuation of treatment (including summary of patients who stopped treatment due to COVID-19), patients completed the study, patients discontinued from the study, primary reason for discontinuation from the study (including summary of patients who discontinued due to COVID-19), patients rolled over to long term extension (LTE), and patients completed follow-up. Patients who stopped treatment or discontinued study due to COVID-19 were identified using other specify field in CRF.	All patients in the screened population were accounted for in this study. Patient disposition was summarised based on the ITT population by treatment and overall. Summaries included patients randomised, patients randomised but not treated, patients treated, patients who completed treatment, patients who discontinued treatment, primary reason for discontinuation of treatment (including summary of patients who stopped treatment due to COVID-19), patients who completed the study, patients who discontinued from the study, primary reason for discontinuation from the study (including summary of patients who discontinued due to COVID-19), patients who entered the LTE, and patients who completed follow-up. Patients who stopped treatment or discontinued the study due to COVID-19

	OLYMPIA 1 (NCT04501666)	OLYMPIA 2 (NCT04501679)
		were identified using the “other specify” field in the eCRF. Patient disposition was also summarised by site for the ITT population. The number and percentage of patients screened and failed were presented by reason for screen failure (including a summary of patients who failed due to COVID-19). Patients in each analysis population (ITT, safety, PP, and PK analysis) were summarised by treatment group for the ITT population. In addition, the time (days since the first dose of study drug) to permanent discontinuation of study drug by reason for discontinuation was displayed graphically for patients who permanently discontinued from study drug.

Source: Galderma. OLYMPIA 1 SAP;[68] Galderma. OLYMPIA 2 SAP.[69]

Abbreviations: AE, adverse event; AESI, adverse event of special interest; ANCOVA, analysis of covariance; CI, confidence interval; CMH, Cochran-Mantel-Haenszel; CSR, clinical study report; ECG, electrocardiogram; eCRF, electronic case report form; HADS, Hospital Depression and Anxiety Score; ICF, informed consent form; IGA, Investigator’s Global Assessment; ITT, intent-to-treat; kg, kilogram; LTE, long term extension; MAR, missing at random; MI, multiple imputation; MMRM, mixed-effect model for repeated measures; NRS, Numerical Rating Scale; PK, pharmacokinetics; PP, per-protocol; PT, preferred term; SAE, serious adverse event; SOC, system organ class; TEAE, treatment emergent adverse event;

B.2.4.2. LTE study

A summary of the statistical analysis is provided in Table 10 using the LTE study statistical analysis plan.

Table 10. Statistical analysis and definition of study groups in the LTE study

	LTE study (NCT04204616)
Analysis populations	The **screened population** will comprise all patients who signed the ICF and had screening data entered the database. This population included screen failures and enrolled patients. Screen failed patients were defined as those patients who failed to meet inclusion criteria or met exclusion criteria and discontinued the study prior to enrolment. Patients who were re-screened were only counted once, under the patient identification assigned for the repeat screening. Unless otherwise specified, this population was used for patient listings and summaries of patient disposition. The **safety population** will consist of all patients who received at least one administration of LTE study drug (blinded or open label). This population was used for all analyses of efficacy and safety. The **PK analysis population** will consist of all patients included in the safety population who had at least one measurable post-baseline PK assessment. This population was used for the analyses of PK.
Statistical analysis of primary endpoints	All efficacy analyses will be performed on the SAF and will be descriptive in nature. The efficacy analyses will be carried out using observed cases (OC, without imputing missing data). All efficacy assessments will be summarised by LTE treatment and by previous treatment at each analysis visit using descriptive statistics. Scheduled, unscheduled and early termination visits will be windowed based on the analysis visit window which is based on study day as in the SAP. No hypothesis testing will be performed.
Statistical analysis of secondary endpoints	For binary secondary endpoints, efficacy data collected on/after the use of rescue therapy will be treated as treatment failure, except for OC analysis (where observed data will be used regardless of the use of rescue therapy). Continuous variables will be set to the worst-case value, and patient's binary response will be based on the underlying continuous value prior to impute missing data. Continuous secondary endpoints will be analysed using MI assuming MAR for missing data. Binary endpoints will be analysed using non-responder imputation for missing data.

	LTE study (NCT04204616)
Statistical analysis of safety endpoints	All safety data will be summarised by LTE treatment group and listed on the safety population. If not stated otherwise, baseline is defined as LTE baseline for safety analysis. Safety assessments will be conducted for all patients at the screening visit (upon signing of the ICF) and at every subsequent visit. Safety will be assessed based on AEs (including TEAEs, AESIs, and SAEs), physical examination and vital signs, clinical laboratory tests, ECG, respiratory examination and assessments.
Sample size and power calculation	No formal sample size calculations were performed for this LTE study. It is expected that approximately 450 patients will enrol into LTE study, depending on rollover rate from the lead-in studies.
Handling of missing data and participant withdrawals	**Binary Endpoints:** The OC approach will be used for the binary secondary endpoints. For sensitivity analysis all missing values will be treated as a non-responder to impute the missing values. The MI under MAR assumption approach will be used as sensitivity analysis to impute the missing values for the secondary endpoints. If applicable, the continuous response will be imputed first, and the response will then be categorised. **Continuous Endpoints:** For continuous secondary endpoints during treatment period, the MI under MAR assumption approach will be used to handle the missing data for sensitivity analysis. **Use of rescue therapy:** For sensitivity analysis all efficacy data will be treated as treatment failure. Binary endpoints will be based on the underlying values and continuous variables will be imputed using the worst-case score (questionnaires) or worst-case value (diary data), on or after rescue therapy is used, independent if visit was attended or not. This procedure will be completed before imputing missing data under different assumptions (i.e., non-responder, MI under MAR). In OC analysis, all observed data will be used. There will be no imputations for missing data. **Adverse events and concomitant medications/procedures:** Missing assessment times will have imputed times for the purposes of assessing treatment emergence for AEs or classifying medications/procedures into prior/concomitant. However, the assessment date and time (start date, stop date, and time if collected from CRF) without imputation will be presented in the listings.

Abbreviations: AESI, adverse events of special interest; CRF, case report form; ECG, electrocardiogram; ICF, informed consent form; LTE, long term extension; MAR, missing at random; MI, multiple imputation; OC, observed case; PK, pharmacokinetics; SAE, serious adverse event; SAP, statistical analysis plan; TEAE, treatment emergent adverse event
Source: Galderma. OLYMPIA LTE CSR[3]

B.2.5. Critical appraisal of the relevant clinical effectiveness evidence

The clinical effectiveness evidence provided in this submission is derived from two Phase 3 trials (OLYMPIA 1 and OLYMPIA 2) and a Phase 3b LTE study, conducted within the requirements of the regulatory bodies. The complete quality assessment of OLYMPIA 1, OLYMPIA 2 and the LTE study is provided in Table 11.

Table 11. Quality assessment results for OLYMPIA 1, OLYMPIA 2 and LTE study

	OLYMPIA 1 (NCT04501666)	OLYMPIA 2 (NCT04501679)	LTE study (NCT04204616)
Was randomisation carried out appropriately?	Yes - a 2:1 randomisation was selected to minimise the number of patients exposed to placebo for an extended period. Randomisation through interactive response technology (IRT) guarded against selection bias. The randomisation scheme was stratified by the study site and baseline body weight (< 90 kg and ≥ 90 kg) using the Randomisation Trial Supply Management system.		N/A - no re-randomisation occurred for the LTE study
Was the concealment of treatment allocation adequate?	Yes - to avoid bias and to ensure the integrity of the blind, personnel directly involved with the ongoing conduct of the study from the Sponsor, blinded statistical team at the CRO, or other investigational study centres will not have access to any information that may lead to unblinding		Yes - while the LTE study uses an open-label study drug, due to the fact that the LTE study will be ongoing while the Phase 3 and Phase 3b studies are still blinded, a blinded loading dose is required for applicable patients in order to maintain the blind of the previous study
Were the groups similar at the onset of the study in terms of prognostic factors?	Yes - see Section B.2.6.1.2		N/A - The LTE study is being conducted as a single-arm trial
Were the care providers, participants, and outcome assessors blind to treatment allocation?	Yes - to avoid bias and to ensure the integrity of the blind, personnel directly involved with the ongoing conduct of the study from the Sponsor, blinded statistical team at the CRO, or other investigational study centres will not have access to any information that may lead to unblinding		Yes - while this LTE study utilises open-label study drug, due to the fact that the LTE study will be ongoing while the Phase 3 and Phase 3b studies are still blinded, a blinded loading dose is required for applicable patients in order to maintain the blind of the previous study
Were there any unexpected imbalances in dropouts between groups?	No - see Section B.2.6.1.1		No - see section B.2.6.2.1

	OLYMPIA 1 (NCT04501666)	OLYMPIA 2 (NCT04501679)	LTE study (NCT04204616)
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No – all outcomes that were recorded in the trials have been reported in the CSRs, with those outcomes related to the decision problem included in this submission.		
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Yes - Multiple Imputation (MI) method for missing data (or where rescue medication was received), assuming all missing data are Missing at Random (MAR). An ITT was conducted which consisted of all randomised patients. The ITT population was the primary population for efficacy analyses. In all analyses of the ITT population, patients were included in the treatment group to which they were randomised.		

Adapted from Systematic reviews: CRD's guidance for undertaking reviews in health care (University of York Centre for Reviews and Dissemination)[70]

B.2.6. Clinical effectiveness results of the relevant studies

B.2.6.1. OLYMPIA 1 and OLYMPIA 2

B.2.6.1.1. Patient disposition

Patient disposition of the OLYMPIA 1 and 2 trials is summarised in Table 12. In OLYMPIA 1, 424 patients were screened at 68 study sites, and 286 patients were randomised 2:1, 190 received nemolizumab and 96 received placebo. Of those who were randomised, [redacted] discontinued prematurely in the nemolizumab arm and [redacted] discontinued prematurely in the placebo arm. The primary reasons for premature discontinuation of treatment were AEs ([redacted] from nemolizumab; [redacted] from placebo), patient request ([redacted] from nemolizumab; [redacted] from placebo), and protocol deviation ([redacted] from nemolizumab; [redacted] from placebo). One patient in the placebo arm discontinued following physicians' decision ([redacted]) (Table 12).

In OLYMPIA 2, 274 patients were randomised 2:1, 183 patients to the nemolizumab arm and 91 to the placebo arm. Of those randomised, 174 (95.6%) in the nemolizumab arm and 88 (95.6%) in the placebo arm completed the trial. There were 9 (4.9%) discontinuations in the nemolizumab arm and 3 (3.3%) in the placebo arm. The primary reason for discontinuation in both arms was adverse events (2.2% in both arms). Withdrawn consent, lost to follow-up, and physician's decision were all recorded as reasons for discontinuation in the nemolizumab arm only (1.1%, 1.1%, and 0.5%, respectively). One discontinuation in the placebo arm was attributed to pregnancy (1.1%) (Table 12).

Table 12. Patient disposition in OLYMPIA 1 and OLYMPIA 2

	OLYMPIA 1		OLYMPIA 2	
	Nemolizumab	Placebo	Nemolizumab	Placebo
Patient status				
Randomised	[redacted]	[redacted]	183 (100)	91 (100)
Completed	[redacted]	[redacted]	174 (95.6)	88 (95.6)
Discontinuations	[redacted]	[redacted]	9 (4.9)	3 (3.3)
Reasons for discontinuation				
Adverse events	[redacted]	[redacted]	4 (2.2)	2 (2.2)
Patients request	[redacted]	[redacted]	0	0
Withdrew consent	[redacted]	[redacted]	2 (1.1)	0
Protocol deviation	[redacted]	[redacted]	0	0
Physician’s decision	[redacted]	[redacted]	1 (0.5)	0
Lost to follow-up	[redacted]	[redacted]	2 (1.1)	0
Pregnancy	[redacted]	[redacted]	0	1 (1.1)

Source: Stander et al. (2023)[71] ; OLYMPIA 1 CSR[1]; OLYMPIA 2 CSR[2].

B.2.6.1.2. Patient characteristics

A summary of baseline characteristics for both OLYMPIA 1 and OLYMPIA 2 trials is presented in Table 13, and a breakdown of patient baseline disease characteristics in Table 14.

Demographic and baseline characteristics between the nemolizumab arm and placebo arm were generally similar in both the OLYMPIA 1 and OLYMPIA 2 trials. In both the nemolizumab and placebo arms of the OLYMPIA 1 trial, most patients were female (57.9% and 58.4%, respectively), European (74.2% and 74.0%, respectively) and white (84.2% and 84.4%, respectively). Mean age, height, and body mass index (BMI) were also comparable between the nemolizumab arm and placebo arm (57.5 and 57.6; 170.0 and 169.8; 30.0 and 28.2, respectively) (Table 13).[1] In both the nemolizumab and placebo arms of the OLYMPIA 2 trial, the majority of patients were female (61.7% and 60.4%, respectively), European (66.7% and 67.0%, respectively) and white (80.3% and 74.7%, respectively). Mean height, weight, and BMI were also comparable between the nemolizumab and placebo arms (Table 13).

In the OLYMPIA 1 trial, slightly more patients with severe PN were randomised to the nemolizumab arm compared with the placebo arm (43.7% vs. 35.4%). Baseline mean PP NRS, SD NRS, and DLQI were comparable between the nemolizumab and placebo arms (PP NRS: 8.5 and 8.4, respectively; SD NRS: 7.0 and 6.9, respectively; DLQI: 17.1 and 16.9, respectively) (Table 14).[1] Baseline disease characteristics of patients in the nemolizumab arm and placebo arm of the OLYMPIA 2 trial were also generally comparable. The proportion of patients with moderate and severe IGA at baseline were similar (moderate: 59.0% and 52.7%, respectively; severe: 41.0% and 47.3%, respectively). Mean PP NRS, SD NRS and DLQI were all also similar between the nemolizumab and placebo arms (PP NRS: 8.5 and 8.4, respectively; SD NRS: 7.2 and 7.3, respectively; DLQI: 16.5 and 17.1, respectively) (Table 14).

Table 13. Baseline characteristics of patients in OLYMPIA 1 and OLYMPIA 2

	OLYMPIA 1		OLYMPIA 2	
	Nemolizumab	Placebo	Nemolizumab	Placebo
Male	80 (42.1)	40 (41.7)	70 (38.3)	36 (39.6)
Female	110 (57.9)	56 (58.3)	113 (61.7)	55 (60.4)
Age, years, Mean (SD)	57.5 (12.8)	57.6 (13.4)	53.7 (14.4)	50.8 (15.0)
Weight (kg) at baseline				
Mean (SD)	87.1 (21.8)	80.8 (17.8)	79.7 (17.8)	80.8 (22.3)
BMI (kg/m^2)				
Mean (SD)	30.0 (6.5)	28.2 (5.2)	28.2 (5.3)	28.5 (5.9)
Height (cm) at baseline				
Mean (SD)	170.0 (9.5)	168.9 (9.9)	167.9 (8.5)	167.7 (10.8)
Region				
Europe	141 (74.2)	71 (74.0)	122 (66.7)	61 (67.0)
North America	49 (25.8)	25 (26.0)	47 (25.7)	22 (24.2)
Ethnicity				
Hispanic or Latino	4 (2.1)	5 (5.2)	5 (2.7)	7 (7.7)
Not Hispanic nor Latino	184 (96.8)	88 (91.7)	173 (94.5)	79 (86.8)
Unknown	1 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)
Not reported	1 (0.5)	3 (3.1)	5 (2.7)	5 (5.5)
Race				
White	160 (84.2)	81 (84.4)	147 (80.3)	68 (74.7)
Black or African America	18 (9.5)	10 (10.4)	5 (2.7)	7 (7.7)
Asian	10 (5.3)	2 (2.1)	23 (12.6)	14 (15.4)
American Indian or Alaska native	1 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)

	OLYMPIA 1		OLYMPIA 2	
	Nemolizumab	Placebo	Nemolizumab	Placebo
Other	1 (0.5)	2 (2.1)	5 (2.7)	2 (2.2)
Not reported	0 (0.0)	1 (1.0)	1 (0.5)	0
Multiple	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Hawaiian or Other Pacific Islander	0 (0.0)	0 (0.0)	2 (1.1)	0
Smoking status				
Never	109 (57.4)	44 (45.8)	109 (59.6)	61 (67.0)
Former	49 (25.8)	28 (29.2)	45 (24.6)	20 (22.0)
Current	32 (16.8)	24 (25.0)	29 (15.8)	10 (11.0)

Abbreviations: cm, centimetre; kg, kilogram; Q1, quarter one; Q3, quarter three; SD, standard deviation.
Source: Stander et al. (2023)[71] ; OLYMPIA 1 CSR[1]; OLYMPIA 2 CSR[2]

Table 14. Baseline disease characteristics from OLYMPIA 1 and OLYMPIA 2

	OLYMPIA 1		OLYMPIA 2	
	Nemolizumab	Placebo	Nemolizumab	Placebo
IGA category				
Clear (0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Almost clear (1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Mild (2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Moderate (3)	107 (56.3)	62 (64.6)	108 (59.0)	48 (52.7)
Severe (4)	83 (43.7)	34 (35.4)	75 (41.0)	43 (47.3)
Weekly average PP NRS	n = 184	n = 96		
Mean (SD)	8.5 (0.9)	8.4 (1.0)	8.47 (0.90)	8.37 (0.99)
Weekly average AP NRS	n = 184	n = 94	N = 178	N = 90
Mean (SD)	8.2 (1.1)	8.2 (1.1)	8.29 (0.95)	8.21 (1.09)
Weekly average SD NRS			n = 182	N = 91
Mean (SD)	7.0 (2.4)	6.9 (2.3)	7.19 (2.21)	7.3066 (2.23)
Pain frequency				
Never	15 (7.9)	3 (3.1)	7 (3.8)	2 (2.2)
Less than once a week	11 (5.8)	3 (3.1)	9 (4.9)	9 (9.9)
1-2 days a week	6 (3.2)	11 (11.5)	11 (6.0)	3 (3.3)
3-4 days a week	25 (13.2)	7 (7.3)	24 (13.1)	8 (8.8)
5-6 days a week	19 (10.0)	4 (4.2)	16 (8.7)	5 (5.5)
Everyday	114 (60.0)	68 (70.8)	116 (63.4)	64 (70.3)
Pain intensity				
Mean (SD)	7.1 (2.9)	7.6 (2.5)	7.7 (2.37)	7.8 (2.32)

	OLYMPIA 1		OLYMPIA 2	
	Nemolizumab	Placebo	Nemolizumab	Placebo
Prurigo Activity Score item 4: number of lesions in representative area				
Mean (SD)	23.0 (18.4)	17.7 (13.3)	21.7 (18.52)	25.5 (22.00)
Prurigo Activity Score item 5a: excoriation/crusts n, (%)				
0%	0	0	1 (0.5)	0
1-25%	9 (4.7)	7 (7.3)	11 (6.0)	11 (12.1)
26-50%	39 (20.5)	17 (17.7)	34 (18.6)	20 (22.0)
51-75%	54 (28.4)	23 (24.0)	64 (35.0)	29 (31.9)
76-100%	88 (46.3)	49 (51.0)	73 (39.9)	31 (34.1)
Prurigo Activity Score item 5b: healed lesion stages n, (%)				
100%	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
76-99%	1 (0.5)	2 (2.1)	3 (1.6)	0 (0.0)
51-75%	22 (11.6)	12 (12.5)	23 (12.6)	13 (14.3)
26-50%	41 (21.6)	23 (24.0)	47 (25.7)	26 (28.6)
0-25%	126 (66.3)	59 (61.5)	110 (60.1)	52 (57.1)
DLQI total score at baseline				
Mean (SD)	17.1 (7.0)	16.9 (6.7)	16.5 (6.79)	17.1 (6.60)
Atopy background n, (%)				
Yes	60 (31.6)	33 (34.4)	57 (31.1)	31 (34.1)
No	130 (68.4)	63 (65.6)	126 (68.9)	60 (65.9)
Time since PN diagnosis (months)				
Mean (SD)	86.9 (85.3)	100.6 (98.6)	104.16 (100.715)	108.60 (114.927)

Abbreviations: AP NRS, Average Pruritis Numerical Rating Scale; DLQI: Dermatology life quality index; IGA, Investigator Global Assessment; N, number of patients in the population; PP NRS, Peak Pruritus Numerical Rating Scale; SD, standard deviation; SD NRS, Sleep Disturbance Numerical Rating Scale.
Source: Stander et al. (2023)[71] ; OLYMPIA 1 CSR[1]; OLYMPIA 2 CSR[2]

B.2.6.1.3. Co-primary endpoints

For both co-primary endpoints in both the OLYMPIA 1 and 2 trials, nemolizumab was clinically and statistically superior to placebo in terms of efficacy, resulting in a greater reduction in itch and disease severity in patients in the nemolizumab arm compared with those in the placebo arm.

In OLYMPIA 1, a significantly greater proportion of patients reported a PP NRS improvement of ≥ 4 points from baseline at Week 16 (58.4% vs. 16.7%; strata-adjusted $p < 0.0001$) (Table 15 and Figure 10).[1] This change in patient reported PP NRS demonstrates a dramatic reduction in itch following nemolizumab treatment.

A significantly greater proportion of patients also presented with an IGA success (defined as an IGA of 0 [clear] or 1 [almost clear]) and a ≥ 2 grade improvement from baseline at Week 16 in the nemolizumab arm compared with the placebo arm (26.3% vs. 7.3%; strata adjusted $p = 0.0025$) (Table 15 and Figure 11).[1] This difference in IGA success demonstrates the effectiveness of nemolizumab in reducing the number of nodules present on the skin of patients, and the ability of nemolizumab to reduce PN disease activity.

In OLYMPIA 2, a significantly greater proportion of patients achieved a ≥ 4-point improvement from baseline in PP NRS at Week 16 vs. placebo (56.3% vs. 20.9%; strata adjusted $p < 0.0001$) (Table 15 and Figure 12), demonstrating a significant reduction in itch in patients with PN after initiating nemolizumab. A greater proportion of patients also achieved IGA success (defined as an IGA of 0 or 1 and a ≥ 2 grade improvement from baseline) at Week 16 vs. placebo (37.7% vs. 11.0%, strata adjusted $p < 0.0001$) (Table 15 and Figure 13).

Table 15. Proportion of patients with an improvement of ≥ 4 from baseline in weekly average PP NRS and proportion of patients with an IGA of success at Week 16 and 24 - OLYMPIA 1 and OLYMPIA 2 ITT population

	OLYMPIA 1		OLYMPIA 2	
Week 16	**Nemolizumab (N = 190)**	**Placebo (N = 96)**	**Nemolizumab (N = 183)**	**Placebo (N = 91)**
Improvement of ≥ 4 from baseline in PP NRS, n (%)	111 (58.4)	16 (16.7)	103 (56.3)	19 (20.9)
Strata-adjusted proportion difference, (%)	40.1	-	37.4	-
Strata-adjusted 95% CI	29.4, 50.8	-	26.3, 48.5	-
Strata-adjusted p-value	< 0.0001	-	< 0.0001	-
IGA success, n (%)	50 (26.3)	7 (7.3)	69 (37.7)	10 (11.0)
Strata-adjusted proportion difference, (%)	14.6	-	28.5	-
Strata-adjusted 95% CI	6.7, 22.6	-	18.8, 38.2	-
Strata-adjusted p-value	0.0025	-	< 0.0001	-
Week 24	**Nemolizumab (N = 190)**	**Placebo (N = 96)**		
Improvement of ≥ 4 from baseline in PP NRS, n (%)	[redacted]	[redacted]		
Strata-adjusted proportion difference, (%)	[redacted]	-		
Strata-adjusted 95% CI	[redacted]	-		
Strata-adjusted p-value	[redacted]	-		
IGA success, n (%)	[redacted]	[redacted]		
Strata-adjusted proportion difference, (%)	[redacted]	-		
Strata-adjusted 95% CI	[redacted]	-		
Strata-adjusted p-value	[redacted]	-		

Abbreviations: CI, confidence interval; IGA, Investigator Global Assessment; N, number of patients in the population; n, number of patients with available data; NR, not recorded; PP NRS, Peak Pruritis Numerical Rating Scale; Q4W, every four weeks.
Source: Stander et al. (2023)[71] ; OLYMPIA 1 CSR[1]; Kwatra et al. (2023)[72] ; OLYMPIA 2 CSR[2]

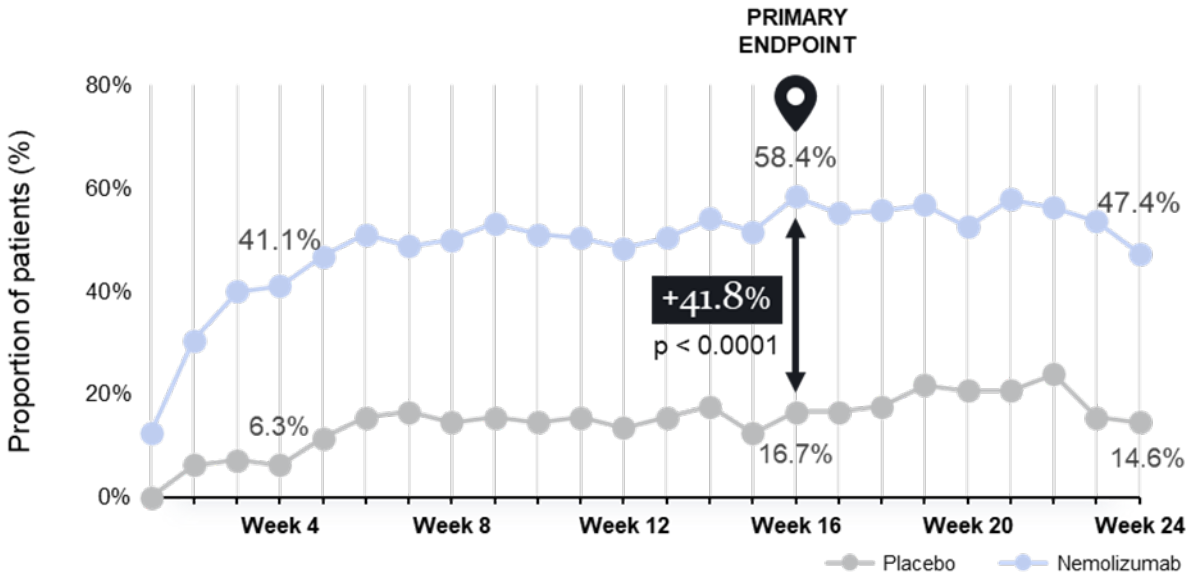

Figure 10. Line graph of proportion of patients with an improvement of ≥ 4-points from baseline in weekly average PP NRS– OLYMPIA 1 ITT population

Abbreviations: ITT, intent to treat; PP NRS, Peak Pruritis Numerical Rating Scale; Q4W, every four weeks.

Source: Galderma. OLYMPIA 1 CSR[1]

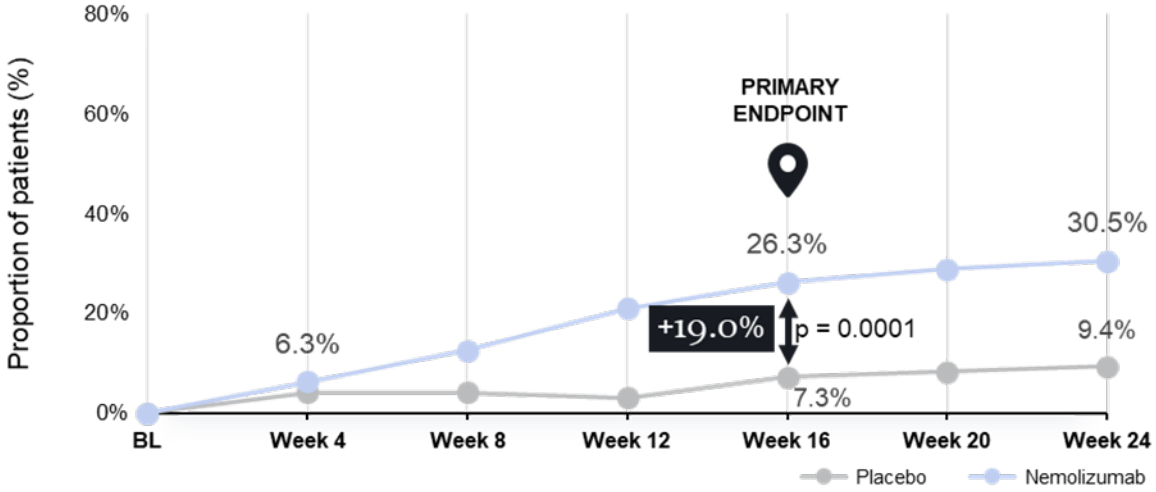

Figure 11. Line graph of proportion of patients with an IGA of success – OLYMPIA 1 ITT population[1]

Abbreviations: IGA, Investigators Global Assessment; ITT, intent to treat; Q4W, every four weeks.

Source: Galderma. OLYMPIA 1 CSR[1]

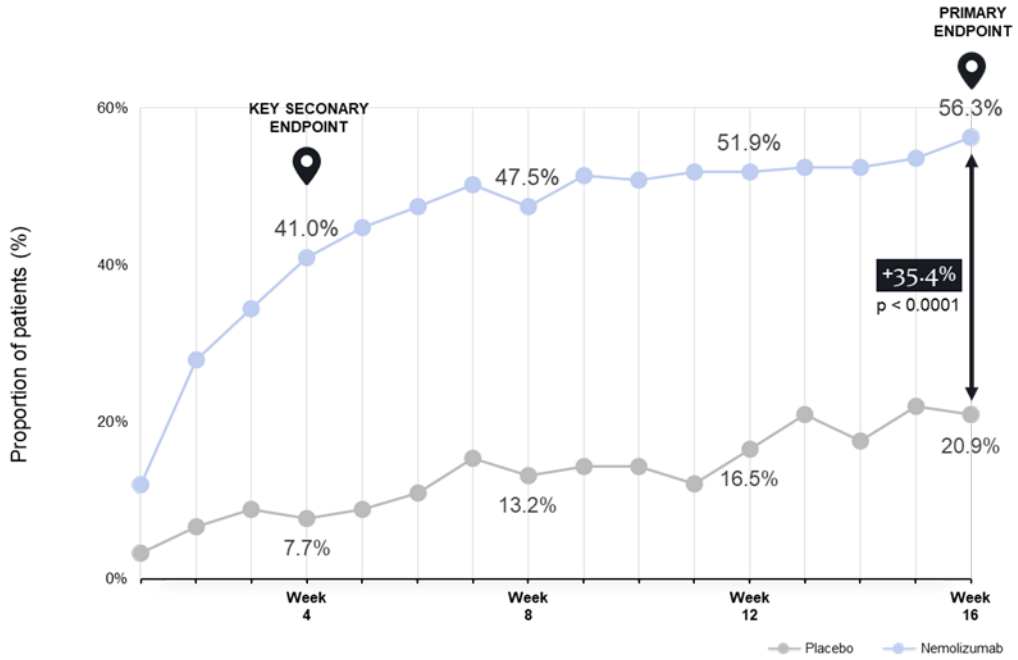

Figure 12. Proportion of patients with an improvement of ≥ 4-points from baseline in weekly average PP NRS (missing as non-responder) – OLYMPIA 2 ITT population

Abbreviations: ITT, intent to treat; PP NRS, Peak Pruritis Numerical Rating Scale; Q4W, every four weeks.
Source : OLYMPIA 2 CSR[2]

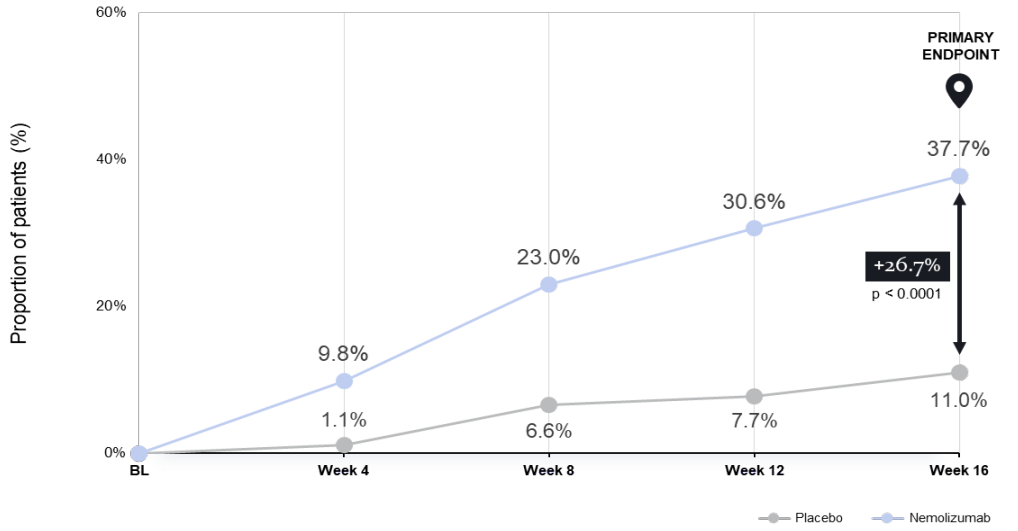

Figure 13. Proportion of patients with an IGA success (missing as non-responder) – OLYMPIA 2 ITT population

Abbreviations: IGA, Investigators Global Assessment; ITT, intent to treat; Q4W, every four weeks.

Source: OLYMPIA 2 CSR[2]

B.2.6.1.4. Key secondary endpoints

For the following secondary endpoints in both the OLYMPIA 1 and OLYMPIA 2 trials, nemolizumab was clinically and statistically superior to placebo in terms of efficacy.

B.2.6.1.4.1. Improvement in itch

A greater proportion of patients in the nemolizumab group of both the OLYMPIA 1 and 2 trials reported an improvement of ≥ 4-points in PP NRS from baseline at Week 4 vs. the placebo group (OLYMPIA 1: 41.1% vs. 6.3%, strata adjusted p < 0.0001; OLYMPIA 2: 41.0% vs. 7.7%, strata adjusted p < 0.0001) (Table 16). This demonstrates that nemolizumab causes a clinically meaningful reduction in itch in patients with PN. Some patients experienced a rapid clinically meaningful itch response as early as 48 hours after the first dose compared with placebo (Figure 14).

In OLYMPIA 1, a greater proportion of patients in the nemolizumab group reported a PP NRS of < 2 at Week 16 vs. the placebo group (34.2% vs. 4.2%, respectively, strata adjusted p < 0.0001) (Table 17). Similarly, in OLYMPIA 2, a greater proportion of patients in the nemolizumab group reported a PP NRS < 2 at Week 16 vs. the placebo group (35.0% vs. 7.7%, respectively, strata adjusted p < 0.0001) (Table 17). Patients reporting a PP NRS score of < 2 experience a near itch free state following nemolizumab treatment, demonstrating the impact of nemolizumab on their symptomatic burden.

Table 16. The proportion of patients with an improvement of ≥ 4 points from baseline in PP NRS at Week 4 in OLYMPIA 1 and OLYMPIA 2 ITT population

	OLYMPIA 1		OLYMPIA 2	
Timepoint	**Nemolizumab N=190**	**Placebo N=96**	**Nemolizumab (N = 183)**	**Placebo (N = 91)**
At week 4, n (%)	78 (41.1)	6 (6.3)	75 (41.0)	7 (7.7)
Strata-adjusted proportion difference, (%)	31.7	-	33.4	-
Strata-adjusted 95% CI	23.0, 40.4	-	24.3, 42.4	-
Strata-adjusted p-value	< 0.0001	-	<0.0001	-

Abbreviations: CI, confidence interval; PP NRS, Peak Pruritis Numerical Rating Scale.

Source: Galderma. OLYMPIA 1 CSR[1]; Kwatra et al. (2023)[72] ; OLYMPIA 2 CSR[2]

Table 17. The proportion of patients with PP NRS < 2 at Week 16 in OLYMPIA 1 and OLYMPIA 2 ITT population

	OLYMPIA 1		OLYMPIA 2	
Timepoint	**Nemolizumab N=190**	**Placebo N=96**	**Nemolizumab N = 183**	**Placebo N = 91**
At Week 16, n (%)	65 (34.2)	4 (4.2)	64 (35.0)	7 (7.7)
Strata-adjusted proportion difference, (%)	30.5	-	30.0	-
Strata-adjusted 95% CI	22.3, 38.7	-	21.3, 38.6	-
Strata-adjusted p-value	< 0.0001	-	< 0.0001	-

Abbreviations: CI, confidence interval; PP NRS, Peak Pruritus Numerical Rating Scale.

Source: Galderma. OLYMPIA 1 CSR;[1] Kwatra et al. (2023);[72] OLYMPIA 2 CSR[2]

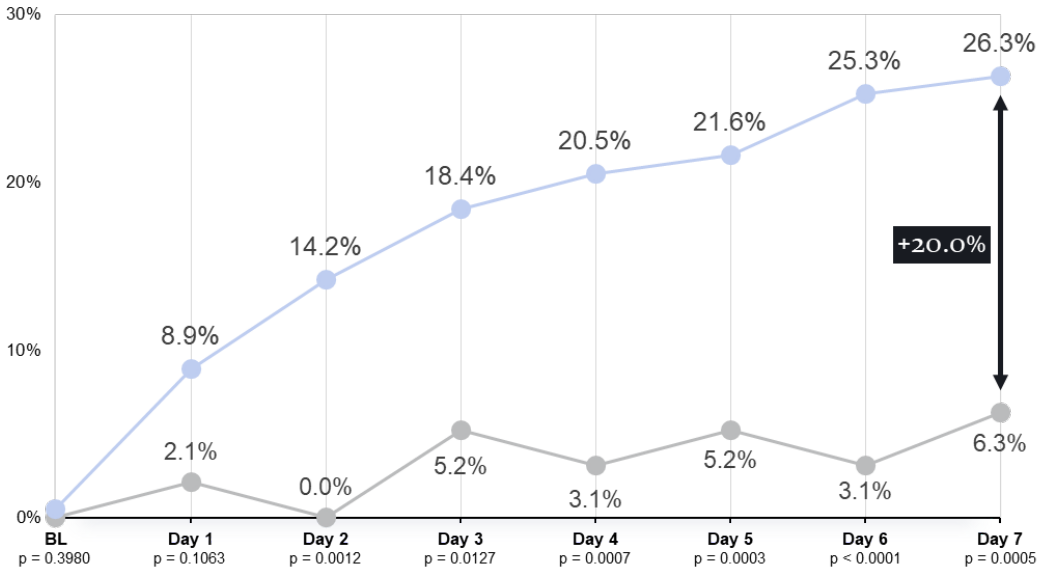

Figure 14. ≥ 4-point improvement in PP NRS from BL in ITT Population in OLYMPIA 1 - NRI Analysis

B.2.6.1.4.2. Improvement in both skin clearance and itch

In OLYMPIA 1, significantly more patients achieved both IGA success and an improvement of ≥ 4 in PP NRS in OLYMPIA 1 vs. placebo (Week 16: [redacted] vs. [redacted] Week 20: [redacted] vs. [redacted] Week 24: [redacted] vs. [redacted], respectively; strata adjusted p = [redacted] at each time point), with results remaining consistent in the nemolizumab arm of the trial at each time point. Similar results were observed at Week 16 in OLYMPIA 2 (29.5% vs. 5.5%, respectively; strata adjusted p [redacted]) (Table 18).

Table 18. Proportion of patients with IGA success and an improvement of ≥ 4 from baseline in PP NRS at Week 16, 20 and 24 in OLYMPIA 1 and OLYMPIA 2 ITT population

	OLYMPIA 1		OLYMPIA 2	
Timepoint	**Nemolizumab N = 190**	**Placebo N = 96**	**Nemolizumab N = 183**	**Placebo N = 91**
At Week 16, n (%)	[redacted]	[redacted])	54 (29.5)	5 (5.5)
Strata-adjusted proportion difference, (%)	[redacted]	-	26.1	-
Strata-adjusted 95% CI	[redacted]	-	17.4, 34.8	-
Strata-adjusted p-value	[redacted]	-	[redacted]	-
At Week 20, n (%)	[redacted]	[redacted]		
Strata-adjusted proportion difference, (%)	[redacted]	-		
Strata-adjusted 95% CI	[redacted]	-		
Strata-adjusted p-value	[redacted]	-		
At Week 24, n (%)	[redacted]	[redacted])		
Strata-adjusted proportion difference, (%)	[redacted]	-		
Strata-adjusted 95% CI	[redacted]	-		
Strata-adjusted p-value	[redacted]	-		

Abbreviations: CI, confidence interval; PP NRS, Peak Pruritus Numerical Rating Scale.

Source: Galderma. OLYMPIA 1 CSR[1]; Kwatra et al. (2023)[72] ; OLYMPIA 2 CSR[2]

B.2.6.1.4.3. Reduction in sleep disruption

During OLYMPIA 1 and OLYMPIA 2, a greater proportion of patients in the nemolizumab groups reported an improvement of ≥ 4 points in SD NRS from baseline at both Week 4 and 16 vs. the placebo groups (OLYMPIA 1: Week 4: [redacted] vs. [redacted]; Week 16: [redacted] vs. [redacted], respectively, strata adjusted p < [redacted] at both timepoints; OLYMPIA 2: Week 4: 37.2% vs. 9.9%, respectively; Week 16: 51.9% vs.

20.9%, respectively, strata adjusted p [redacted] at both timepoints) (Table 19). This significant reduction in SD NRS in as little as 4 weeks after initiating nemolizumab demonstrates a rapid treatment response in patients.

Table 19. Proportion of patients with ≥ 4-point improvement from baseline in weekly average SD NRS at Weeks 4 and 16 in OLYMPIA 1 and OLYMPIA 2 ITT population

	OLYMPIA 1		OLYMPIA 2	
Timepoint	**Nemolizumab N = 190**	**Placebo N = 96**	**Nemolizumab N = 183**	**Placebo N = 91**
Improvement of ≥ 4 from baseline at Week 4, n (%)	[redacted]	[redacted]	68 (37.2)	9 (9.9)
Strata-adjusted proportion difference, (%)	[redacted]	-	27.9	-
Strata-adjusted 95% CI	[redacted]	-	[redacted]	-
Strata-adjusted p-value	[redacted]	-	[redacted]	-
Improvement of ≥ 4 from baseline at Week 16, n (%)	[redacted]	[redacted]	95 (51.9)	19 (20.9)
Strata-adjusted proportion difference, (%)	[redacted]	-	31.9	-
Strata-adjusted 95% CI	[redacted]	-	[redacted]	-
Strata-adjusted p-value	[redacted]	-	[redacted]	-

Abbreviations: CI, confidence interval; SD NRS, Sleep Disturbance Numerical Rating Scale.

Source: Galderma. OLYMPIA 1 CSR[1]; Kwatra et al. (2023)[72] ; OLYMPIA 2 CSR[2]

B.2.6.1.4.4. Improvement in QoL

In OLYMPIA 1, a greater proportion of patients in the nemolizumab group reported an improvement of ≥ 4 points in DLQI from baseline at Week 4, 16 and 24 vs. the placebo group (Week 4: 70.0% vs. 42.7%; Week 16: 70.5% vs. 42.7%; Week 24: [redacted] vs. [redacted], respectively, strata adjusted p < [redacted] at all timepoints) (Table 20). Similar results were observed during OLYMPIA 2, where a greater proportion of patients in the nemolizumab group reported an improvement of ≥ 4 points in DLQI from baseline at both Week 4 and 16 vs. the placebo group (Week 4: 68.9% vs. 39.6%; Week 16: 74.9% vs. 39.6%, respectively, strata adjusted p < [redacted] at both timepoints) (Table 20). This shows the significant effect nemolizumab has on the QoL of patients with PN..

At Weeks 16 and 24 in OLYMPIA 1, nemolizumab was more effective than placebo in increasing the EQ-5D VAS (Week 16: [redacted] vs. [redacted]strata adjusted p[redacted]; Week 24: [redacted] vs. [redacted], strata adjusted p[redacted], respectively) (Table 21). Likewise, at Week 16 in OLYMPIA 2, nemolizumab was more effective than placebo in increasing EQ-5D VAS (15.04 vs. 3.99, respectively, strata adjusted p [redacted]) (Table 21).

In OLYMPIA 1 and OLYMPIA 2, patients treated with nemolizumab reported a greater reduction from baseline in HADS total anxiety score (OLYMPIA 1: [redacted] vs. [redacted]; OLYMPIA 2: -2.57 vs. -1.39, respectively) and HADS total depression score (OLYMPIA 1: [redacted] vs. [redacted]; OLYMPIA 2: - 2.30 vs. - 0.75, respectively) at Week 16 compared with those who received placebo. Both differences in HADS scores were deemed statistically significant in OLYMPIA 1 and OLYMPIA 2 (HADS anxiety: strata adjusted p[redacted] and strata adjusted p[redacted]; HADS depression: strata adjusted p[redacted] and strata adjusted p[redacted], respectively) (Table 22).

At Week 24 in OLYMPIA 1, patients treated with nemolizumab reported a greater reduction from baseline in HADS total anxiety score ([redacted] vs. [redacted], respectively) and HADS total depression score ([redacted] vs. [redacted], respectively); both differences were deemed statistically significant (strata adjusted p[redacted] and strata adjusted p [redacted], respectively) (Table 22).

Table 20. Proportion of patients with an improvement of ≥ 4-points from baseline in DLQI total score at Week 4, 16 and 24 in OLYMPIA 1 and OLYMPIA 2 ITT population

	OLYMPIA 1		OLYMPIA 2	
Timepoint	**Nemolizumab N = 190**	**Placebo N = 96**	**Nemolizumab N = 183**	**Placebo N = 91**
Week 4				
Improvement of ≥ 4 from baseline in DLQI total score, n (%)	133 (70.0)	41 (42.7)	126 (68.9)	36 (39.6)
Strata-adjusted proportion difference, (%)	26.5	-	29.9	-
Strata-adjusted 95% CI	14.0, 39.0	-	17.3, 42.5	-
Strata-adjusted p-value	< 0.0001	-	<0.0001	-
Week 16				
Improvement of ≥ 4 from baseline in DLQI total score, n (%)	134 (70.5)	41 (42.7)	137 (74.9)	36 (39.6)
Strata-adjusted proportion difference, (%)	27.5	-	37.4	-
Strata-adjusted 95% CI	15.8, 39.2	-	25.7, 49.0	-
Strata-adjusted p-value	< 0.0001	-	<0.0001	-
Week 24				
Improvement of ≥ 4 from baseline in DLQI total score, n (%)	[redacted]	[redacted]		
Strata-adjusted proportion difference, (%)	[redacted]	-		
Strata-adjusted 95% CI	[redacted]	-		

Strata-adjusted p-value	[redacted]	-

Abbreviations: CI, confidence interval; DLQI, Dermatology Life Quality Index.; N/A, not available.
Source: Galderma. OLYMPIA 1 CSR[1]; Kwatra et al. (2023)[72] ; OLYMPIA 2 CSR[2]

Table 21. Change from baseline in EQ-5D total score at Week 16 and 24 in OLYMPIA 1 and OLYMPIA 2 ITT population

	OLYMPIA 1		OLYMPIA 2	
Timepoint	**Nemolizumab N = 190**	**Placebo N = 96**	**Nemolizumab N = 183**	**Placebo N = 91**
Baseline				
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Week 16	[redacted]	[redacted]	n =176	n =88
LS mean (SE)	[redacted]	[redacted]	15.04 (1.523)	3.99 (2.050)
95% CI	[redacted]	[redacted]	[redacted]	[redacted]
LS mean difference (95% CI)	[redacted]	-	11.06 (6.53, 15.59)	-
p-value	[redacted]	-	[redacted]	-
Week 24	[redacted]	[redacted]		
LS mean (SE)	[redacted]	[redacted]		
95% CI	[redacted]	[redacted]		
LS mean difference (95% CI)	[redacted]	-		
p-value	[redacted]	-		

Abbreviations: CI, confidence interval; DLQI, Dermatology Life Quality Index.; LS, least-squares; N/A, not available; SE< standard error.
Source: Galderma. OLYMPIA 1 CSR[1]; OLYMPIA 2 CSR[2]

Table 22. Change from baseline in HADs score at Week 16 and 24 in OLYMPIA 1 and OLYMPIA 2 ITT population

	OLYMPIA 1		OLYMPIA 2	
Timepoint	**Nemolizumab N = 190**	**Placebo N = 96**	**Nemolizumab N = 183**	**Placebo N = 91**
HADS – total score anxiety				
Baseline				
Mean (SD)	[redacted]	[redacted]	8.1 (4.45)	7.2 (4.21)
Week 16	[redacted]	[redacted]	[redacted]	[redacted]
LS mean (SE)	[redacted]	[redacted]	- 2.57 (0.268)	- 1.39 (0.360)
95% CI	[redacted]	[redacted]	[redacted]	[redacted]
LS mean difference (95% CI)	[redacted]		- 1.18 (- 1.98, -0.38)	
p-value	[redacted]		[redacted]	
Week 24	[redacted]	[redacted]		
LS mean (SE)	[redacted]	[redacted]		
95% CI	[redacted]	[redacted]		
LS mean difference (95% CI)	[redacted]			
p-value	[redacted]			

	OLYMPIA 1		OLYMPIA 2	
Timepoint	**Nemolizumab N = 190**	**Placebo N = 96**	**Nemolizumab N = 183**	**Placebo N = 91**
HADS – total score depression				
Baseline				
Mean (SD)	[redacted]	[redacted]	6.6 (4.24)	5.4 (3.99)
Week 16	[redacted]	[redacted]	[redacted]	[redacted]
LS mean (SE)	[redacted]	[redacted]	- 2.30 (0.265)	- 0.75 (0.356)
95% CI	[redacted]	[redacted]	[redacted]	[redacted]
LS mean difference (95% CI)	[redacted]		- 1.55 (-2.34, -0.75)	
p-value	[redacted]		[redacted]	
Week 24	[redacted]	[redacted]		
LS mean (SE)	[redacted]	[redacted]		
95% CI	[redacted]	[redacted]		
LS mean difference (95% CI)	[redacted]			
p-value	[redacted]			

Abbreviations: CI, confidence interval; DLQI, Dermatology Life Quality Index.; N/A, not available.
Source: Galderma. OLYMPIA 1 CSR[1]; Kwatra et al. (2023)[72] ; OLYMPIA 2 CSR[2]

B.2.6.2. LTE study

B.2.6.2.1. Patient disposition

Patient disposition for the OLYMPIA LTE trial is summarised in Table 23. In total [redacted]patients were screened at [redacted]study sites, with [redacted]patients enrolled at the latest data cutoff (Week 52). Patients were enrolled from prior clinical studies investigating nemolizumab, a Phase 2a trial (n = [redacted], NCT04501666) and the Phase 3 OLYMPIA 1 and OLYMPIA 2 trials (n = [redacted], NCT04501666; n = [redacted], NCT04501679, respectively). Patients could also be re-enrolled to this study after entering into the Phase 3b durability clinical study (n = [redacted], NCT05052983).

A total of [redacted] ([redacted]) patients discontinued treatment. The most common reason overall for discontinuation of treatment was due to AEs (n = [redacted]). Lack of efficacy and patient's request were also reported as leading reasons for discontinuation in this LTE cohort (n = [redacted], n = [redacted], respectively).

Table 23. Patient disposition in OLYMPIA LTE

Number of patients	Nemolizumab	By lead-in study			Re-entered from durability study
		Phase 2a trial	OLYMPIA 1	OLYMPIA 2	
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	n (%)	n (%)	n (%)	n (%)	n (%)
Treated	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Completed Tx	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Discontinued Tx	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Primary reason for discontinuation from the study					
Pregnancy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Lack of efficacy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Adverse event	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Patient's request	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Lost to follow-up	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Protocol deviation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Physician/primary investigator decision	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Sponsor decision	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Other					
COVID-19	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PEF criteria not met	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Site closure	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Number of patients	Nemolizumab	By lead-in study			Re-entered from durability study
		Phase 2a trial	OLYMPIA 1	OLYMPIA 2	
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	n (%)	n (%)	n (%)	n (%)	n (%)
Visit schedule	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Rolled over to Durability study	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Re-entered from Durability study	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Completed follow-up	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: N, number of patients in the population; n, number of patients with available data; PEF, Peak Expiratory Flow; Q4W, every 4 weeks; Tx, treatment

Note: Percentages were based on the number of patients.

Source: Galderma. OLYMPIA LTE CSR[3]

B.2.6.2.1. Baseline characteristics

Baseline characteristics and demographics of patients enrolled in the OLYMPIA LTE study can be found in Table 24; baseline disease characteristics of the LTE cohort can be found in Table 25.

Table 24. Baseline characteristics of patients in OLYMPIA LTE study

Number of patients	Nemolizumab	By lead-in study			Re-entered from durability study
		Phase 2a trial	OLYMPIA 1	OLYMPIA 2	
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	n (%)	n (%)	n (%)	n (%)	n (%)
Age (years)					
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Age group, n (%)					
18-65 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
> 65 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Sex, n (%)					
Male	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Female	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Region, n (%)					
Europe	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
North America	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Asia Pacific	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Number of patients	Nemolizumab	By lead-in study			Re-entered from durability study
		Phase 2a trial	OLYMPIA 1	OLYMPIA 2	
	n (%)	n (%)	n (%)	n (%)	n (%)
Ethnicity, n (%)					
Hispanic or Latino					
Not Hispanic or Latino					
Unknown					
Not reported					
American Indian or Alaska Native					
Asian					
Black or African American					
Native Hawaiian or Other Pacific Islander					
White					
Other					
Multiple					
Not reported					
Weight (kg)					
Mean (SD)					

Number of patients	Nemolizumab	By lead-in study			Re-entered from durability study
		Phase 2a trial	OLYMPIA 1	OLYMPIA 2	
	n (%)	n (%)	n (%)	n (%)	n (%)
Weight subgroup, n (%)					
< 90 kg without change					
≥ 90 kg without change					
< 90 kg with change*					
≥ 90 kg with change*					
Weight (kg) at LTE baseline					
Mean (SD)					
Body mass index (kg/m2)					
Mean (SD)					
Smoking status, n (%)					
Never					
Former					
Current					
Missing					
Treatment exposure to nemolizumab in previous study, n (%)					
Yes					
No					

Number of patients	Nemolizumab	By lead-in study			Re-entered from durability study
		Phase 2a trial	OLYMPIA 1	OLYMPIA 2	
	n (%)	n (%)	n (%)	n (%)	n (%)
Duration between last lead-in study dose and first LTE study dose					
Mean (SD)					
Duration between last lead-in study dose and first LTE study dose, n (%)					
< 12 weeks					
≥ 12 weeks					

* weight subgroups referred to as being 'with change' refer to the patients whose weight changed during the study such that they crossed the boundary of 90 kg, either rising above it or falling below, and as such requiring a dose change

Abbreviations: cm, centimetre; kg, kilogram; Q1, quarter one; Q3, quarter three; SD, standard deviation

Source: Galderma. OLYMPIA LTE CSR[3]

Table 25. Baseline disease characteristics from OLYMPIA LTE study

Number of patients	Nemolizumab	By lead-in study			Re-entered from durability study
		Phase 2a trial	OLYMPIA 1	OLYMPIA 2	
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	n (%)	n (%)	n (%)	n (%)	n (%)
Pain frequency (At LTE baseline, n [%])					
Never	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Less than once a week	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
1-2 days a week	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
3-4 days a week	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
5-6 days a week 0	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Everyday	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Missing	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pain intensity					
At lead-in baseline	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
At LTE baseline	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Prurigo Activity Score item 4 (number of lesions in representative area)					
At lead-in baseline	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Number of patients	Nemolizumab	By lead-in study			Re-entered from durability study
		Phase 2a trial	OLYMPIA 1	OLYMPIA 2	
	n (%)	n (%)	n (%)	n (%)	n (%)
At LTE baseline					
Mean (SD)					
Prurigo Activity Score item 5a (excoriation/crusts)					
At lead-in baseline, n (%)					
0%					
1-25%					
26-50%					
51-75%					
76-100%					
Missing					
At LTE baseline, n (%)					
0%					
1-25%					
26-50%					
51-75%					
76-100%					

Number of patients	Nemolizumab	By lead-in study			Re-entered from durability study
		Phase 2a trial	OLYMPIA 1	OLYMPIA 2	
	n (%)	n (%)	n (%)	n (%)	n (%)
Missing					
Prurigo Activity Score item 5b (healed lesion stages)					
At lead-in baseline, n (%)					
100%					
76-99%					
51-75%					
26-50%					
0-25%					
Missing					
At LTE baseline, n (%)					
100%					
76-99%					
51-75%					
26-50%					
0-25%					
Missing					

Number of patients	Nemolizumab	By lead-in study			Re-entered from durability study
		Phase 2a trial	OLYMPIA 1	OLYMPIA 2	
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	n (%)	n (%)	n (%)	n (%)	n (%)
DLQI total score					
At lead-in baseline	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
At LTE baseline	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Time since PN diagnosis (months)					
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: AP NRS, Average Pruritus Numerical Rating Scale; DLQI, dermatology life quality index; IGA, Investigator's Global Assessment; LTE, long-term extension; N, number of patients in the population; n, number of patients with available data; PN, prurigo nodularis; PP NRS, Peak Pruritus Numerical Rating Scale; Q1, first quartile; Q3, third quartile; Q4W, every 4 weeks; SD NRS, Sleep Disturbance Numerical Rating Scale

Note: Percentages were based on number of patients. Baseline LTE was the last non-missing value prior to first dose of study drug in this study. Lead-in baseline was defined as the last non-missing value before the first dose of study drug in Lead-in study. Phase 2 patients did not contribute to change from lead-in study baseline, since there were ≥6 months from completion of phase 2 to entry into LTE

Source: Galderma. OLYMPIA LTE CSR[3].

B.2.6.2.2. Long-term efficacy endpoints

B.2.6.2.2.1. Improvement in itch

Following nemolizumab treatment in the LTE, the proportion of patients with an improvement of ≥ 4 points from lead-in baseline in weekly average PP NRS generally increased over time. At Week 4, the proportion in nemolizumab-naïve patients converged with that of previously treated patients ([redacted]% nemolizumab-naïve, [redacted]% previously treated), demonstrating the rapid itch relief experienced by previously nemolizumab naïve patients (Table 26 and Figure 15).

At Weeks 40 and 52, the proportion remained generally consistent between nemolizumab-naïve patients and previously treated patients; therefore, treatment effectiveness was maintained with long-term treatment. No meaningful conclusions can be made for re-treated patients, due to the limited number of patients with available data at each timepoint.

The proportion of patients with weekly average PP NRS < 2 at LTE baseline was [redacted]% in all patients, with [redacted]% in nemolizumab-naïve patients and a higher proportion in patients who received continuous nemolizumab ([redacted]%) (Table 26). Following nemolizumab treatment in the LTE, the proportion of patients with weekly average PP NRS < 2 generally increased over time. By Week 4, the proportion in nemolizumab-naïve patients converged with that of previously treated patients ([redacted]% nemolizumab-naïve, [redacted]% previously treated), again demonstrating a rapid response in terms of itch relief in patients who were previously treatment naïve. At each subsequent visit, the proportion remained consistent between nemolizumab-naïve and previously treated patients, demonstrating lasting effectiveness of nemolizumab in the treatment of PN.

Figure 15. PP NRS improvement of ≥ 4-points from baseline over Treatment Period, overall nemolizumab Q4W group and by prior exposure – OLYMPIA LTE study

Abbreviations: BL, baseline; OC, observed cases; LTE, long-term extension; PP NRS, Peak Pruritus Numerical Rating Scale; Q4W, every four weeks

Source: Galderma. OLYMPIA LTE Interim Results[73]

B.2.6.2.2.2. Improvement in skin clearance

The proportion of patients with IGA success (defined as an IGA of 0 [clear] or 1 [almost clear]) at LTE baseline was [redacted]% in the total population, with [redacted]% in nemolizumab-naïve patients and a higher proportion in patients who received continuous nemolizumab ([redacted]%) (Table 26 and Figure 16).

At Week 28, the proportion of patients with IGA success in nemolizumab-naïve patients converged with that of previously treated patients ([redacted]% nemolizumab-naïve, [redacted]% previously treated). At Week 40 and Week 52, the proportion of patients with IGA success remained consistent between nemolizumab-naïve patients and previously treated patients. Therefore, nemolizumab effectiveness was maintained over 52 weeks in those patients who previously received nemolizumab. In addition, those who were nemolizumab naïve upon enrolling in the LTE study quickly experienced clinical benefit following initiation of nemolizumab and converged with nemolizumab-experienced patients within a short period of time.

Figure 16. IGA success over Treatment Period, overall nemolizumab Q4W group and by prior exposure – OLYMPIA LTE study

Abbreviations: BL, baseline; IGA, Investigator's Global Assessment; LTE, long-term extension; OC, observed cases; Q4W, every four weeks.
Source: Galderma. OLYMPIA LTE Interim Results[73]

B.2.6.2.2.3. Reduction in disruption of sleep

Following nemolizumab treatment in the LTE, the proportion of patients with an improvement of ≥ 4 points from lead-in baseline in SD NRS generally increased over time (Table 26). At Week 28, the proportion of patients with an improvement of ≥ 4 points from lead-in baseline in SD NRS in nemolizumab-naïve patients converged with that of previously treated patients ([redacted]% nemolizumab-naïve, [redacted]% previously treated).

At Week 40 and Week 52, the proportion of patients with an improvement of ≥ 4 points from lead-in baseline in SD NRS remained consistent between nemolizumab-naïve patients and previously treated patients, demonstrating ongoing effectiveness. No meaningful conclusions can be made for re-treated patients, due to the limited number of patients with available data at each timepoint.

B.2.6.2.2.4. Improvement in QoL

By Week 16, the proportion of patients with an improvement of ≥ 4-points from LTE baseline in DLQI total score had converged between the nemolizumab-naïve patients and previously treated patients. DLQI scores continued to decrease in both the naïve and previously treated patients between Week 16 and 52, demonstrating the quick onset and lasting clinical benefit experienced by patients following initiation of nemolizumab for the treatment of PN (Table 26 and Figure 17).

Figure 17. DLQI, overall nemolizumab Q4W group and by prior exposure – OLYMPIA LTE study

Abbreviations: BL, baseline; DLQI, Dermatology Life Quality Index; LTE, long-term extension; OC, observed cases; Q4W, every four weeks.

Source: Galderma. OLYMPIA LTE Interim Results[73]

Table 26. Summary of secondary outcomes from the LTE study at Week 52

Visit	By previous treatment				
	Nemolizumab	Previously treated by nemolizumab			Nemolizumab-naïve
		All	Continuous nemolizumab	Re-treatment	
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	m/n (%)	m/n (%)	m/n (%)	m/n (%)	m/n (%)
IGA success – Week 52					
IGA success (0/1) (%), (from LTE baseline) (OC)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PP-NRS improvement ≥ 4 - Week 52					
PP-NRS improvement ≥ 4 (%), (from lead in-baseline) (OC)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PP-NRS < 2 - Week 52					
PP-NRS < 2 (%) (from LTE baseline) (OC)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SD NRS improvement ≥ 4* - Week 52					
SD NRS improvement ≥ 4 (%) (from lead in baseline) (OC)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
DLQI – Week 52					
DLQI improvement ≥ 4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: DLQI, Dermatology Life Quality Index; IGA, Investigator's Global Assessment; LTE, long-term extension; OC, observed cases; PP NRS, Peak Pruritus Numerical Rating Scale; SD NRS, Sleep Disturbance Numerical Rating Scale.

B.2.7. Subgroup analysis

For each primary and key secondary endpoint in the OLYMPIA 1 and 2 trials, the estimate of the treatment difference, corresponding 2-sided 95% CI and unadjusted and strata-adjusted p-values for between-group comparisons were summarised by subgroups defined by:

- Region
- Age group
- Sex
- Race
- Body weight at randomisation
- Baseline IGA score

Due to the limited population in each subgroup, a pooled analysis of OLYMPIA 1 and 2 was conducted when considering subgroups. This increased the number of patients considered, making the analysis more robust and the conclusions of the analysis more meaningful. The results for the race and weight subgroups are presented here, in line with those specified in the decision problem.

The proportion of patients with an improvement of ≥ 4 points in PP NRS by subgroup in OLYMPIA 1 and 2 is shown in Figure 18. Results show that nemolizumab resulted in a statistically significant improvement in PP NRS regardless of weight at randomisation. Due to the small population size in each subgroup for race, ranging from 10-33 patients for the black or African-American, Asian and other subgroups, these results are difficult to interpret any meaningful conclusions.

Similar results were seen in the subgroups analyses considering the proportion of patients with IGA success (defined as an IGA of 0 [clear] or 1 [almost clear] and a ≥ 2-grade improvement from baseline) at Week 16 in OLYMPIA 1 and 2 (Figure 19).

Figure 18. Forest plot of proportion of patients with an improvement > 4 from baseline in weekly average pruritis numerical rating scale at week 16 – OLYMPIA 1 and 2 ITT population

Abbreviations: IGA, Investigator's Global Assessment; PP NRS, Peak Pruritus Numerical Rating Scale.
Note: Weekly values were calculated as the average of 7 consecutive days of data up to the target study day (excluding) and set to missing, if less than 4 days of data were available. Baseline was defined as the last non-missing weekly value before the first dose of study drug. If a patient received any rescue therapy, composite variable strategy was applied, the underlying data at/after receipt of rescue therapy were set as worst possible value, and the response was derived from underlying data value. Patients with missing result at a visit were considered as non-responders for that visit. Unadjusted and strata-adjusted p-values for between-group comparisons were from CMH test. Strata-adjusted p-values were from CMH test using the randomised stratification variables (analysis centre and body weight at randomisation [<90 kg, ≥90 kg]). Forest plot was based on the result of strata-adjusted and unadjusted difference between treatment groups.
Source: Galderma. OLYMPIA 1 CSR[1]

Figure 19. Forest plot of proportion of patients with an IGA success at Week 16 – OLYMPIA 1 and 2 ITT population

Abbreviations: IGA, Investigator's Global Assessment Note: IGA success was defined as patients with 0 (clear) or 1 (almost clear) and at least a 2-grade improvement from baseline. Baseline was defined as the last non-missing weekly value before the first dose of study drug. If a patient received any rescue therapy, composite variable strategy was applied, the underlying data at/after receipt of rescue therapy were set as worst possible value, and the response was derived from underlying data value. Patients with missing result at a visit were considered as non-responders for that visit. Unadjusted and strata-adjusted p-values for between-group comparisons were from CMH test. Strata-adjusted p-values were from CMH test using the randomised stratification variables (analysis centre and body weight at randomisation [<90 kg, ≥90 kg]). Forest plot was based on the result of strata-adjusted difference and unadjusted difference between treatment groups.
Source: Galderma. OLYMPIA 1 CSR[1]

B.2.8. Meta-analysis

A network meta-analysis (NMA) was not conducted for this submission, see Section B.2.9 for details.

B.2.9. Indirect and mixed treatment comparisons

There are currently no NICE-recommended treatments for PN, and all treatments included as comparators in the decision problem are used off-label in the UK. As discussed in Section B.1.3.2.2, BSC for PN typically comprises emollients, TCSs, and TCIs. In addition to BSC, there are off-label systemic treatments offered, which have considerable variation in their use in clinical practice.

There is a lack of RCT evidence to support the use of current off-label comparator treatments included in the decision problem. An SLR was conducted to identify all the relevant clinical effectiveness evidence (efficacy and safety) of interventions for the treatment of PN. Full details of the process and methods to identify and select the relevant clinical evidence are summarised in Appendix D. The SLR did not identify any RCT evidence regarding the use of off-label treatments for the treatment of PN. Therefore, an indirect treatment comparison (ITC) was not considered feasible or appropriate to compare nemolizumab against the off-label comparators treatments included in the decision problem, due to insufficient evidence to inform this analysis.

B.2.10. Adverse reactions

Key points

- Nemolizumab was generally well tolerated, with a safety profile comparable to that of placebo in both the OLYMPIA 1 and 2 clinical trials.
- In OLYMPIA 1, treatment emergent adverse events (TEAEs) were reported in 71.7% of patients in the nemolizumab group vs. 65.3% in the placebo group, with corresponding figures of 61.2% and 53.8%, respectively, in OLYMPIA 2. The majority of TEAEs were of mild or moderate severity, and only one TEAE was recorded as leading to the death of a patient, which occurred in the placebo group of OLYMPIA 1.

- Study drug related TEAEs were experienced by 46 (24.6%) patients in the nemolizumab arm and 18 (18.9%) in the placebo arm in OLYMPIA 1, and by 46 (25.1%) of patients in the nemolizumab arm and 16 (17.6%) of patients in the placebo arm in OLYMPIA 2.
- Most study drug related TEAEs in both the nemolizumab and placebo arms were mild (OLYMPIA 1: nemolizumab; n = 23, 12.3%; placebo; n = 11, 11.6%; OLYMPIA 2: nemolizumab; n = 31, 16.9%; placebo; n = 9, 9.9%).
- Over 52 weeks of follow-up in the LTE study, nemolizumab was seen to be well tolerated with no new safety concerns emerging over this time. A total of [redacted]) patients experienced at least one TEAE after 52 weeks of follow up, of which, [redacted] of patients experienced TEAEs related to nemolizumab; the majority experienced a TEAE that was considered mild or moderate in severity.

B.2.10.1. OLYMPIA 1 and OLYMPIA 2

B.2.10.1.1. Treatment-emergent adverse events

In both the OLYMPIA 1 and OLYMPIA 2 trials, nemolizumab was shown to be well tolerated with a similar AE profile to that of placebo, with no concerning AEs being observed. Those that did occur were managed in line with current clinical guidelines.

In OLYMPIA 1, 134 (71.7%) patients receiving nemolizumab and 62 (65.3%) receiving placebo experienced at least one treatment-emergent adverse event (TEAE); most of TEAEs experienced by those in the nemolizumab arm were mild (n = 58 [31.0%]) or moderate (n = 66 [35.3%]). Study drug related TEAEs were experienced by 46 (24.6%) patients in the nemolizumab arm and 18 (18.9%) in the placebo arm. Most study drug related TEAEs in both the nemolizumab and placebo arms were mild (nemolizumab: n = 23, 12.3%; placebo: n = 11, 11.6%) (Table 27).

Serious AEs (SAEs) were experienced by 21 (11.2%) of patients in the nemolizumab arm and 10 (10.5%) in the placebo arm; of these, 2 (1.1%) and 1 (1.1%) were attributed as being related to the study drug in the nemolizumab and placebo arms, respectively (Table 27).

A similar number of TEAEs leading to drug withdrawal were experienced by patients in both the nemolizumab and placebo arms of the OLYMPIA 1 trial (nemolizumab: n = 10, 5.3%; placebo: n = 3, 3.2%). Furthermore, the number of patients who experienced TEAEs that led to study discontinuation was comparable between the nemolizumab and placebo arms (nemolizumab: n = 11, 5.9%; Placebo: n = 4, 4.2%). No TEAEs leading to death were recorded in the nemolizumab arm of this trial; one (1.1%) TEAE leading to death was reported in the placebo arm (Table 27).

The most common TEAEs (reported by ≥ 5% of participants In either treatment arm) were COVID-19 (8.0% nemolizumab; 14.7% placebo), nasopharyngitis (6.4% nemolizumab; 8.4% placebo), headache (7.0% nemolizumab; 2.1% placebo), cough (4.8% nemolizumab; 5.3% placebo), dyspnoea (3.2% nemolizumab; 5.3% placebo), neurodermatitis (9.6% nemolizumab; 20.0% placebo), eczema (5.3% nemolizumab; 1.1% placebo) (Table 28).

In OLYMPIA 2, a total of 112 (61.2%) patients in the nemolizumab arm and 49 (53.8%) of patients in the placebo arm experienced at least one TEAE. The majority of TEAEs in both the nemolizumab and placebo arms were considered mild (n = 70, 38.3%; n = 29, 31.9%, respectively). Study drug related TEAEs were experienced by 46 (25.1%) of patients in the nemolizumab arm and 16 (17.6%) of patients in the placebo arm (Table 27). SAEs related to the study drug were reported in four (2.2%) nemolizumab and six (6.6%) placebo participants; of these, one (0.5%) and one (1.1%) were related to the study drug of the nemolizumab and placebo arms, respectively (Table 27).

Incidence of TEAEs leading to study drug withdrawal was similar between both the nemolizumab arm and placebo arm (nemolizumab: n = 5, 2.7%; placebo: n = 2, 2.2%). Furthermore, similar proportions of patients experienced TEAEs which led to study discontinuation between the nemolizumab and placebo arms (nemolizumab: n = 4, 2.2%; placebo: n = 2, 2.2%). No patients in either arm of the OLYMPIA 2 trial died during the treatment period (Table 27). The most common TEAEs were headache (6.6% nemolizumab, 4.4% placebo), dermatitis atopic (5.5% nemolizumab, 0.0% placebo), and neurodermatitis (3.8% nemolizumab; 11.0% placebo) (Table 28).

Table 27. Overall summary of TEAE incidence in OLYMPIA 1 and OLYMPIA 2

	OLYMPIA 1		OLYMPIA 2	
	Nemolizumab	Placebo	Nemolizumab	Placebo
TEAE (any)	134 (71.7)	62 (65.3)	112 (61.2)	49 (53.8)
TEAE by maximum severity				
Mild	58 (31.0)	32 (33.7)	70 (38.3)	29 (31.9)
Moderate	66 (35.3)	22 (23.2)	39 (21.3)	16 (17.6)
Severe	10 (5.3)	8 (8.4)	3 (1.6)	4 (4.4)
Study drug related TEAE	46 (24.6)	18 (18.9)	46 (25.1)	16 (17.6)
Study drug related TEAE by maximum severity				
Mild	23 (12.3)	11 (11.6)	31 (16.9)	9 (9.9)
Moderate	22 (11.8)	4 (4.2)	14 (7.7)	6 (6.6)
Severe	1 (0.5)	3 (3.2)	1 (0.5)	1 (1.1)
TEAE related to protocol procedure	8 (4.3)	3 (3.2)	4 (2.2)	3 (3.3)
SAE	21 (11.2)	10 (10.5)	4 (2.2)	6 (6.6)
SAE related to study drug	2 (1.1)	1 (1.1)	1 (0.5)	1 (1.1)
Severe TEAE	10 (5.3)	8 (8.4)	3 (1.6)	4 (4.4)
TEAE leading to study drug interruption	10 (5.3)	7 (7.4)	4 (2.2)	2 (2.2)
TEAE leading to study drug withdrawal	10 (5.3)	3 (3.2)	5 (2.7)	2 (2.2)
TEAE leading to study discontinuation	11 (5.9)	4 (4.2)	4 (2.2)	2 (2.2)
AESIs by categories	32 (17.1)	19 (20.0)	21 (11.5)	9 (9.9)

Injection-related reactions	2 (1.1)	0	0	0
Newly diagnosed asthma or worsening of asthma,	7 (3.7)	4 (4.2)	5 (2.7)	1 (1.1)
Infections	21 (11.2)	16 (16.8)	10 (5.5)	6 (6.6)
Peripheral oedema: limbs, bilateral, facial oedema	5 (2.7)	1 (1.1)	6 (3.3)	2 (2.2)
Elevated ALT or AST (>3 x ULN) in combination with elevated bilirubin	0	0	0	0
TEAE leading to death	0	1 (1.1)	0	0
TEAE related to study drug leading to death	0	0	0	0

Abbreviations: AESI: adverse event of special interest; ALT: alanine transaminase; AST: aspartate aminotransferase; ULN: upper limit of normal; SAE: serious adverse event; TEAE: treatment emergent adverse event.

Source: OLYMPIA 1 CSR[1]

Table 28. Treatment-emergent adverse events experienced by ≥ 2.0% of patients in either treatment group during the overall study period (safety population) – OLYMPIA 1 and OLYMPIA 2

	OLYMPIA 1		OLYMPIA 2	
	Nemolizumab	Placebo	Nemolizumab	Placebo
Patients ≥1 TEAE	134 (71.7)	62 (65.3)	112 (61.2)	49 (53.8)
GI Disorders	12 (6.4)	11 (11.6)	11 (6.0)	5 (5.5)
Gastritis	1 (0.5)	2 (2.1)	-	-
Diarrhoea	-	-	3 (1.6)	2 (2.2)
General disorders and administration site conditions	18 (9.6)	7 (7.4)	15 (8.2)	7 (7.7)
Fatigue	8 (4.3)	3 (3.2)	6 (3.3)	2 (2.2)
Injection site erythema	1 (0.5)	2 (2.1)	-	-
Immune system disorders	2 (1.1)	3 (3.2)	-	-
Seasonal allergy	2 (1.1)	2 (2.1)	-	-
Oedema peripheral	-	-	4 (2.2)	1 (1.1)
Infections and infestations	58 (31.0)	28 (29.5)	40 (21.9)	19 (20.9)
COVID-19	15 (8.0)	14 (14.7)	9 (4.9)	3 (3.3)
Nasopharyngitis	12 (6.4)	8 (8.4)	5 (2.7)	4 (4.4)
Urinary tract infections	7 (3.7)	2 (2.1)	-	-
Cellulitis	1 (0.5)	2 (2.1)	-	-
Oral herpes	1 (0.5)	2 (2.1)	-	-
Sinusitis	-	-	4 (2.2)	0

	OLYMPIA 1		OLYMPIA 2	
	Nemolizumab	Placebo	Nemolizumab	Placebo
Investigations	12 (6.4)	8 (8.4)	8 (4.4)	1 (1.1)
Aspartate aminotransferase increased	2 (1.1)	2 (2.1)	-	-
Alanine aminotransferase increased	1 (0.5)	2 (2.1)	-	-
Blood creatinine phosphokinase increased	1 (0.5)	4 (4.2)	-	-
Blood lactate dehydrogenase increased	1 (0.5)	2 (2.1)	-	-
Peak expiratory flow decreased	-	-	4 (2.2)	0
Musculoskeletal and connective tissue disorders	22 (11.8)	7 (7.4)	21 (11.5)	7 (7.7)
Back pain	5 (2.7)	0	3 (1.6)	2 (2.2)
Arthralgia	3 (1.6)	2 (2.1)	-	-
Myalgia	2 (1.1)	2 (2.1)	3 (1.6)	2 (2.2)
Pain in extremity	-	-	4 (2.2)	0
Nervous system disorders	21 (11.2)	9 (9.5)	17 (9.3)	9 (9.9)
Headache	13 (7.0)	2 (2.1)	12 (6.6)	4 (4.4)
Polyneuropathy	0	2 (2.1)	-	-
Presyncope	0	2 (2.1)	-	-
Dizziness	-	-	2 (1.1)	2 (2.2)
Psychiatric disorders	1 (0.5)	3 (3.2)	0	0
Depression	0	2 (2.1)	-	-
Renal and urinary disorders	2 (1.1)	3 (3.2)	-	-
Proteinuria	0	2 (2.1)	-	-

	OLYMPIA 1		OLYMPIA 2	
	Nemolizumab	Placebo	Nemolizumab	Placebo
Respiratory, thoracic and mediastinal disorders	21 (11.2)	12 (12.6)	13 (7.1)	5 (5.5)
Cough	9 (4.8)	5 (5.3)	5 (2.7)	2 (2.2)
Dyspnoea	6 (3.2)	5 (5.3)	-	-
Asthma	4 (2.1)	4 (4.2)	-	-
Skin and subcutaneous tissue disorders	59 (31.6)	28 (29.5)	44 (24.0)	21 (23.1)
Neurodermatitis	18 (9.6)	19 (20.0)	7 (3.8)	10 (11.0)
Eczema	10 (5.3)	1 (1.1)	4 (2.2)	3 (3.3)
Eczema nummular	7 (3.7)	0	6 (3.3)	0
Dermatitis atopic	7 (3.7)	1 (1.1)	10 (5.5)	0
Dyshidrotic eczema	1 (0.5)	2 (2.1)	-	-
Pruritus	-	-	2 (1.1)	3 (3.3)
Dry skin	-	-	1 (0.5)	2 (2.2)
Vascular disorders	7 (3.7)	3 (3.2)	6 (3.3)	2 (2.2)
Hypertension	4 (2.1)	2 (2.1)	5 (2.7)	2 (2.2)

Abbreviations: COVID-19: coronavirus disease; GI: gastrointestinal; TEAE: treatment emergent adverse event.

Source: OLYMPIA 1 CSR[1]; OLYMPIA 2 CSR[2]

B.2.10.2. LTE study

B.2.10.2.1. Treatment emergent adverse events

Over 52 weeks of follow-up in the LTE study, nemolizumab was seen to be well tolerated by patients, with no new safety concerns emerging. A total of [redacted] patients experienced at least one TEAE (Table 29). Of these patients, the majority experienced a TEAE that was considered mild or moderate in severity. Study drug related TEAEs were experienced by [redacted] patients. Treatment-emergent SAEs were experienced by [redacted] patients. Treatment-emergent AEs leading to study drug withdrawal were experienced by [redacted] patients; [redacted] patients experienced a TEAE leading to study discontinuation. AESIs (by Investigator) were experienced by [redacted] patients. [redacted] patients experienced a TEAE leading to death, which were due to myocardial infarction and end stage renal disease. Neither were related to the study drug or protocol procedure.

The most common TEAEs experienced by ≥ 2.0% of patients treated with nemolizumab during the overall study period were COVID-19 ([redacted]), nasopharyngitis ([redacted]) and neurodermatitis ([redacted]) (Table 30).

Table 29. Overall summary of TEAEs – LTE study

	Nemolizumab [redacted] n (%)
TEAE	[redacted]
TEAE by maximum severity[a]	
Mild	[redacted]
Moderate	[redacted]
Severe	[redacted]
Study drug related TEAE[b]	[redacted]
Mild	[redacted]
Moderate	[redacted]
Severe	[redacted]
SAE	[redacted]
SAE related to study drug	[redacted]
Severe TEAE	[redacted]
Any TEAE leading to study drug interruption	[redacted]
Any TEAE leading to study drug withdrawal	[redacted]
Any TEAE leading to study discontinuation	[redacted]
AESIs by categories (by Investigator)	[redacted]
Injection-related reactions	[redacted]
Newly diagnosed asthma or worsening of asthma	[redacted]
Infections	[redacted]
Peripheral oedema: limbs, bilateral; facial oedema	[redacted]
TEAE leading to death	[redacted]
TEAE related to study drug leading to death	[redacted]

Abbreviations: AE: adverse event; AESI, adverse event of special interest; N, number of subjects in the population; n, number of subjects who experienced the events; TEAE: treatment emergent adverse event.

Source: Galderma. OLYMPIA 2 CSR[2]

Note: Percentages were based on the number of subjects. Adverse events were coded using the Medical Dictionary for Regulatory Activities Version 25.0. The TEAEs during the overall study period were defined as AEs with onset date on or after the first dose to the follow-up visit date. For each row category, a subject with 2 or more AEs in that category was counted only once.

[a] If subjects experienced multiple events, the subjects were counted once at the event with maximum severity

[b] Study drug-related TEAEs were those for which a reasonable possibility of relationship was reported (or with a missing relationship).

Table 30. Treatment-emergent adverse events experienced by ≥ 2% of patients during the overall study period (safety population) – LTE study

	Nemolizumab [redacted]n (%)
Patients with ≥ 1 TEAE	[redacted]
Gastrointestinal disorders	[redacted]
Diarrhoea	[redacted]
Nausea	[redacted]
General disorders and administration site conditions	[redacted]
Pyrexia	[redacted]
Oedema peripheral	[redacted]
Fatigue	[redacted]
Infections and infestations	
COVID-19	[redacted]
Nasopharyngitis	[redacted]
Upper respiratory tract infection	[redacted]
Urinary tract infection	[redacted]
Bronchitis	[redacted]
Influenza	[redacted]
Sinusitis	[redacted]
Investigations	[redacted]
Blood creatine phosphokinase increased	[redacted]
Musculoskeletal and connective tissue disorders	
Arthralgia	[redacted]
Back pain	[redacted]
Myalgia	[redacted]
Pain in extremity	[redacted]
Osteoarthritis	[redacted]
Nervous system disorders	[redacted]
Headache	[redacted]
Dizziness	[redacted]
Respiratory, thoracic, and mediastinal disorders	[redacted]
Cough	[redacted]
Asthma	[redacted]

	Nemolizumab [redacted]n (%)
Dyspnoea	[redacted]
Oropharyngeal pain	[redacted]
Skin and subcutaneous tissue disorders	[redacted]
Neurodermatitis	[redacted]
Eczema nummular	[redacted]
Eczema	[redacted]
Dermatitis atopic	[redacted]
Urticaria	[redacted]
Hand dermatitis	[redacted]
Vascular disorders	[redacted]
Hypertension	[redacted]

Abbreviations: N, number of patients in the population; n, number of patients who experienced the events; TEAE, treatment-emergent adverse event.
Note: Percentages were based on the number of patients. Adverse events were coded using the Medical Dictionary for Regulatory Activities Version 25.0. The TEAEs during the overall study period were defined as adverse events with onset date on or after the first dose to the follow-up visit date.
Source: Galderma. OLYMPIA 2 CSR[2]

B.2.11. Ongoing studies

The LTE study (NCT04204616),[74] which is considering the long-term safety and efficacy of nemolizumab, is currently ongoing.

B.2.12. Interpretation of clinical effectiveness and safety evidence

B.2.12.1. Principal findings from the clinical evidence

There is a significant unmet need for a safe and efficacious targeted treatment for moderate to severe PN. Treating patients with PN in current clinical practice is challenging due to the lack of reimbursed targeted systemic therapies. Current treatment options are prescribed off-label and aim to relieve symptoms, rather than address the underlying pathophysiology of the disease. Symptomatic control currently relies on topical therapies, which often do not provide adequate symptom management,[10,75] and systemic therapies that are often associated with adverse events.[10,58-60,75,76]

During OLYMPIA 1, nemolizumab treatment caused significant improvements in both PP NRS and IGA score (success) after 16 weeks compared with placebo.[1,71] These improvements in PP NRS quantify the demonstrable improvement in itch that nemolizumab offers, which plays a significant role in patient QoL. Improvements in IGA scores demonstrate the effect that nemolizumab has on the disease itself, rather than just the symptom of itch, as improvements in these scores suggest that this intervention is likely to be halting disease progression.

Consistent with OLYMPIA 1, during OLYMPIA 2, nemolizumab treatment caused significant improvements in itch and skin lesions at Week 16 (≥ 4 point improvement in PP NRS and IGA success). In both the OLYMPIA 1 and OLYMPIA 2 trials, significant improvements were also seen in reduction of sleep disturbance, QoL and clearance of skin lesions at Weeks 4 and 16 after nemolizumab treatment compared with placebo.[2,77]

The PP NRS response and IGA success were maintained over 24 weeks, demonstrating a durable and lasting treatment effect in the OLYMPIA 1 trial, and were maintained over 52-weeks in the LTE study in those who were previously exposed to nemolizumab.[3] The proportions of patients with PP NRS response (≥ 4 point improvement from baseline) in patients who were nemolizumab-naïve upon entry to the LTE study, converged quickly with those who were treatment experienced by Week 4, and remained consistent between these treatment arms until Week 52. Nemolizumab also demonstrated long-term benefits to patients enrolled in the LTE study including a reduction in sleep disturbance, as well as improvements in patient reported QoL outcomes which included EQ-5D, and HADS assessment for both anxiety and depression.

There were no new safety concerns identified during either the OLYMPIA 1 or OLYMPIA 2 trials or during the LTE study; with the frequency of TEAEs being similar between treatment arms in all studies.[1-3,77]

B.2.12.2. Strengths and limitations of the clinical evidence base

Limitations of the clinical evidence:

This submission is informed by a wealth of RCT evidence. The evidence to support this submission includes the pivotal OLYMPIA 1 and 2 clinical trials and the OLYMPIA LTE study. While the study populations of the trials are limited in size due to the rarity of PN in the population, the trials were powered to demonstrate statistical significance compared with placebo across multiple clinically meaningful measures of response. There is extensive follow-up data over 52-weeks in the LTE study, demonstrating the long-term efficacy and safety of nemolizumab treatment in patients with PN. The LTE study is ongoing with data at later timepoints expected. While these studies have some limitations, they must be considered alongside the many strengths of the trials included in this clinical programme.

As the SLR did not identify any RCT evidence regarding the use of off-label treatments included as comparators in the decision problem for PN, it was not feasible or appropriate to perform an ITC (Section B.2.9). Therefore, we consider the placebo arm of the OLYMPIA 1 and OLYMPIA 2 trials, where patients were permitted to receive concomitant treatment alongside placebo, to represent the best available evidence for BSC in moderate to severe PN.

The proposed weight-based dosing regimen of nemolizumab in patients with moderate to severe PN differs to some treatments otherwise used in this patient population. However, subgroup analyses from the pooled analysis of the OLYMPIA 1 and 2 trials have demonstrated that differences in patients' weight (i.e., < 90 kg and ≥ 90 kg) did not result in any significant differences in the outcomes of patients receiving nemolizumab to manage PN.

In the OLYMPIA 1 and OLYMPIA 2 trials, nemolizumab was compared against placebo with permitted concomitant therapy including basic skin care, moisturisers, bleach baths and topical anaesthetics. In OLYMPIA 1, a total of [redacted] ([redacted]) patients in the nemolizumab arm and [redacted] ([redacted]) in the placebo arm received at least 1 concomitant medication during the study. In OLYMPIA 2, similar percentages of

patients in the nemolizumab and placebo arms received at least 1 concomitant medication during the study ([redacted] and [redacted], respectively).

Prohibited concomitant therapy and rescue therapy in OLYMPIA 1 and 2 are presented in Table 7 and included the off-label comparator treatments from the decision problem, such as TCSs, TCIs, antihistamines, systemic corticosteroids and immunosuppressants. In these trials, for the purposes of the efficacy analysis, patients who received rescue therapy were classed as treatment failures. Therefore, given nemolizumab is anticipated to be used alongside BSC (which can include emollients, TCSs and TCIs), this may not be considered to align with UK clinical practice. However, in the OLYMPIA 1 and 2 trials, if a non-permitted concomitant therapy was required for the treatment of the patient for a condition other than PN, the patient was allowed to continue the concomitant therapy without it being classed as rescue therapy. The use of non-permitted concomitant therapy was acceptable provided that it was discussed and agreed upon with the Investigator and the medical monitor. The off-label comparator treatments included in the decision problem, used as non-permitted concomitant therapies (but not classed as rescue therapy in the pooled OLYMPIA 1 and OLYMPIA 2 trials) are presented in Table 31.

Based on the significant variation in the use of off-label treatments in patients with moderate to severe PN and the association of underlying conditions in patients with PN (87% of patients with PN report underlying conditions),[42] the OLYMPIA 1 and OLYMPIA 2 trials can be considered generalisable to UK clinical practice. Furthermore, based on the lack of RCT evidence regarding the use of off-label treatments, the OLYMPIA 1 and OLYMPIA 2 trials can be considered the best evidence for nemolizumab and BSC in patients with moderate to severe PN to support this submission.

Table 31. Non-permitted concomitant therapy allowed by the Investigator and medical monitor in the pooled OLYMPIA 1 and 2 trials

	Nemolizumab (N=373)	Placebo (N=187)	Overall (N=560)
Antihistamines*	[redacted]	[redacted]	[redacted]
Emollients	[redacted]	[redacted]	[redacted]
TCSs	[redacted]	[redacted]	[redacted]
Systemic corticosteroids	[redacted]	[redacted]	[redacted]
Immunosuppressants	[redacted]	[redacted]	[redacted]
TCI	[redacted]	[redacted]	[redacted]

Abbreviations: N, number of patients in the population; TCI, topical calcineurin inhibitors; TCS, topical corticosteroids
Note: these patients received the non-permitted concomitant therapy which was not classed as rescue therapy as it was necessary for a condition other than PN which was discussed and agreed upon with the Investigator and the medical monitor.
* Oral antihistamines were prohibited unless taken at a stable dose for 3 months prior to screening or for a seasonal allergy

Strengths of the clinical evidence

This submission is informed by two robust Phase 3 clinical trials conducted in relevant European and US settings, in line with regulatory requirements. Additional long-term follow up data from the LTE study demonstrates that the benefits of nemolizumab are maintained over an extended period of 52 weeks, with further follow up expected at later time points.

The population considered by this submission is patients with moderate to severe PN. This is the same as the population included in the nemolizumab clinical programme, which included 17 patients enrolled in the UK during the OLYMPIA 1 clinical trial. Other countries involved in OLYMPIA 1, OLYMPIA 2 and the LTE study included predominantly Western European countries and the US, which are generalisable to UK patient populations in PN. As such, the outcomes of patients involved in this clinical programme reflect the population indicated in the scope of this submission. All patients in this clinical programme were diagnosed with moderate or severe PN, in line with the scope (Table 14 and Table 25).

These trials demonstrate that nemolizumab is well tolerated and associated with few safety concerns when used in the treatment of patients with PN, both in the OLYMPIA 1 and OLYMPIA 2 trials, which covered treatment periods of 24 and 16 weeks, respectively, and over 52 weeks as demonstrated by the OLYMPIA LTE

study. Nemolizumab was also associated with significant improvements in patients' QoL in both OLYMPIA 1 and 2 trials and the LTE. Nemolizumab naïve patients in the LTE reported DLQI scores that improved dramatically over the first 16 weeks of treatment and persisted through to 52 weeks of treatment. As PN is a chronic condition, patients highly value any benefits to their overall condition and QoL. This improvement in DLQI comes as a result in improvements in symptoms, which place a considerable clinical and humanistic burden on patients with PN, including intensity of itch (PP NRS), sleep disturbance (SD NRS), and number and distribution of pruriginous lesions on the body. All studies presented in this submission considered a large number of varied clinical endpoints as primary and secondary outcomes, which fully characterise the burden of the disease and demonstrates the variety of benefits that patients experience following nemolizumab treatment for moderate to severe PN.

B.3. Cost-effectiveness

Model overview

- A cost-effectiveness analysis was conducted to compare nemolizumab in combination with BSC versus BSC alone for the treatment of moderate to severe PN in a UK population.
- A hybrid model structure was developed that includes a 16-week decision tree followed by a subsequent long term three-state Markov model to facilitate the inclusion of short and long-term treatment effects in PN.
    - This model structure was considered appropriate for decision making in TA955 and has been validated by UK clinician experts.[5]
- In the 16-week decision tree, response was determined at Week 16 using the composite endpoint of a ≥ 4-point improvement in PP NRS and IGA success based on data from the OLYMPIA 1 and 2 clinical trials. At 16 weeks, patients exit the short-term decision tree and progress into a long-term Markov model, which includes three health states: 'Maintained response,' 'No response' and 'Dead.'
- The model takes into account QoL with utility values by response status, based on EQ-5D data from the OLYMPIA 1 and OLYMPIA 2 clinical trials. The model also takes into account costs, which include treatment costs, disease management and monitoring costs, and costs associated with AEs.

Cost-effectiveness analysis results

- Nemolizumab was associated with an incremental cost-effectiveness ratio (ICER) of £34,447 per quality-adjusted life year (QALY) gained versus BSC, which is slightly above the willingness-to-pay (WTP) threshold of £30,000 per QALY gained.
- Long-term projections indicated that nemolizumab was associated with an improved QALY gain compared with BSC, which was driven by an improved

response to treatment and increased time spent in the ‘Maintained response’ health state.

- Nemolizumab was associated with increased costs compared with BSC, which was driven by the low cost of the off-label BSC comparator treatments and low cost of subsequent BSC for patients who did not respond to nemolizumab treatment. Despite the greater overall cost of nemolizumab versus BSC, nemolizumab was associated with a lower disease management and monitoring costs, driven in part by a greater response to treatment.
- Extensive sensitivity analysis demonstrated that the cost-effectiveness estimates were robust to changes in the model parameters and assumptions. However, scenario analysis showed that the dose of nemolizumab used in the analysis had a significant impact on the cost-effectiveness estimates. In the scenario where 100% of patients in the nemolizumab arm were assumed to receive the < 90 kg nemolizumab dose (30 mg Q4W), nemolizumab was associated with a reduced ICER of £25,762 per QALY gained versus BSC, which is below the WTP threshold of £30,000 per QALY gained.

Conclusions

- Based on the significant unmet need for a targeted systemic treatment that can address the underlying pathophysiology of PN, nemolizumab should be considered an appropriate use of NHS resources in England.
    - Furthermore, based on the < 90 kg nemolizumab dose, nemolizumab represents a cost-effective use of NHS resources.

B.3.1. Published cost-effectiveness studies

An SLR was conducted to identify all relevant cost-effectiveness studies in moderate to severe PN. The objective of this review was to identify the optimal modelling framework for treatment of patients with moderate to severe PN in the UK, thus, the review was primarily focused on cost-effectiveness models that have been designed

and developed as a part of submissions for already recommended treatments in the UK. Database searches were initially conducted on 25 September 2023 and subsequently updated on 17 May 2024. Three economic evaluations were identified from three publications for inclusion in this review (Table 32). Full details of the SLR are given in Appendix G.

Table 32. Summary of published cost-effectiveness studies

Study	Year	Summary of model	Patient population	QALYs (intervention, comparator)	Costs (currency) (intervention, comparator)	ICER (per QALY gained)
Prada[78]	2023	Simulation of outcomes and costs was undertaken using a 1-Year decision tree followed by a lifetime horizon Markov to estimate the ICER of dupilumab vs current standard of care, used to treat PN in Italy	Patients with uncontrolled moderate to severe PN.	NR	Dupilumab versus standard of care incremental cost: €54,888	€34,991 per QALY
Whang[79]	2021	Cost utility analysis to quantify the impact of PN on quality of life and its economic implications.	Patients with PN	Average loss of 6.5 years per patient.	Individual lifetime burden: $323,292 Societal lifetime burden: $38.80 billion.	NR
NICE TA955[80]	2024	24-week decision tree followed a lifetime horizon Markov model to evaluate the clinical- and cost-effectiveness of dupilumab as a treatment option for moderate to severe PN.	Adult patients with PN inadequately controlled with topical prescription therapies.	NR	NR	£26,886 per QALY

Abbreviations: ICER, incremental cost-effectiveness ratio; NR, not reported; PN. prurigo nodularis; QALY, quality-adjusted life year

B.3.2. Economic analysis

B.3.2.1. Choice of modelling approach

Out of the three cost-effectiveness models identified in the SLR, the cost-effectiveness model developed during the NICE technology appraisal for dupilumab in patients with moderate to severe PN [TA955][80] can be considered the most comprehensive cost-effectiveness analysis in moderate to severe PN to date.

Although dupilumab was not recommended by NICE for the treatment of patients with moderate to severe PN, the NICE Committee concluded that the model structure was representative of PN and acceptable for decision making.[80] Therefore, the NICE TA955 model framework was chosen to primarily inform conceptualisation of a *de novo* cost-effectiveness model for nemolizumab in the treatment of patients with moderate to severe PN. To improve on the model developed as part of TA955, the limitations identified by the external assessment group (EAG) and Committee were noted and have been addressed to minimise uncertainty in the nemolizumab cost-effectiveness estimates.

B.3.2.2. Patient population

This economic evaluation aligns with the decision problem presented in Section B.1.1 and considers the use of nemolizumab in adults with moderate to severe PN.

The baseline characteristics for the base-case population were aligned with the patient demographics in the OLYMPIA 1 and 2 clinical trials (Table 33). As discussed in Section B.2.2, the OLYMPIA 1 and 2 clinical trials include a patient population with moderate to severe PN that can be considered clinically representative and generalisable to people with moderate to severe PN in UK clinical practice, and thus, represent the best quality evidence to base the cost-effectiveness analysis upon.

Table 33. Summary of cohort characteristics

Parameter	Mean value	Source
Age, years	55.19	OLYMPIA 1 and OLYMPIA 2 overall population[1,2]
Proportion of cohort male, %	40.36	
Weight, kg	82.56	

B.3.2.3. Model structure

B.3.2.3.1. Model overview

The economic model is designed to accurately reflect UK clinical practice for moderate to severe PN. A hybrid model was developed linking a 16-week decision tree and subsequent three-state Markov model. The use of a hybrid model including a decision tree and Markov model facilitates the inclusion of short- and long-term treatment effects and the impact of the disease on the patient population. Costs and clinical outcomes are simulated and recorded over a long-term perspective to assess the value of nemolizumab in patients with moderate to serve PN versus BSC alone. The model concept follows the cost-effectiveness model developed for TA955,[80] and has been validated with clinical and health economic experts to assure methodological appropriateness and alignment with clinical practice in the UK.[5]

The economic model was designed to perform cost-effectiveness analyses by projecting patients' health state occupancy over the time horizon along with transient events (i.e., TRAEs) and valuating health states and the transient events to derive costs and health outcomes. The economic model was developed and implemented in Microsoft Excel® as an interactive tool using a combination of worksheets and Visual Basic for Applications (VBA) functionalities.

B.3.2.3.2. Modelling approach

B.3.2.3.2.1. *Decision tree*

The decision tree component of the model (Figure 20) captures the short-term treatment effects from the OLYMPIA 1 and OLYMPIA 2 clinical trials.[81,82] All patients with moderate to severe PN who enter the model start treatment and continue for 16 weeks (treatment induction phase). Patients are treated with either nemolizumab (intervention arm) or BSC alone (comparator arm).

After 16 weeks, patients in the intervention arm who respond to nemolizumab continue nemolizumab treatment, while non-responders discontinue nemolizumab treatment and receive BSC alone for the remainder of the model time horizon. In the comparator arm, patients on BSC alone will not discontinue treatment regardless of response status; however, utility and costs will be dependent on response status at Week 16. In both treatment arms, responders at Week 16 enter the long-term Markov model through the 'Maintained response' health state and non-responders enter through the 'No response' health state (Figure 19).

The timepoint of 16 weeks was chosen to align with the assessment of response in the OLYMPIA 1 and OLYMPIA 2 clinical trials. Response to treatment was evaluated via the PP NRS and IGA instruments. To be classed as a responder, a patient must achieve a composite endpoint of an improvement of ≥ 4 in PP NRS and IGA success (defined as a score of 0 or 1) with an improvement of ≥ 2 based on data from the OLYMPIA 1 and 2 clinical trials.

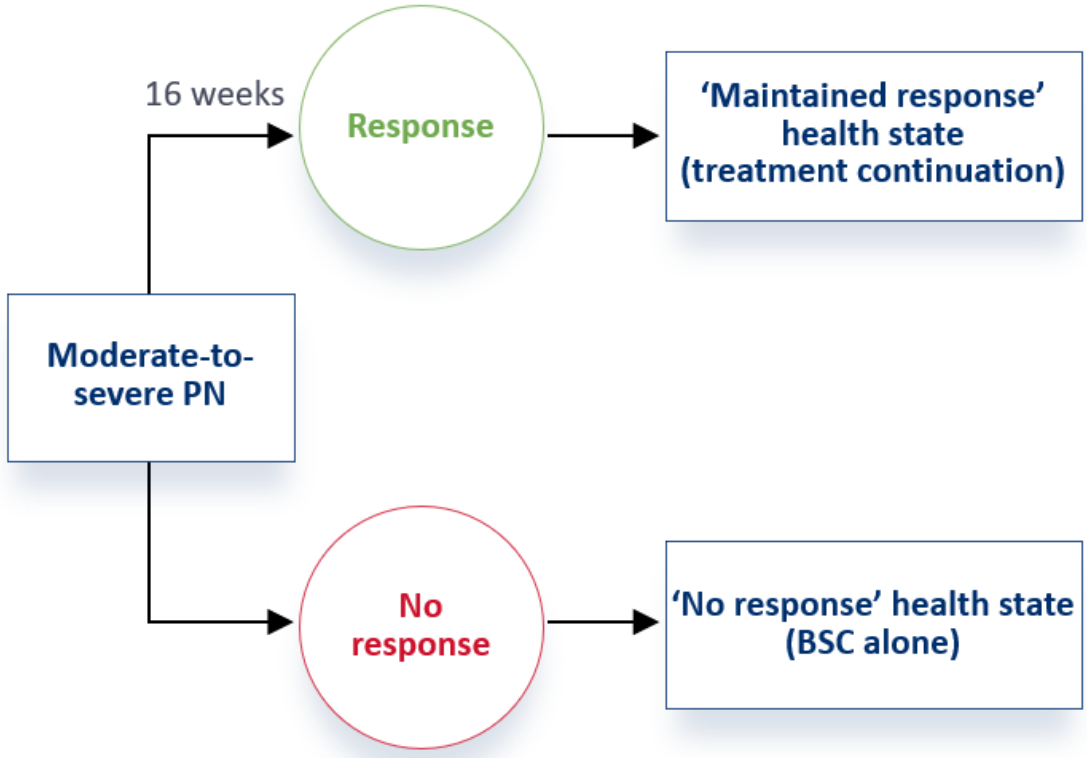

Figure 20. Schematic of the decision tree

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

B.3.2.3.2.2. ***Markov model***

After 16 weeks of treatment, all patients immediately exit the short-term decision tree and progress into a long-term Markov model which includes three health states: 'Maintained response,' 'No response' and 'Dead' (Figure 21).

Patients who respond at Week 16 enter the Markov model through the 'Maintained response' health state, where they continue the treatment received at baseline and remain until loss of response, either via treatment effect waning or discontinuation of treatment for any reason (all-cause discontinuation). In the event of loss of response (treatment effect waning) or treatment discontinuation due to any reason, patients transition to the 'No response' health state where they receive BSC alone.

Treatment effect waning was included within the 'Maintained response' health state of the model, as over time patients may experience a diminishing response to treatment. In the OLYMPIA 1 and OLYMPIA 2 clinical trials, lack of efficacy is a reason for treatment discontinuation; therefore, there was a risk of an overlap between the proportion of patients who stop responding to treatment and long-term discontinuation of treatment for all causes. Although there is limited data on the size of this overlap, it is expected to be minimal as treatment effect waning is not expected to be observed at Week 52 or Week 24, i.e., the timepoints where long-term discontinuation for nemolizumab and BSC were obtained, respectively. Furthermore, the inclusion of both treatment effect waning and all-cause discontinuation was validated by UK clinical experts in a modified Delphi panel exercise.[4]

Patients who do not respond to treatment at Week 16, enter the Markov model through the 'No response' health state and remain there until death (transition to the 'Dead' health state). At any point in the model, patients have the potential to transition to the 'Dead' health state, which is an absorbing health state from which no transitions are possible.

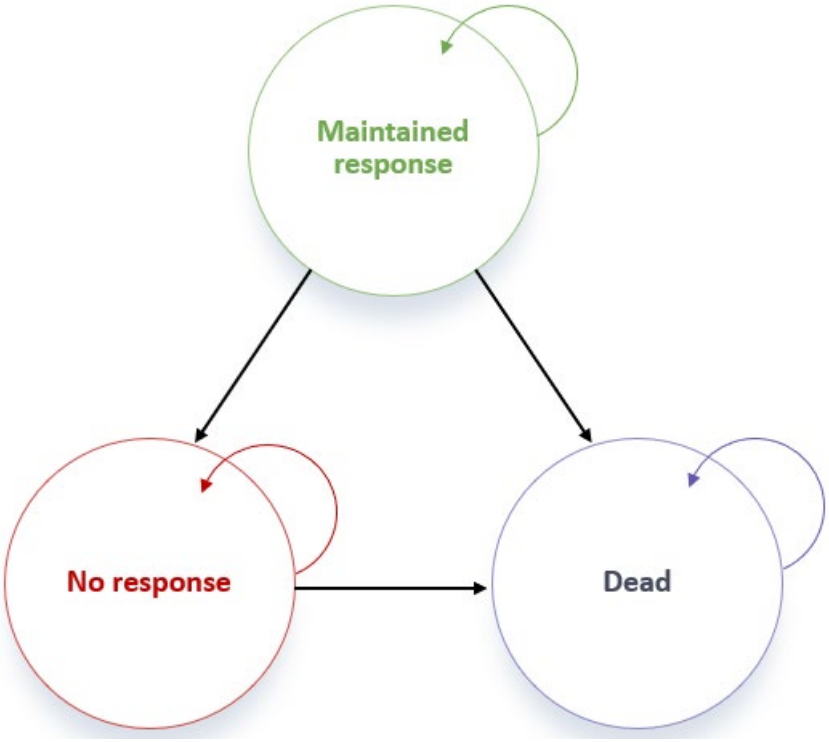

Figure 21. Schematic of the Markov model

B.3.2.4. Features of the economic analysis

Table 34 summarises the features of the economic analysis and compares these with the published NICE technology appraisal for dupilumab [TA955].[80]

Table 34. Features of the economic analysis

	Previous appraisal	Current appraisal	
Factor	**NICE TA955**	**Chosen values**	**Justification**
Population	Adults with moderate to severe PN who had inadequate response or intolerance to existing topical treatments	Adults with moderate to severe PN	This population is aligned with the Decision Problem in Section B.1.1. Furthermore, this population is aligned with the anticipated use nemolizumab in UK clinical practice, and the populations included OLYMPIA 1 and OLYMPIA 2 clinical trials.[83,84]
Intervention	Dupilumab + BSC	Nemolizumab with BSC	In line with UK clinical practice and treatment guidelines, active treatment is administered alongside BSC which can include emollients, TCSs and TCIs.
Comparators	Established clinical management without dupilumab, including topical emollients, TCSs, TCIs, antihistamines, oral steroids, phototherapy, immunosuppressive therapies, SSRIs, and SNRIs.	Established clinical management, including: topical emollient, TCSs, TCIs, antihistamines, systemic corticosteroids, and immunosuppressants.	Treatment options for patients with PN are limited, as there are currently no treatments recommended by NICE for patients with PN. All treatments included in the final scope are currently used off-label in UK clinical practise. Based on the limited treatments currently available, UK clinical experts in a modified Delphi panel exercise considered BSC for patients with PN to consist of emollients, TCSs, and TCIs.[4] The clinical experts stated that there is significant variation in the use of subsequent off-label systemic treatments, including antihistamines, systemic corticosteroids, and immunosuppressive therapies. It is important to note that there is no RCT evidence for these off-label systemic treatments listed as comparators. Furthermore, the limited and low-quality evidence available for the off-label systemic

			treatments means that an ITC would not be feasible or appropriate.
Perspective	The NHS and PSS perspective	The NHS and PSS perspective	Consistent with NICE modelling guidance.[85]
Model structure	A hybrid decision tree Markov state-transition model with patients on/off treatment, depending on treatment response status	A hybrid decision tree Markov state-transition model with patients on/off treatment, depending on treatment response status	Consistent with the model structure used in TA955, which was considered acceptable for decision making by NICE.[80] The model structure reflects the different nature of treatment effects in the short- and long-term.
Cycle length	One year	One year	Appropriate time interval to capture long-term effect of systemic treatments in patients with moderate to severe PN.
Time horizon	Lifetime	Lifetime	Consistent with NICE modelling guidance.[85]
Outcomes	• Total and incremental costs with subcategories (treatment and other) • Total and incremental QALYs • Total and incremental LYs • ICER	• Total and incremental costs with subcategories (treatment and other) • Total and incremental QALYs • Total and incremental LYs • ICER	Consistent with NICE modelling guidance.[85]
Discounting	3.5% per annum; applied to costs and benefits (QALYs)	3.5% per annum; applied to costs and benefits (QALYs)	Consistent with NICE modelling guidance.[85]
WTP threshold	£20,000 - £30,000 per QALY gained	£20,000 - £30,000 per QALY gained	Consistent with NICE modelling guidance.[85]
Societal perspective	Not included in base case	Not included in base case	Consistent with NICE modelling guidance.[85]

Abbreviations: BSC, best supportive care; ICER, incremental cost-effectiveness ratio; ITC, indirect treatment comparison; LY, life year; NHS, National Health Service; NICE, National Institute of Health and Care Excellence; PSS, Personal Social Services; QALYs, quality-adjusted life-years; SNRI, serotonin and norepinephrine reuptake inhibitors; SSRI, selective serotonin reuptake inhibitors; TA, technology appraisal; TCI, topical calcineurin inhibitors; TCS, topical corticosteroids; WTP, willingness-to-pay; UK, United Kingdom.

B.3.2.5. Intervention technology and comparators

B.3.2.5.1. Intervention

The intervention in the economic analysis was nemolizumab administered Q4W via subcutaneous injection using a pre-filled pen-injector.[86] Nemolizumab was administered with BSC, which included topical emollients, TCSs, TCIs and antihistamines. The treatments used as part of BSC were validated by UK clinical experts in a modified Delphi exercise.[4] For ease, nemolizumab with BSC will be referred to as nemolizumab throughout the remainder of the document. When patients discontinued nemolizumab treatment, they received subsequent BSC alone until death, which consisted of topical emollients, TCSs, TCIs, antihistamines, systemic corticosteroids and immunosuppressants.

In line with the anticipated marketing authorisation and the OLYMPIA 1 and 2 clinical trials,[1,2] the maintenance dose of nemolizumab in the economic analysis was dependent on the patient's weight. Therefore, to calculate the cost of nemolizumab treatment in the economic analysis, it was assumed that 30% of patients were ≥ 90 kg and thus, received 60 mg Q4W dose, and that 70% of patients were < 90 kg and received a 60 mg loading dose followed by 30 mg Q4W. This assumption was based on the patient population included in the OLYMPIA 1 and OLYMPIA 2 clinical trials.

B.3.2.5.2. Comparator

Nemolizumab was compared against BSC alone in the economic analysis, which included topical emollients, TCSs, TCIs, antihistamines, systemic corticosteroids and immunosuppressants. The treatments included as BSC in the economic analysis were validated by UK clinical experts in the modified Delphi exercise.[4] Patients in the comparator arm remained on BSC alone until death.

B.3.3. Clinical parameters and variables

B.3.3.1. Response rate at Week 16

The primary treatment outcome evaluated in the model was treatment response at Week 16, defined by the composite endpoint of an improvement of ≥ 4 PP NRS and IGA success (defined as a score of 0 or 1) with an improvement of ≥ 2 points. The use of the composite endpoint to assess response was validated by UK clinical experts and was considered to represent current UK clinical practice for patients with moderate to severe PN.[5] Furthermore, the Committee in TA955 concluded that the use of a composite endpoint assessing the reduction in both itch and the number of nodules to measure response as being suitable for decision making. An alternative measure of response was explored in scenario analysis using PP NRS alone.

The treatment response data at Week 16 for both nemolizumab and BSC were sourced from the nemolizumab and placebo arms, respectively, of the OLYMPIA 1 and OLYMPIA 2 clinical trials.[1,2] The response probabilities at Week 16 were calculated based on the patient-level data (PLD) and are presented in Table 35. To calculate the response rate for each treatment, the efficacy dataset from the clinical trials was filtered to only investigate those who were randomised to receive either nemolizumab or placebo. As discussed in Section B.2.9 and B.2.12.2, an ITC was not considered feasible or appropriate based on the lack of RCT evidence available for the off-label treatments included as part of BSC in moderate to severe PN. Therefore, the nemolizumab and placebo arms of the OLYMPIA 1 and 2 trials are considered the most appropriate clinical evidence for nemolizumab and BSC, respectively, to support the economic analysis.

Response was determined by evaluating both changes in PP NRS and IGA success at 16 weeks from the index date for each patient. If patients received rescue therapies prior to Week 16, they were automatically classified as non-responders. From the final total patient population in each arm, the rate was calculated as the proportion of patients who responded at Week 16 (Table 35).[1,2] To calculate the response rate for each treatment, the efficacy dataset from the clinical trials were filtered to investigate only those who were randomised to receive nemolizumab or placebo.

$$Response\ rate = \frac{Number\ of\ responders}{Number\ of\ randomised\ patients}$$

Table 35. Response rate at Week 16 for nemolizumab and BSC alone

Response	Nemolizumab	BSC	Source
PP NRS + IGA	[redacted]	[redacted]	OLYMPIA 1 and OLYMPIA 2[1,2]

Abbreviations: BSC, best supportive care; IGA, Investigator Global Assessment

B.3.3.2. Treatment discontinuation

Conditional discontinuation at Week 52 for the nemolizumab arm was calculated based on PLD from the OLYMPIA LTE trial (Table 36). The probability is based on the proportion of patients who responded to nemolizumab at Week 16 but withdrew from treatment at Week 52.[74]

To accurately calculate the long-term conditional discontinuation for nemolizumab from the OLYMPIA LTE study, patients in the study that were not from the lead-in trials (OLYMPIA 1 and OLYMPIA 2) were removed from analysis. Of the remaining patients, all received nemolizumab except for two who had no treatment listed and were removed from the final analysis. The time between the last dose from the lead-in trials and the start of the LTE study was also considered, and for those who this time was > 12 weeks were removed from final analysis.

Time on treatment was calculated using the lead-in study treatment start date alongside the analysis visits dates available in the LTE data. By calculating time on treatment, patient responses could be consistently assessed at key time points (Week 52 based on the data that was available) for the time that treatment was received. Once time on treatment from the start of each patient's lead-in trial date was considered, as well as time between the last dose from the lead-in trial and the first dose in the LTE study, patients were then evaluated to see if they were recorded as discontinuing treatment.

Conditional discontinuation at Week 52 for the BSC arm was calculated based on PLD from the placebo arms of the OLYMPIA 1 and 2 clinical trials (Table 36). The probability is based on the proportion of patients who responded to placebo at Week

16 but withdrew from treatment at Week 24 (the latest available time point).[1,2] Due to the lack of longer term data, discontinuation rates for placebo at Week 24 was considered the best available evidence for conditional discontinuation at Week 52.

Due to a lack of long-term (from year two onward) treatment discontinuation data available for nemolizumab or BSC, it was assumed that discontinuation values at Week 52 were applicable for long-term discontinuation in year 2 onwards (Table 36). This assumption was considered appropriate based on the evidence available and was validated by UK clinical experts.[5]

Table 36. Treatment discontinuation at Week 52 and year 2 onwards

Treatment	Discontinuation at Week 52 and year 2 onwards	Source
Nemolizumab	[redacted]	OLYMPIA LTE[3]
BSC	[redacted]	OLYMPIA 1 and OLYMPIA 2[1,2]

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

B.3.3.3. Treatment effect waning

The approach for modelling the waning of treatment effect was based on the approach used in TA955.[80] An alternative assumption considering no treatment effect waning was explored in a scenario analysis. The treatment effect waning values are presented in Table 37 and were validated by UK clinical experts.[5]

Table 37. Loss of response to treatment

Treatment	Loss of response to treatment (%)				Source
	Year 2	Year 3	Year 4	Year 5 onwards	
Nemolizumab	2.8%	8.6%	9.1%	9.1%	TA955[80]
BSC	25.0%	50.0%	75.0%	100.0%	

Abbreviations: BSC, best supportive care.

B.3.3.4. Mortality

PN has a significant impact on patients' QoL and mental health.[14] It has been reported that 57% of patients with PN experienced depression due to their disease[30] and that 18.5% of patients with PN experienced suicidal ideations.[15] Patients with PN in England have been shown to have increased mortality compared with matched

controls.[49] Therefore, the increased mortality for patients with moderate to severe PN compared with the general population is included in the base-case economic analysis based on CPRD data analysis.[49]

The exclusion of increased mortality rates for patients with moderate to severe PN has been explored in a scenario analysis through assuming mortality rates that mirrored those of the general population. In this scenario, to estimate age-adjusted all-cause mortality, English-specific life tables from the Office for National Statistics were used.[87]

B.3.3.5. Treatment-related adverse events

Adverse events that occurred in at least 1% of patients in any treatment arm were included in the model, which includes AD, eczema nummular and neurodermatitis. The safety profiles of nemolizumab and BSC were assessed based on the rate of TRAEs at Week 16 in the nemolizumab and placebo arms of the OLYMPIA 1 clinical trial. These values were recalculated to obtain annual rates for use in the economic analysis (Table 38). The simplifying assumption was made to base the rates of TRAEs on the OLYMPIA 1 clinical trial. This assumption was explored in a scenario analysis, where rate of TRAEs were based on the OLYMPIA 2 clinical trial.

Table 38. TRAEs rates at Week 16

Treatment	Nemolizumab	BSC	Source
AD	1.07%	0.73%	OLYMPIA 1[1]
Eczema nummular	2.10%	0.00%	
Neurodermatitis	1.10%	1.40%	

Abbreviations: AD, atopic dermatitis; BSC, best supportive care; TRAE, treatment related adverse event.

B.3.3.6. Role of clinical experts

During this submission, UK clinical experts were consulted extensively to ensure that any assumptions made aligned with UK clinical practice, especially during the development of the economic model. The main consultation process was a modified Delphi panel exercise held in June 2024.[4] This consisted of a survey that included 27 statements regarding current treatments for PN aiming to determine a consensus among clinicians from the UK and Canada. To inform the NICE submission, results

were stratified by UK and Canadian experts to ensure that any consensus reached was applicable to the UK. Participants were selected due to their expertise in treating PN within a UK clinical setting.

In addition, two rounds of follow up interviews were held with one clinical expert and one health economist from the UK.[5] These interviews confirmed the findings of the Delphi panel exercise and how they influenced assumptions made in the economic modelling.

B.3.4. Measurement and valuation of health effects

B.3.4.1. Health-related quality-of-life data from clinical trials

In line with the NICE reference case, utility values used in the cost-effectiveness analysis are based on HRQoL measurements collected using the EQ-5D-3L instrument in the OLYMPIA 1 and OLYMPIA 2 clinical trials. The LTE study was not used in HRQoL assessment as utility estimates at Week 56 and Week 104 were not feasible based on low patient numbers.[74] Utility values at baseline for the whole cohort and at Week 16 for responders were estimated based on data from these clinical trials.

Individual patient questionnaires contained responses for the five reported EQ-5D-3L dimensions of HRQoL, comprising mobility, self-care, usual activities, pain/discomfort, anxiety/depression, and the VAS.

The EQ-5D-3L instrument has two components. The first is the assessment of five separate health state dimensions by asking the patient to agree with one of three statements about that dimension (Table 39). The second is the single-dimension assessment of general wellbeing on a scale of 0–100 (the VAS). Whilst neither assessment is entirely independent of the preferences of the population being assessed, the VAS is considered unanchored to the preferences of the general population and so is not intended to generalise, particularly between populations. It is used to support the assessments of the EQ-5D-3L instrument, particularly with respect to perception of changing QoL.

Table 39. EQ-5D-3L dimensions

Dimension	Scoring
Mobility	1 = I have no problems in walking about 2 = I have some problems in walking about 3 = I am confined to bed
Self-care	1 = I have no problems with self-care 2 = I have some problems washing or dressing myself 3 = I am unable to wash or dress myself
Usual activities	1 = I have no problems with performing my usual activities 2 = I have some problems with performing my usual activities 3 = I am unable to perform my usual activities
Pain/discomfort	1 = I have no pain or discomfort 2 = I have moderate pain or discomfort 3 = I have extreme pain or discomfort
Anxiety/depression	1 = I am not anxious or depressed 2 = I am moderately anxious or depressed 3 = I am extremely anxious or depressed

Abbreviations: EQ-5D-3L, EuroQol 5-dimensions 3-level

For each complete questionnaire, an index was derived from the five dimensions of the EQ-5D-3L health profile data to provide a single preference score of the self-assessed health states that would be representative of the preference of a patient in the UK population reporting to the same health states. This index was as determined by Dolan, 1997[88] using the time-trade-off method. The disutilities derived from the Dolan formula were subtracted from a baseline utility of 1 to give an index in the range of -0.595 to 1, where 1 represents perfect QoL, 0 represents no preference for further survival, and values < 0 represent a negative preference for further survival.

For questionnaires where any dimension was scored ≥ 2, the disutility values were > 0 and were determined by the following formula (variable names and associated coefficient values in Table 40):

$$disutility = \alpha + \beta_1 M_O + \beta_2 S_C + \beta_3 U_A + \beta_4 P_D + \beta_5 A_D + \beta_6 M_2 + \beta_7 S_2 + \beta_8 U_2 + \beta_9 P_2 + \beta_{10} A_2 + \beta_{11} N_3$$

Table 40. Values of variables for disutility formula

Variable name	Variable	Associated coefficient	Coefficient Value
-	-	α	0.081
M_O	1 if Mobility = 2 2 if Mobility = 3	β_1	0.069
S_c	1 if Self-care = 2 2 if Self-care = 3	β_2	0.104
U_A	1 if Usual Activities = 2 2 if Usual Activities = 3	β_3	0.036
P_D	1 if Pain/Discomfort = 2 2 if Pain/Discomfort = 3	β_4	0.123
A_D	1 if Anxiety/Depression = 2 2 if Anxiety/Depression = 3	β_5	0.071
M_2	1 if Mobility = 3	β_6	0.176
S_2	1 if Self-care = 3	β_7	0.006
U_2	1 if Usual Activities = 3	β_8	0.022
P_2	1 if Pain/Discomfort = 3	β_9	0.140
A_2	1 if Anxiety/Depression = 3	β_{10}	0.094
N_3	1 if any score = 3	β_{11}	0.269

B.3.4.2. Health-related quality-of-life studies

A SLR was conducted to identify published studies on HRQoL for the analysed population. Database searches were initially conducted on 25 September 2023 and subsequently updated on 17 May 2024. In total 22 studies from 31 publications met the eligibility criteria and were included in this review. Full details of the reviews, including the PRISMA diagrams and description of all relevant studies informing the model are given in Appendix H.

B.3.4.3. Health-related quality-of-life data used in the cost-effectiveness analysis

QALYs were evaluated in the model using health-state specific utility values. An additive approach was used to account for utility decrease due to transient events.

Utility values were estimated from the OLYMPIA 1 and OLYMPIA 2 clinical trials based on utility data at baseline for the full cohort, and utility data at Week 16 for

responders in the nemolizumab arm.[1,2] It was assumed that the long-term utility values were based on the OLYMPIA 1 and 2 clinical trials and not the LTE trial as utility estimates from the LTE at Week 56 and Week 104 were not feasible due to low patient numbers.[74] Therefore, the utility values for responders to nemolizumab at Week 16 in the OLYMPIA 1 and 2 clinical trials were considered the best available evidence for the utility value for responders at year 1 in the economic analysis.

For the first 8 weeks of the treatment, all patients were assumed to have the baseline utility based on the baseline utility data from the full cohort of the OLYMPIA 1 and 2 clinical trials.[1,2] This accounts for the delay in the occurrence of clinical effects after treatment initiation. After 8 weeks, utility values were based on response to treatment and time since treatment initiation. It was assumed that utility values for responders were not treatment-specific based the Committee's preferred assumption in TA955 and input from UK clinical experts.[5]

In both treatment arms, all patients who respond to treatment at Week 16 were assumed to have utility based on responders at Week 16 in the nemolizumab arms of the OLYMPIA 1 and 2 clinical trials (Table 40). These utility values were applied for the first year of the analysis (Week 9–52).

Results from the nemolizumab AD LTE study[89] demonstrated that utility values for responders to nemolizumab treatment increase over time. In the absence of long-term utility data for nemolizumab in patients with PN, it was assumed that the utility values for responders would increase by 5% in Year 2 and this increase will be sustained in Year 3 onwards based on data from the AD LTE study.[89] It was conservatively assumed that the increase would be applied to both the nemolizumab and BSC arms. This observation has been validated by UK clinical experts who confirmed that, in patients with PN, itch relief is observed shortly after treatment initiation, but it will take more time (approximately 1 year) for the skin lesions to heal.[5]

Patients who do not respond to BSC at Week 16 or go on to lose response through discontinuation or treatment effect waning were assumed to have the baseline utility value until death. Patients who do not respond to nemolizumab at Week 16 or go on to lose response through discontinuation or treatment effect waning were assumed

to have utility equal to responders for 6 months, after which their utility returned to the baseline value. This assumption is in line with the approach used in TA955,[7] which was included to account for partial responders to treatment at Week 16.

Table 41. Utilities by response status used in the cost-effectiveness model, based on OLYMPIA 1 and OLYMPIA 2 trials[1,2]

Parameter	Nemolizumab (SE)	BSC (SE)
Baseline	0.579 (0.013)	
Responders		
Responder year 1 (Week 9–52)	0.922 (0.015)	
Responder year 2	0.968 (0.016)	
Responder year 3+	0.968 (0.016)	
Non-responder		
Non-responder year 1	0.751 (0.075)	0.579 (0.013)
Non-responder year 2	0.579 (0.013)	
Non-responder year 3+	0.579 (0.013)	

Abbreviations: BSC, best supportive care; SE, standard error.

QoL decreases due to aging are represented through a utility multiplier being applied to health state utility values. This multiplier is calculated as the ratio of the general population utility at various ages and the general population utility at the age of model entry (0.8448 at age 55). General population utility was estimated based on the formula from the publication by Ara and Brazier, 2010.[90]

B.3.4.3.1. Transient events

In the economic analysis, the impact of TRAEs on QoL were not included in the base-case analysis and were explored in a scenario analysis via an event-related utility decrement (Table 41). This assumption was considered appropriate as the utility values obtained from the OLYMPIA 1 and OLYMPIA 2 clinical trial data would sufficiently capture the impact of TRAEs on QoL. Furthermore, this assumption is aligned with assumptions used in TA955.[80]

The approach for modelling the proportion of patients that receive the event-related utility decrement is discussed in Section B.3.3.5 and is conditional on receipt of

treatment and the modelled incidence of each event in each cycle. Event utility decrements were identified within the literature review and any data gaps were supplemented by UK clinical expert opinion.[5] Event-related utility decrements were applied to health state utilities additively. The duration of each event was assumed to be 14 days based on input from UK clinical experts,[5] which was used to calculate QALY loss for each TRAE (Table 42).

Table 42. TRAEs disutility

TRAE	Disutility value	Source/ assumptions
AD	0.015	Equal to 'psoriasis-like disorders,' Sullivan et al.[91]
Eczema nummular	0.015	Equal to 'psoriasis-like disorders,' Sullivan et al.[91]
Neurodermatitis	0.015	Equal to 'psoriasis-like disorders,' Sullivan et al.[91]

Abbreviations: AD, atopic dermatitis; TRAE, treatment related adverse event

B.3.5. Cost and healthcare resource use identification, measurement and valuation

An SLR was conducted to identify direct costs and healthcare resource use related to the management of moderate to severe PN. Database searches were initially conducted on 25 September 2023 and subsequently updated on 17 May 2024. In total 26 studies from 27 publications met the eligibility criteria and were included in this review. Full details of the review, including a description of all relevant studies informing the model, are given in Appendix I.

All costs were sourced from national databases and literature and were inflated to the present values. Where necessary and where available, appropriate proxy data was used to fill data gaps. Health care resource use was informed by TA955.[7] These inputs were validated by UK clinicians to ensure the most appropriate values were used.

B.3.5.1. Intervention and comparator costs and resource use

B.3.5.1.1. Drug acquisition costs

Costs were accounted for from a UK healthcare payer perspective. All costs were reported as 2023 pounds sterling (GBP). Unit costs of each drug were obtained from the British National Formulary (BNF).[92]

Nemolizumab costs

The dose of nemolizumab in the economic analysis is aligned with the anticipated marketing authorisation and the dosing used in the OLYMPIA 1 and 2 trials.[1,2] A loading dose of 60 mg of nemolizumab is included followed by a maintenance dose of 30 mg or 60 mg Q4W dependent on the patients weight. Patients weighing < 90 kg at baseline receive a Q4W nemolizumab maintenance dose of 30 mg, while those weighing ≥ 90 kg at baseline receive a maintenance dose of 60 mg until treatment discontinuation or death. In the economic analysis, it was assumed that 30% of patients weighed ≥ 90 kg based on the proportion of patients that were ≥ 90 kg at baseline in the OLYMPIA 1 and 2 clinical trials. Therefore, a weighted average dose of nemolizumab was calculated, assuming 70% of patients received a 30 mg maintenance dose and 30% of patients received a 60 mg maintenance dose.

The list price for nemolizumab is [redacted] per 30mg unit. The cost of nemolizumab with the patient access scheme (PAS) is presented in Table 43.

Table 43. Nemolizumab treatment costs with PAS

Parameter	Cost per unit	Units per week	Cost per week	Cost per cycle (annual)
60mg loading dose (one off cost)	[redacted]	2.00	[redacted]	[redacted]
Maintenance dose 30 mg	[redacted]	0.25	[redacted]	[redacted]
Maintenance dose 60 mg	[redacted]	0.50	[redacted]	[redacted]
Maintenance dose – weighted average*	[redacted]	-	[redacted]	[redacted]

* It was assumed that 30% of patients weighed 90 kg or above based on the OLYMPIA 1 and OLYMPIA 2 clinical trials[1,2]

Abbreviations: PAS, patient access scheme

BSC costs

The type, number of, and proportion of treatments considered to represent BSC in a PN prevalent cohort were determined based on UK clinical experts' input in a modified Delphi panel exercise[4] and are presented in Table 44 for both responders and non-responders. Based on the limited treatments currently available in the UK for patients with moderate to severe PN, UK clinical experts considered BSC for responders to consist of emollients, TCSs and TCIs; a minority of responders will

also receive antihistamines. As discussed in Section B.3.2.5, nemolizumab is administered in combination with BSC, therefore, BSC for responders was assumed to be equal for the nemolizumab and BSC arms.

For patients who do not respond to treatment, UK clinical experts considered BSC in UK clinical practice to consist of emollients, TCSs, TCIs, antihistamines, systemic corticosteroids and immunosuppressants. In line with the approach for responders, it was assumed that BSC for non-responders was equal for the nemolizumab and BSC arms and not dependent on prior treatment.

Table 44. BSC for responders and non-responders

Medication	Responders	Non-responders
Antihistamines	5%	30%
Emollients	100%	100%
TCS	20%	100%
Systemic corticosteroids	0%	15%
Immunosuppressants	0%	77%
TCI	30%	100%

Abbreviations: BSC, best supportive care; TCI, topical calcineurin inhibitor, TCS, topical corticosteroid.

The list of emollient products and their usage (Table 45) were based on TA955 and validated by UK clinicians,[7] with costs sourced from the BNF.[92] In line with the approach used in TA955, 250 ml or 250 g usage per week was assumed for responders, and 500 ml or 500 g for non-responders.[7] The average cost of emollient products was used.

Table 45. Cost of emollient products used in the model

Emollient	Cost per pack	Source
Aveeno cream (500 ml)	£6.47	BNF[92]
Cetraben ointment (500 ml)	£5.67	NHS indicative price, BNF[92]
Dermol cream (500 ml)	£6.63	BNF[92]
Epaderm ointment (1000 ml)	£13.01	NHS indicative price, BNF[92]
Hydromol ointment (1 kg)	£11.00	NHS indicative price; based on price per 500 g, BNF[92]
White soft paraffin 50% / Liquid paraffin 50% ointment (500 g)	£4.57	BNF[92]
Oilatum cream (1000 ml)	£10.56	Based on price per 500 ml, BNF[92]

Abbreviations: BNF, British National Formulary; NHS, National Health Service.

Resource use for the medication included in BSC is presented in Table 46. The resource use was determined based on TA955[7] and validated with UK clinical experts.[5] Unit costs of treatments used in BSC were sourced from BNF.[92]

Table 46. BSC resource use and costs

Medication	Unit cost	Responders		Non-responders		Source
		Units per week	Cost per cycle	Units per week	Cost per cycle	
Antihistamines (cetirizine)	£0.02	7.00	£8.28	7.00	£8.28	TA955,[7] BNF[92]
Emollients	-	-	£131.32	-	£262.64	TA955,[7] BNF[92]
TCSs (clobetasol 0.05% cream)	£2.69	0.25	£35.09	1.50	£210.54	TA955,[7] BNF[92]
Systemic corticosteroids (prednisolone)	£0.03	0.00	£0.00	2.50	£3.49	TA955,[7] BNF[92]
Immunosuppressants (methotrexate)	£0.06	0.00	£0.00	8.00	£24.75	TA955,[7] BNF[92]
TCIs (tacrolimus 0.1% ointment)	£34.16	0.13	£222.80	0.50	£891.21	TA955,[7] BNF[92]

Abbreviations: BNF, British National Formulary; BSC, best supportive care; TCI, topical calcineurin inhibitors; TCS, topical corticosteroids.

B.3.5.1.2. Drug administration costs

It was assumed that patients who receive nemolizumab have 30 minutes of training from a healthcare professional on subcutaneous self-administration. The costs associated with training were based on 30 minutes of patient contact with a hospital-based Band 6 nurse, which was sourced from the UK Personal Social Services Research Unit (PSSRU) 2023.[93] This training cost of £29 was implemented as a one-off cost associated with treatment in the first model cycle. After this, it was assumed that patients could successfully self-administer, therefore, no further administration costs are incurred for the remainder of the time horizon. No administration costs were assigned to BSC.

B.3.5.2. Health-state unit costs and resource use

B.3.5.2.1. Cost of disease management and monitoring

Health state costs were incurred by patients during each cycle they reside in a health state, with health state costs capturing disease management costs such as medical appointments, A&E visits, hospitalisations, or blood tests. No costs were assigned to the 'Dead' state.

A summary of annual HCRU and costs stratified by responders and non-responders is presented in Table 47; these values were sourced from TA955.[7] The HCRU values were validated by UK clinical experts[5] and updated where needed to ensure they represent clinical practice in the UK. The unit cost for each healthcare resource was sourced from NHS reference costs[94] and PSSRU 2023.[93] The unit costs are multiplied by the frequency per cycle and summed up for responders and non-responders. The costs for responders and non-responders are then applied in each cycle for the 'Maintained response' and 'No response' health states, respectively.

Table 47. HCRU and costs for responders and non-responders

Resource use	Unit cost	Resource use per cycle (annual)		Cost per cycle (annual)		Source
		Responders	Non-responders	Responders	Non-responders	
Primary care visit	£49.00	2.00	11.00	£98.00	£539.00	PSSRU: cost per 10 mins consultation, including qualifications, and direct care staff costs[93]
Dermatologist outpatient visit	£164.94	2.00	5.00	£329.89	£824.72	NHS reference costs; weighted average of consultant- and non-consultant-led, non-admitted, face-to-face attendance, follow-up visits; code WF01A[94]
Dermatology nurse visit	£29.00	1.00	2.00	£29.00	£58.00	PSSRU: Cost per hour including qualifications for hospital-based nurse, band 6[93]
Hospitalisation (inpatient; dermatology)	£1,812.40	0.01	0.04	£18.12	£72.50	NHS reference costs: weighted average of non-elective long and short stay for skin disorders without interventions with CC score 0–19+, code JD07E-JD07K[94]
Day case	£518.41	0.00	0.17	£0.00	£88.13	NHS reference costs; weighted average of day case costs for skin disorders without interventions, with CC score 0–19+, code JD07E-JD07K[94]
Full blood count	£3.00	0.00	3.00	£0.00	£9.00	NHS reference costs; haematology; code DAPS05[94]
Phototherapy	£765.00	1.00	1.20	£765.00	£918.00	NHS reference costs; Day case costs of phototherapy or photochemotherapy; code JC47Z[94]
Psychologist	£257.46	0.00	0.10	£0.00	£25.75	NHS reference costs; weighted average of consultant- and non-consultant-led non-admitted face-to face attendance, follow-up; code WF01A, 656 Clinical psychology service[94]
Total cost (per cycle)				**£1,240.01**	**£2,535.09**	

Abbreviations: CC, complexity and comorbidity; HCRU, healthcare resource utilisation; NHS, National Health Service; PSSRU, Personal Social Services Research Unit.

B.3.5.3. Transient events unit costs and resource use

The model incorporated the costs associated with TRAEs via the application of one-off event-related costs sourced from published literature for the UK which are presented in Table 48. This approach has been validated by UK clinical experts.[5]

The approach for modelling the proportion of patients that receive the TRAEs costs is discussed in Section B.3.3.5 and is conditional upon receipt of treatment and modelled incidence of each event.

Table 48. TRAEs costs

Event	Resource use	Cost per event	Source
AD	GP consultation	£49	PSSRU; cost per 10 mins consultation, including qualifications, including direct care staff costs[93]
Eczema nummular	GP consultation	£49	PSSRU; cost per 10 mins consultation, including qualifications, including direct care staff costs[93]
Neurodermatitis	GP consultation	£49	PSSRU; cost per 10 mins consultation, including qualifications, including direct care staff costs[93]

Abbreviations: AD, atopic dermatitis; GP, general practitioner; PSSRU, Personal Social Services Research Unit; TRAE, treatment-related adverse event

B.3.5.4. Indirect costs

The impact of including the societal perspective is explored in scenario analyses via the incorporation of indirect costs. In this scenario, the cost of lost productivity is estimated via the human capital approach.[95] Under the human capital approach, costs associated with loss of productivity were estimated as the product of three user-defined variables:

- The proportion of the population employed
- Average annual salary
- Number of workdays lost due to the disease, specified by response status

The employment rate was based on data from ONS[96] and the average annual salary for full time employees in UK was reported as £34,963 (as of April 2023).[96] The monthly workdays lost for both responders and non-responders were derived from the TA955[7] and validated with the UK experts (Table 49).[5]

Table 49. Productivity loss inputs for responders and non-responders

Parameter	Responders	Non-responders	Reference
Number of workdays lost per patient per cycle	11.76	53.76	TA955[7]
Employment rate (%)	75.10%		ONS 2023[96]
Average annual salary	£34,963		ONS 2023[96]

Abbreviations: ONS, Office for National Statistics.

In addition to productivity loss, sleep duration specified by response status and work impairment due to sleep disturbance was included in the indirect cost calculations. Sleep duration for responders and non-responders was estimated based on the OLYMPIA 1 and 2 clinical trials and work impairment due to sleep disturbance was obtained from Hafner et al. (2016).[1,2,97]

Table 50. Sleep duration and work impairment for responders and non-responders

Sleep duration	Responders	Non-responders	Work impairment
< 6 hours	[redacted]	[redacted]	2.36%
6–7 hours	[redacted]	[redacted]	1.47%
> 7 hours	[redacted]	[redacted]	0.00%

The total indirect costs calculated based on productivity loss and work impairment due to sleep disturbance for responders and non-responders are [redacted] and [redacted], respectively (Table 51).

Table 51. Annual indirect costs for responders and non-responders

Patients with moderate to severe PN	Annual indirect costs (£)
Annual indirect costs due to workdays lost	
Responders	£1,188
Non-responders	£5,429
Annual indirect costs due to sleep duration reduction	
Responders	[redacted]
Non-responders	[redacted]
Total annual indirect costs	
Responders	[redacted]
Non-responders	[redacted]

Abbreviations: PN, prurigo nodularis.

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 base-case analysis inputs is provided in Appendix M.

B.3.6.2. Assumptions

During the development of an economic model, assumptions are required where there is limited evidence available. Key assumptions and their justification are provided listed in Table 52.

Table 52. Key model assumptions and limitations

Aspect	Assumption	Current approach/rationale
Treatment effect waning	Treatment effect waning leads to treatment discontinuation and transition to 'No response' health state	The approach to modelling treatment effect waning was influenced by evidence from clinical practice, aligning with the Committee's preferred assumption in TA814.[98] This assumption was validated by UK clinical experts[4,5] and explored in scenario analysis.
Response rate at Week 16	Response to treatment at Week 16 was defined by composite PP NRS improvement and IGA success	The composite of PP NRS improvement and IGA success is considered the most appropriate measure of response for the base-case; the Committee in TA955 concluded that the use of the composite endpoint which assessed both reduction in itch and the number of nodules as suitable for measuring response.[80] UK clinical experts confirmed that this outcome is the most relevant in clinical practice.[5] Furthermore, the measure of response at week 16 has been explored in scenario analysis.
Long-term discontinuation	Long-term discontinuation was assumed to be equal to conditional discontinuation at Week 52	Due to the limited long-term discontinuation data available, the discontinuation rate at Week 52 was used as a proxy for long-term (year 2 onwards) discontinuation. In the absence of long-term data this was considered the most appropriate assumption.
Mortality	Increased mortality was assumed for patients with moderate to severe PN in the base case	Based on the increased mortality for patients with PN in the CPRD study,[99] increased mortality for patients with moderate to severe PN was assumed in the base-case. This assumption was explored in scenario analysis.
Non-responder utility	Utility for non-responders to BSC is equal to baseline. For non-responders to nemolizumab, utility reverts to baseline utility after six months.	It was assumed that non-responders to BSC have a utility value equal to utility baseline. In line with the assumption used in TA955,[80] it was assumed that patients who do not respond to nemolizumab at Week 16 or go onto lose response through discontinuation or treatment effect waning were assumed to have utility equal to responders for 6 months to account for partial responders to treatment, after which it returned to the baseline value
Responder utility	Utility values for responders were assumed to increase after the first year of treatment	In the absence of long-term data for nemolizumab in PN, based on data from the LTE study in AD it was assumed that the utility for responders would increase by 5% in year 2 onwards in both treatment arms.[100]. This assumption has been validated by UK clinical experts, who confirmed that in patients with PN itch relief is observed shortly after treatment initiation, but it will take more time (approximately 1 year) for the skin lesions to heal.[5]
Treatment for non-responders	BSC alone was assumed for non-responders to initial treatment	It was assumed in the economic model that after failure of initial treatment, patients move to 'No response' health state where they receive BSC alone as no other active treatments are available in UK. This assumption was validated by UK clinical experts.[4]

Abbreviations: AD, atopic dermatitis; BSC, best supportive care; CPRD, Clinical Practice Research Datalink; IGA, Investigator's Global Assessment; LTE, long-term extension; PN, prurigo nodularis; PP NRS, peak pruritus numeric rating score; UK, United Kingdom.

B.3.7. Base-case results

B.3.7.1. Base-case incremental cost-effectiveness analysis results

The base-case cost-effectiveness analysis results for nemolizumab versus BSC in patients with moderate to severe PN, are presented in Table 53. The cost-effectiveness analysis results for nemolizumab are presented with the PAS price applied.

In the base-case analysis, there was a mean incremental improvement of [redacted] discounted QALYs for nemolizumab versus BSC and a total mean incremental discounted cost of [redacted]. Therefore, the base-case ICER estimate for nemolizumab was £34,477 per QALY gained versus BSC, which is just above the WTP threshold of £30,000 per QALY gained.

The results demonstrate that nemolizumab offers improved clinical outcomes and HRQoL for patients with moderate to severe PN. Therefore, based on the significant unmet need for a targeted treatment that can address the underlying pathophysiology of PN rather than just address the symptoms of the disease, nemolizumab should be considered an appropriate use of NHS resources.

Table 53. Base-case results with PAS

	Total costs	Total LYs	Total QALYs	Incremental costs	Incremental LYs	Incremental QALYs	ICER (per QALYG)
Nemolizumab	[redacted]	24.895	[redacted]	[redacted]	0.000	[redacted]	£34,477
BSC	[redacted]	24.895	[redacted]				

Abbreviations: BSC, best supportive care; ICER, incremental cost-effectiveness ratio; LYs, life years; PAS, patient access scheme; QALYs, quality-adjusted life years; QALYG, quality-adjusted life years gained.

B.3.7.2. Base-case long-term QALY outcomes

A breakdown of the QALYs for nemolizumab and BSC from the base-case cost-effectiveness analysis is presented in Table 54.

Table 54. Base-case QALY breakdown

QALY component	Nemolizumab	BSC	Incremental
Maintained response health state	[redacted]	[redacted]	[redacted]
No response health state	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]

Abbreviations: QALY, quality adjusted life year.

B.3.7.3. Base-case long-term cost outcomes

A breakdown of the costs for nemolizumab and BSC from the base-case cost-effectiveness analysis is presented in Table 55.

Table 55. Base-case cost breakdown with PAS

Cost component	Nemolizumab	BSC	Incremental
Maintained response health state	[redacted]	[redacted]	[redacted]
No response health state	[redacted]	[redacted]	[redacted]
Disease management and monitoring	[redacted]	[redacted]	[redacted]
Adverse events	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]

Abbreviations: BSC, best supportive care; PAS, patient access scheme.

B.3.8. Sensitivity analyses

B.3.8.1. Probabilistic sensitivity analysis

In the probabilistic sensitivity analysis (PSA), the economic model samples values from distributions around the means of the input parameters. The probabilistic results are comparable to the base-case analysis and are presented in Table 56.

Scatterplots for the base case analysis, arising from 1,000 simulations of the model with all parameters sampled are presented in Figure 22 and the cost-effectiveness acceptability curves are presented in Figure 23. The PSA results show that the probability that nemolizumab is cost-effective versus BSC is [redacted] at a WTP threshold of £30,000 per QALY gained.

Table 56. PSA results with PAS

	Total costs	Total LYs	Total QALYs	Incremental costs	Incremental LYs	Incremental QALYs	ICER (per QALYG)
Nemolizumab	[redacted]	24.721	[redacted]	[redacted]	0.000	[redacted]	£34,421
BSC	[redacted]	24.721	[redacted]				

Abbreviations: BSC, best supportive care; ICER, incremental cost-effectiveness ratio; LYs, life years; PAS, patient access scheme; PSA, probabilistic sensitivity analysis; QALYs, quality-adjusted life years; QALYG, quality-adjusted life years gained.

[redacted]Figure 22. ICER scatterplot with PAS

Abbreviations: ICER, incremental cost effectiveness ratio; PAS, patient access scheme; PSA, probablistic sensitivity analysis; QALY, quality adjusted life year; WTP, willingness-to-pay.

[redacted]Figure 23. Cost-effectiveness acceptability curve with PAS

Abbreviations: PAS, patient access scheme; WTP, willingness-to-pay.

B.3.8.2. Deterministic sensitivity analysis

The deterministic sensitivity analysis (DSA) involves varying one parameter at a time and assessing the subsequent impact on the incremental costs, incremental QALYs, and ICER. Each parameter is allocated a ‘low’ value and a ‘high’ value; for all parameters apart from discount rates, the low value and high value is -/+ 20% of the mean value used in the base-case analysis and demonstrates the impact of specific parameters on ICER estimates.

The ten most influential parameters in the DSA are presented as a tornado plot in Figure 24. The results demonstrate that the parameter with the highest impact on results is the utility value for non-responders in which the ICER varied from negative values (dominated) to highly cost-effective. Overall, the results of the model economic analysis were mostly robust to parameter uncertainty.

[redacted]Figure 24. Tornado plot with PAS

Abbreviations: BSC, best supportive care; ICER, incremental cost effectiveness ratio; PAS, patient access scheme; QALY, quality adjusted life year.

B.3.8.3. Scenario analysis

A number of scenario analyses were performed, which explored the robustness of the base-case cost-effectiveness estimates to the key model assumptions and parameters. The scenario analysis results are presented in Table 57. With the

exception of the nemolizumab dose, the results of all of the scenario analyses were comparable or improved in relation to the base-case cost-effectiveness analysis. These results demonstrate that the cost-effectiveness estimates were robust to alternate model assumptions and parameters.

A scenario with a significant impact on the cost-effectiveness estimates was variation in the assumption regarding the nemolizumab dose. In the scenario where 100% of patients in the nemolizumab arm were assumed receive the < 90 kg nemolizumab dose (30mg Q4W), nemolizumab was associated with an ICER of £25,762 per QALY gained, which is below the WTP threshold of £30,000 per QALY gained. An additional scenario analysis with a significant impact on the cost-effectiveness estimates was the inclusion of the indirect costs associated with PN based on the productivity loss due to absenteeism and work impairment as a result of sleep disturbance. In this scenario, nemolizumab had an ICER of £24,652 per QALY gained versus BSC, which is also below the WTP threshold of £30,000 per QALY gained.

Table 57. Scenario analyses results with PAS

Base-case assumption	Scenario	Incremental costs	Incremental LYs	Incremental QALYs	ICER (per QALYG)
Base-case		[redacted]	0.000	[redacted]	£34,477
Response at Week 16 based on PP NRS + IGA	Response at Week 16 based on PP NRS ≥ 4	[redacted]	0.000	[redacted]	£35,044
No indirect costs included	Inclusion of indirect costs	[redacted]	0.000	[redacted]	£24,652
Disutilities due to AEs not included	Inclusion of disutilities due to AEs	[redacted]	0.000	[redacted]	£34,483
Treatment effect waning included	No treatment effect waning	[redacted]	0.000	[redacted]	£36,760
30% of patients received ≥ 90kg nemolizumab maintenance dose	100% of patients received ≥ 90kg nemolizumab maintenance dose (60mg Q4W)	[redacted]	0.000	[redacted]	£54,812
70% of patients received < 90kg nemolizumab maintenance dose	100% of patients received < 90kg nemolizumab maintenance dose (30mg Q4W)	[redacted]	0.000	[redacted]	£25,762
Increased mortality for patients with PN	No increased mortality in PN patients	[redacted]	0.000	[redacted]	£34,429
TRAE rates based on OLYMPIA 1	TRAE rates based on OLYMPIA 2	[redacted]	0.000	[redacted]	£34,493

Abbreviations: AE, adverse event; ICER, incremental cost effectiveness ratio; IGA, Investigator's Global Assessment; kg, kilogram; LY, life year; mg, milligram; PAS, patient access scheme; PN, prurigo nodularis; PP NRS, peak pruritus numerical rating scale; Q4W, every four weeks; QALY, quality adjusted life year; QALYG, quality adjusted life year gained; TRAE, treatment related adverse event.

B.3.9. Subgroup analysis

No economic subgroup analysis was conducted as part of this submission.

B.3.10. Benefits not captured in the QALY calculation

There are several potential value considerations that may not have been fully captured in the QALY calculations included in the model. The economic analyses presented in this submission are based on EQ-5D outcomes; however, it is known that the impact of relentless and severe itch is multi-faceted[101] and its impact on patient QoL is unlikely to be fully captured by EQ-5D.

Persistent itching impacts the quality and quantity of sleep that a patient gets, with > 70% of patients reporting nocturnal itch.[13,37] The itch associated with PN can lead to sleep deprivation, with 42.5% of patients with PN experiencing sleep impairment.[13] In addition, a study in patients with PN reported that 100% of patients had sleep disturbance as a result of their disease, with 29% of patients reporting disturbance to their daily life or work as a result of the sleep disturbance.[30] Poor sleep is related to depression, suicide and anxiety, which are significantly increased in patients with PN and are observed at the highest rates amongst skin diseases.[45,102] Furthermore, people affected by insomnia, and in general by sleep disturbances, have a higher level of absenteeism (full days or partial days), decreased productivity or presenteeism and as a result, a lower work performance.[103] It has been reported that patients with PN are more prone to absenteeism at work because of their disease.[34] The ramifications of nocturnal itch on sleep, mental health and absenteeism are unlikely to be captured by EQ-5D, therefore, the impact of the reduction in sleep disturbance following nemolizumab treatment (Section B.2.6.1) have not been fully accounted for in the economic analysis.

Patients with PN have also been shown to experience significant out-of-pocket costs, which have been shown to increase with disease severity, that have not been captured in the economic analysis,.[51,52] In addition to the out-of-pocket costs in PN, there are significant indirect societal costs, related to productivity loss due to sleep deprivation, absenteeism and presenteeism. The impact of indirect costs to patients with moderate to severe PN is not included in the base-case, but has been explored in scenario analysis.

Nemolizumab has a convenient treatment regimen, where once patients have completed their training, they can self-administer nemolizumab subcutaneously Q4W. Many of the off-label treatments patients currently receive require at least once daily applications or administration, with immunosuppressive treatments, such as methotrexate, requiring frequent monitoring and follow-up appointments. This additional burden to the healthcare system has not been fully captured in this economic analysis. Likewise, the improved convenience of nemolizumab to patients has not been captured in the model.

B.3.11. Validation

B.3.11.1. Validation of cost-effectiveness analysis

Following the Professional Society for Health Economics and Outcomes Research Good Research practice guidelines on model validation and transparency, the following aspects of model validation were assessed:

- Model verification – the major spreadsheet calculations and VBA subroutines were assessed for accuracy, and to ensure they operate as intended. Model parameters were reviewed against their source, to ensure that there are no transcription errors. Input derivation and implementation were reviewed, to ensure that the inputs were derived and implemented correctly. Sensitivity and extreme value analyses were conducted to ensure model output is internally consistent and that the direction and magnitude of model outputs behave as expected.
- Model face validity – the model structure, key model assumptions, and inputs have been validated by health economics and clinical experts specialising in the treatment of PN in a modified Delphi panel and two rounds of expert interviews.[4,5]
- Model cross validation – different models were identified that addressed the same problem and compared similar predicted outcomes. The model outcomes for the BSC comparator arm were validated against outcomes reported in TA955.[80]

B.3.12. Interpretation and conclusions of economic evidence

B.3.12.1. Interpretation of economic evidence

Long-term cost-effectiveness analysis was conducted using data from the OLYMPIA 1 and 2 clinical trials to compare nemolizumab versus BSC in patients with moderate to severe PN in a UK setting. The cost-effectiveness analysis showed that:

- Nemolizumab was associated with improved clinical outcomes compared with BSC based on improved QALYs. This QALY gain was driven by a greater response to treatment at Week 16 in the nemolizumab arm and patients

residing in the ‘Maintained response’ health state for longer. There was no difference in life years gained between nemolizumab and BSC as there is no measured impact of PN treatment on survival.

- Nemolizumab was associated with a greater cost than BSC, which was driven by the low treatment cost for the BSC comparator and the limited, low-cost subsequent therapies available for patients who do not respond to treatment. Despite the greater total cost of nemolizumab compared with BSC, nemolizumab was associated with a lower disease management and monitoring cost than BSC, in part driven by the greater response to treatment.
    - The increased response to nemolizumab versus the BSC comparator results in more patients remaining on nemolizumab treatment in the ‘Maintained response’ heath state rather than discontinuing to subsequent low-cost BSC alone. This greater response to treatment drives the increased costs for nemolizumab compared to BSC, which is supported by the significantly higher costs for nemolizumab versus BSC in the ‘Maintained response’ health state [redacted], respectively). It is important to note that the low-cost treatments included as part of BSC are prescribed off-label and aim to relieve symptoms, rather than address the underlying pathophysiology of the disease.
- The ICER with PAS for nemolizumab versus BSC was £34,477 per QALY gained. This ICER is slightly above the WTP threshold of £30,000 per QALY gained. Based on the significant unmet need for a targeted treatment that can address the underlying pathophysiology of PN rather than just address the symptoms of the disease, nemolizumab should be considered an appropriate use of NHS resources.

Extensive sensitivity analyses were conducted, representing a key strength of the economic analysis, which showed that the cost-effectiveness results are robust to changes in the input parameters and assumptions:

- The PSA results were comparable to the base-case deterministic results, supporting that there is limited uncertainty in the base-case cost-effectiveness estimates. Based on the PSA, the probability that nemolizumab is cost-effective versus BSC is [redacted] at a WTP threshold of £30,000 per QALY gained.

- The DSA results demonstrate that overall, the cost-effectiveness results were robust to parameter uncertainty. The input parameter with the highest impact on the cost-effectiveness results was non-responder utility.

- Scenario analysis results showed that the cost-effectiveness results were robust to changes in the data sources and model assumptions. With the exception of the nemolizumab dose, the results of all of the scenario analyses were comparable or improved in relation to the base-case cost-effectiveness result.

The nemolizumab dose used in the economic analysis had a significant impact on the cost-effectiveness of nemolizumab. As discussed in Section B.3.2.5.1, to calculate the nemolizumab treatment cost, it was assumed that in the base-case, 30% of patients received the ≥ 90 kg dose (60 mg Q4W) and 70% of patients receives the < 90 kg nemolizumab dose (30 mg Q4W). Scenario analysis where 100% of patients in the nemolizumab arm received the < 90 kg nemolizumab dose shows that the ICER decreased to £25,762 per QALY gained, which is below the WTP threshold of £30,000 per QALY gained. This result demonstrates that the increased nemolizumab dose for patients ≥ 90 kg is driving the base-case ICER above the WTP threshold of £30,000 per QALY gained and that based on the nemolizumab dose for patients with moderate to severe PN < 90 kg, nemolizumab represents a cost-effective use of NHS resources.

In addition, the inclusion of indirect costs also has a significant impact on the cost-effectiveness of nemolizumab in patients with moderate to severe PN. A study in patients with PN reported that 100% of patients had sleep disturbance as a result of their disease, with 29% of patients reporting disruption to their daily life or work as a result of the sleep disturbance.[30] Insufficient sleep has been shown to result in large economic costs, with sleep disturbance increasing work impairment due to

absenteeism and presenteeism.[97] Furthermore, patients with PN have also reported that pruritis has a negative effect on QoL and that patients with PN are more prone to absenteeism at work because of their disease.[34] Therefore, the NHS and PSS perspective alone would undervalue the benefits of nemolizumab in PN to society. This is supported by scenario analysis which showed that inclusion of indirect costs associated with PN based on the productivity loss due to absenteeism and work impairment as a result of sleep disturbance reduced the ICER to £24,652 per QALY gained, which is below the WTP threshold of £30,000 per QALY gained. This demonstrates the wider benefits of nemolizumab to society which are not captured in the base-case cost-effectiveness estimates.

B.3.12.2. Strengths and limitations of the economic evidence

The structure of the economic model used in this submission is aligned with the model structure that was considered acceptable for decision making in the NICE technology appraisal for dupilumab in PN [TA955][80] and has been further validated by UK clinical experts.[5] In addition to validating the model structure, the model inputs, assumptions, PN treatment pathway, and model results were also validated by UK health economic and clinical experts. Therefore, the economic model used in this submission is considered to accurately reflect UK clinical practice for patients with moderate to severe PN.

The economic model is primarily based on data from the OLYMPIA 1 and 2 clinical trials. These are robust Phase 3 clinical trials that provide efficacy and safety data for nemolizumab in patients with moderate to severe PN conducted in relevant European, US and UK settings. The OLYMPIA 1 and 2 clinical trial data can be considered generalisable to a UK population and to be the most appropriate evidence to support the submission and economic analysis.

A limitation of the cost-effectiveness analysis was the reliance on short-term clinical trial data, which is a common challenge in health economic modelling for new treatments. The approach to make lifelong projections based on short-term data remains one of the essential principles of health economic modelling and is a commonly used approach in the absence of long-term clinical trial data. However,

the use of nemolizumab in PN is supported by the ongoing LTE study, which provides extensive follow up data over 52-weeks.

During the construction of an economic model, it is also necessary to make some assumptions. To minimise the uncertainty related to these assumptions, extensive sensitivity and scenario analyses were conducted which demonstrated that the cost-effectiveness estimates were robust to changes in key model assumptions and input parameters. In addition, PN is a rare disease with limited data available specific to a population of patients with moderate to severe PN to support the economic model. Therefore, where appropriate, inputs and assumptions were aligned with those used in TA955.[80]

As discussed in Section B.2.9, there is no RCT evidence for the off-label systemic treatments listed as part of BSC. The limited and low-quality evidence available for the off-label systemic treatments means that an ITC would not be feasible or appropriate. Therefore, the placebo comparator arms of the OLYMPIA 1 and 2 clinical trials were considered the most appropriate evidence to model BSC in the economic analysis.

B.3.12.3. Conclusions

There are currently no treatments recommended by NICE for patients with PN in the UK. Furthermore, current treatment options included as part of BSC in the decision problem are used off-label and aim solely to relieve symptoms, rather than address the underlying pathophysiology of PN. A European cross-sectional study in patients with PN found that 56.8% of patients were not satisfied with their previous therapy, and that 9.8% did not receive any therapy despite having active disease.[13] Therefore, there is a significant unmet need for a targeted treatment option for patients with PN that will address the underlying pathophysiology of the disease.

Clinical trial data in the OLYMPIA 1 and 2 trials have shown that nemolizumab is associated with improved clinical outcomes for patients with moderate to severe PN. The cost-effectiveness analysis suggests that these short-term improvements result in improved long-term HRQoL outcomes compared with BSC. In the base-case analysis, nemolizumab was associated with an ICER of £34,477 per QALY gained

versus BSC. Based on the significant unmet need for a targeted systemic treatment that can address the underlying pathophysiology of PN, nemolizumab should be considered an appropriate use of NHS resources in England.

Comprehensive sensitivity analyses have shown that, overall, the cost-effectiveness estimates are robust to changes in the input parameters and model assumptions. However, scenario analysis demonstrated that the dose of nemolizumab used in the economic analysis has a significant impact on the cost-effectiveness estimates. Based on the nemolizumab dose for patients with moderate to severe PN weighing < 90 kg, nemolizumab represents a cost-effective use of NHS resources with an ICER below the WTP threshold of £30,000 per QALY gained. There are several additional benefits related to nemolizumab treatment that are not currently captured in the base-case cost-effectiveness analysis, including the significant indirect costs associated with PN.

Nemolizumab offers patients with moderate to severe PN a new, safe and effective treatment option that targets IL-31, a known major pruritogen.[8] Nemolizumab would be the only treatment recommended by NICE for patients with moderate to severe PN, which addresses the underlying pathophysiology of the disease rather than just addressing symptoms.

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Nemolizumab for adults with moderate to severe prurigo nodularis [ID6451]

Summary of Information for Patients (SIP)

October 2024

File name	Version	Contains confidential information	Date
[ID6451] Nemolizumab SIP 151124 [noCON]	V2.0	No	15/11/24

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's a plain English summary of their submission written for patients participating in the evaluation. It's 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's 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

Both generic and brand name.

Nemolizumab (Nemluvio®)

1b) Population this treatment will be used by

Please outline the main patient population that is being appraised by NICE:

Nemolizumab will be used by patients aged 18 years or older who have been diagnosed with moderate-to-severe prurigo nodularis (PN).

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.

A marketing authorisation application was submitted via Access Consortium NASWSI for nemolizumab for the treatment of PN on 18 March 2024. An opinion from the UK Medicines and Healthcare Products Regulatory Agency (MHRA), the organisation that gives companies legal permission to sell a medicine in the UK, is expected. Additonal detail on the marketing authorisation is presented in Section B.1.1. of the main company submission.

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:

There are no collaborations or conflicts of interest that require disclosure.

Note, for transparency, Galderma work with patient groups and healthcare professionals in a variety of ways, including, as examples, global awareness campaigns and training/education programmes.

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.

What is PN?

PN is a rare skin condition,[1,2] defined by the presence of nodules on the skin (i.e., small lumps, caused by abnormal growth of skin tissue just below the surface layer of the skin that may feel hard to touch), an intense itch,[3,4] and a constant urge to scratch the skin, which can often be painful.[5] The itch experienced by patients is often relentless and affects various aspects of a patient's life, including both a physical and emotional burden.[6] There is a major impact on the quantity and quality of sleep,[7,8] which affects patients' day-to-day activities, their work and/or education and their home life.[9]

The number of lesions or nodules on the skin varies between patients. They may also be different sizes (from a few millimetres to a few centimetres) and colours (from natural skin colour, to pink, red, brown and black).[4,10,11] These lesions typically appear symmetrically in what is referred to as the 'butterfly' sign. They appear on the arms and legs, as well as the torso in areas that are reachable and can be scratched, meaning that few, if any, lesions are found on the centre of the back.[4,5,12] The palms of the hands, soles of the feet, scalp and genitals are also unlikely to have lesions.[4,13]

The underlying cause of PN is not completely understood. Studies suggest that PN is caused by a mix of chemical signals related to inflammation, and itch-causing molecules. These lead to inflammation and problems with sensation through the activation of immune cells.[14] One of these chemical signals is called interleukin-31 (IL-31), which is produced by cells in the body's immune system.[13,15] Patients with PN produce up to 50-times more of this substance than those not affected by the condition.[16] IL-31 causes itching and has a major role in the communication between the skin and the nervous system.[17,18] This itch results in patients scratching the skin, which forms part of a cycle of itching and scratching that aggravates and sustains PN.[19]

How many people are living with PN in the UK?

It is estimated that PN affects 3.27 out of every 10,000 people (0.0327%) in England.[20] While the condition can affect people of any age, it is more common in those aged over 50 years, women and those of an Afro-Caribbean background.[4,21,22]

How does PN affect patients and their families?

- **Chronic (long-lasting) itch:** The primary symptom associated with PN, which is reported by 100% of patients, is an intense, long-lasting itch.[23] PN

is associated with what is known as an 'itch-scratch cycle', where a cycle of itching and scratching can make the symptoms of PN worse, so as the itch worsens so does the scratching, which in turn causes more itching and so on.[19]

- **Sleep disruption:** Because of the chronic itch experienced by patients with PN, which is often more prominent in the evening,[13,37] patients often experience significant disruption to their sleep, which can impact their mood and wellbeing,[6] day-to-day activities, days lost from work or education, and limited working capacity when attending work or education.[24]
- **Decreased quality of life:** PN is associated with a significant reduction in quality of life (QoL) compared with the normal population, and those with other skin conditions. Itch is seen as a key driver on the impact on QoL, especially nocturnal itch, which is strongly associated with sleep disturbance.[7,25]
- **Self-esteem:** The lesions associated with PN can affect a patient's self-esteem, and impact day-to-day things like their choice of clothing.[12] The lesions can also cause relationship issues, with patients reporting that the appearance of their skin has lead them to avoiding social interactions and caused issues in romantic relationships.[6,24] Constant itching paired with these lesions/nodules can result in bleeding, which can cause further discomfort, pain and emotional distress.[6,24]
- **Burdensome treatment schedule:** Patients often apply creams, lotions, and ointments throughout the day, in an attempt to reduce itch and clear the lesions/nodules. This can cause frustration and/or side effects due to the frequent nature of these applications, as well as the sometimes unpleasant feeling these treatments have on the skin, and the possibility to stain clothes following application.[12]
- **Absence from work/education:** As their symptoms worsen, patients are more likely to seek the advice of healthcare professionals. This impacts their ability to work, and can also lead to costs through travel to and from healthcare centres, loss of wages through missed work days, and further costs if private specialist care is sought.[26]
- **Co-morbidities:** Many patients experience other conditions alongside PN (such as kidney diseases, diabetes, stroke and/or heart attacks, and human immunodeficiency virus (HIV), and mental health conditions such as depression and/or anxiety)[21,27,28] which have been shown to impact life expectancy. The relationship between PN and these conditions is not fully understood, but they have been shown to be more common in patients with PN than in populations who do not have the condition.

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?

There are no new diagnostic tests required for the treatment of PN using nemolizumab.

The diagnosis of PN is based upon assessments by a doctor or skin care specialist, with cases confirmed following complaints of long-term intense itching (6+ weeks) and flesh-coloured lesions on the skin, most commonly on the arms, legs and/or torso.[5,12,29] Itching is generally reported first by patients,[5] followed by the development and presence of lesions on the skin. However, patients may also describe burning, stinging, and/or pain among other sensations.[5] A skin sample may also be used to confirm a diagnosis in the laboratory.[12]

Patients may also describe an emotional impact, including loss of sleep, obsessive or compulsive behaviours, and feelings such as sadness, shame, disgust, helplessness, or anger.[12]

The severity of PN can be determined using different scales:

- The **Investigator's Global Assessment** (IGA) Scale is a 5-point scale used by the Investigator or healthcare professional to evaluate the disease severity of PN, according to the estimated number of pruriginous lesions

Score	Category	Description
0	Clear	No nodules
1	Almost clear	Rare palpable pruriginous nodules
2	Mild	Few palpable pruriginous nodules
3	Moderate	Many palpable pruriginous nodules
4	Severe	Abundant palpable pruriginous nodules

- The **Peak Pruritus Numeric Rating Scale (PP-NRS)** is a scale used by patients to report the maximum intensity of their itch during the last 24 hours to evaluate the severity of a patient's itch. The scale requests a score on an 11-point scale (0 to 10), where 0 is "no itch" and 10 is the "worst itch imaginable." The question asked to patients is "On a scale of 0 to 10, with 0 being "no itch" and 10 being the "worst itch imaginable," how would you rate your itch at the worst moment during the previous 24 hours?"[25]

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.

Current treatments

The aims when treating PN are to reduce itching and prevent scratching to allow lesions on the skin to heal, which should also improve quality of sleep.[24,30]

Current treatment options are limited, with very few guidelines informing treatment decisions for patients with PN. The International Forum for the Study of Itch (IFSI) guidelines were the first international guidelines to provide recommendations for the treatment of PN.[11] All treatments currently used to manage PN in UK clinical practice are used 'off-label,'[31] meaning that they have not been specifically approved for use in patients with PN, and only aim to provide relief from the symptoms of PN, rather than targeting the underlying cause of the condition.

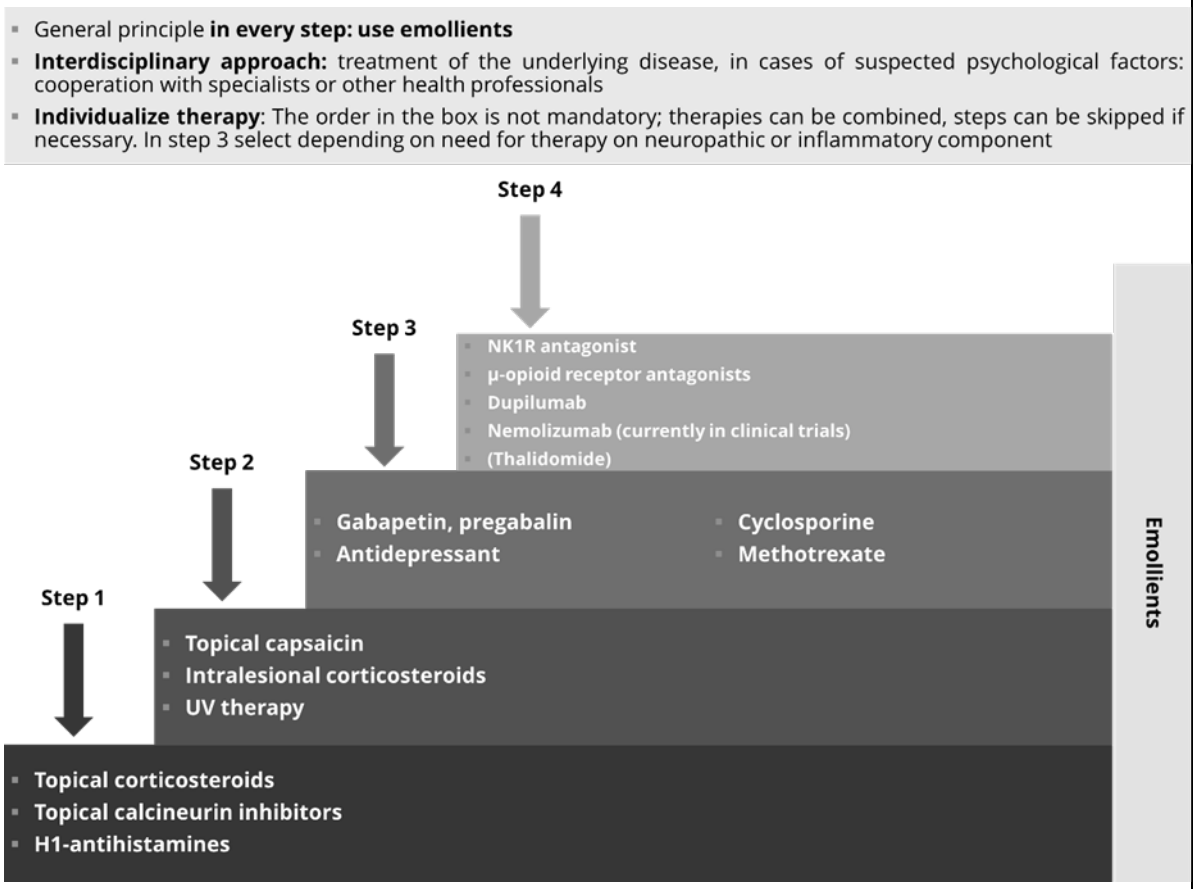
Current treatments used to manage PN include those applied directly to the skin, (including moisturising creams, topical corticosteroids, topical calcineurin inhibitors, and topical capsaicin),[18,32,33] tablets taken by mouth (such as antihistamines, steroids, neuropathic painkillers, anaesthetics, immunosuppressants),[18,34] and other supporting therapies which may include antidepressants and anti-anxiety medications.[18,33] Corticosteroids can alternatively be injected directly into the lesions themselves; however, this is restricted to patients with low numbers of nodules due to side effects this can cause, and the pain associated with repeated injections into the lesions over a number of sessions.[18,31]

UK clinical experts have validated that best supportive care (BSC; i.e., treatment that is focused on managing symptoms, but does not cure or treat the condition itself) is considered to consist of moisturising creams, topical corticosteroids, topical calcineurin inhibitors.[35] Following these treatments, significant variation exists in the subsequent treatments recommended.[35]

Treatment decisions are typically based on the judgement of a doctor or skin care specialist, rather than a strict step-by-step approach which is more common in

other skin conditions. The IFSI have published a stepwise treatment plan which forms the basis of most clinical decisions in the management of PN (**Figure 1**).[11]

Figure 1. IFSI stepwise treatment recommendations



Abbreviations: IFSI, International Forum for the Study of Itch; NK1R, neurokinin-1 receptor; UV, ultraviolet.

Nemolizumab

It is anticipated that nemolizumab will be used by patients aged 18 years or older who have been diagnosed with moderate to severe PN (i.e., patients with ≥ 20 lesions). Nemolizumab will be used with existing topical treatments, which can include topical emollients, topical corticosteroids, and topical calcineurin inhibitors.

Nemolizumab will fulfil a significant unmet need for patients with moderate-to-severe PN. Unlike the currently available 'off-label' treatments used to treat PN in clinical practice in England, nemolizumab will act by treating the underlying cause of the disease, rather than aiming solely to relieve the symptoms of the condition.

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.

The impact of PN on patients can present in a variety of ways, and often depends on the main symptoms, and the patient's life situation and experiences. Itch is often the first and most prominent symptom experienced, followed by the disruption of sleep; both symptoms can directly impact a patient's mood and QoL in several ways. Several studies have investigated how patients' lives are affected by PN.[23] The personal burden of PN has been investigated in two studies which interviewed patients with PN about their experience with the condition; one study recruited 21 patients[24] while the other recruited 10.[36]

The constant and often intense itch experienced by patients frequently leads to feelings of irritability and can cause wider health related anxiety in patients.[24,36] The need for regular application of treatments to the skin and attendance of medical appointments has also been described as '*burdensome*.'[36] In one study, all patients reported itching, pain related to PN, bleeding or scabbing, and dry skin (n = 21). Itching was the worst, or one of the worst symptoms for 15 of the 17 participants who indicated which symptoms was seen as being the worst (88%).[24]

> *"I had always thought of myself as a perfectly healthy person. I always regarded myself as almost – typical of men, maybe – as almost invulnerable"*[36]
>
> *"I have severe itching and then the sores sometimes or the bumps, they will break open or I itch 'em open and they bleed, and they hurt—like, my clothes will rub on them and they're painful."*[24]
>
> *"When I feel an episode coming, I already know: Then I become quiet, then I want to be left alone."*[36]
>
> Participants described their itching using the terms *'uncontrollable'*, *'constant'*, *'very severe'*, *'so intense'*, or *'extreme'*[24]

Disturbance in sleep due to constant itching also greatly impacts how a patient feels, with many reporting difficulties in falling asleep (90%), nighttime awakenings (90%) and overall poor quality of sleep (90%).[24] This poor sleep has knock-on effects to the following day, with feelings of being tired or exhausted (52%), disturbances to daily life and work (29%), the need to nap throughout the day if

possible (14%), and a negative impact on overall mood as well as social life (5%, each).[24]

> *"I wake up 3 or 4 times a night even when I take sleeping aids. A lot of times I'm waking up scratching, or I'll wake up and my pillow's all bloody, or my bed sheets have blood on them."*[24]

> *"Sleep is poorly at night, as I wake up at 3 or 4 am and there is an incredible itch."*[36]

The presence of lesions on the skin can greatly impact a patient's self-esteem and cause them to choose clothing based on its ability to cover these (59%), often regardless of the weather (29%).[24] In summer, patients may opt to wear trousers or jeans to cover lesions on the legs, which themselves can cause distress due to the rubbing or scratching of lesions by these clothes,[24] which further stresses the skin and the symptoms they experience. Another consideration patients make when choosing their outfits is the colour of their clothing, often opting for darker colours and longer sleeves which may disguise stains that come from the bleeding of lesions following scratching.[36] Light coloured clothing offers the benefit of less heat retention, however, it runs the risk of blood stains being noticeable. Some patients' self-esteem stems from the way the lesions are perceived by others, with some patients stating that others around them fear the condition is contagious, causing further emotional distress and feelings of shame.[24]

> *"When I arrive at home, the fingernails are bloodstained, the skin is bleeding, the car is bloodstained, the clothes are bloodstained"*[36]

> *"'It is always in the back of my mind so that even when it is 40 or 35 degrees outside, I am always wearing jeans and long pants and even a long-sleeved T-shirt. I am always conscious of that."*[36]

Patients reported on the impact of the condition on their relationships, both socially and romantically, claiming that the condition is a major cause of problems.[24,36] Some patients described being asked inappropriate questions relating to their condition and the presence of lesions on their skin, as well as discrimination which has led to social avoidance and isolation.[24,36] Patients often resort to declining invitations and restricting travel, which negatively impacts overall enjoyment of life.[36] Due to the self-esteem impact of visible lesions, patients have reported avoiding intimacy.[36]

> *"can't wear short sleeves, […] don't want to be in public […] with a rash exposed, because […] it's embarrassing. People think you're contagious."*[24]

> *"Some people would not take me seriously and then say things like: "You must have a psychological problem if you rip out pieces of skin.""*[36]

Day-to-day activities, from employment or school (71%), housework and gardening (29%), leisure (33%) and exercise (38%), have been impacted by this condition.[24] Feelings of depression can stem from this inability of patients to live their lives as they would have before developing PN, with the impact on the day-to-day life of patients spanning self-care or personal hygiene (71%), planning activities (57%), and chores, housework, or gardening (29%).[24]

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.

The itch experienced by patients with PN is a result of miscommunication between the skin, the immune system, and the nervous system. A substance known as IL-31 is released by immune cells and activates receptors on nerve cells.[19] When these receptors are activated, they cause the feeling of itch in patients, which in turn causes the patient to scratch instinctively. Because of this scratching, the skin becomes inflamed which causes the release of more IL-31.[25,37]

Effective treatment must have a positive effect on both nerves and the immune cells to control the sensation of itch in patients with PN. Due to its role in the communication between these two systems, IL-31 is an ideal target to bring about itch relief in patients with PN.[25]

Currently, there are no treatments available and approved by NICE that specifically target itch, and as such nemolizumab would be the first to fulfil this unmet need following approval. Inside the body, nemolizumab binds to the IL-31 receptor so that it can no longer bind to IL-31. This blocking of the receptor stops itching in patients with PN, which in turn stops patients scratching their skin and allows lesions the time they need to heal.[38-40] Other treatments given as BSC for the management of PN, such as creams, ointments, and lotions, require frequent applications to the skin, or in the case of antihistamines tablets or solutions should be taken at least once per day by mouth. In contrast, nemolizumab is conveniently administered once every four weeks via an injection, which can be self-administered by most patients following a brief tutorial session with a healthcare professional.

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.

It is anticipated that nemolizumab will be used with BSC (which can include emollients, topical corticosteroids or calcineurin inhibitors) for patients with moderate to severe PN. Emollients, topical corticosteroids or calcineurin inhibitors provide local relief to affected areas, while nemolizumab provides a systemic effect on the processes that contribute to itch, inflammation, and dysfunction of the skin barrier.

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?

Nemolizumab is administered by an injection beneath the skin; patients/carers who are to use/administer nemolizumab will need to be taught the proper technique by a healthcare professional before they are able to administer this drug.[41]

The dose will depend on a patient's weight:[41]

- Patients weighing **less than 90 kg** will administer an initial dose of 60 mg given as two injections, followed by 30 mg given as one injection every four weeks thereafter
- Patients weighing **90 kg or more** will receive 60 mg given as two injections every four weeks

Treatment will continue for as long as patients respond positively to treatment; if at any point a patient notices that the drug becomes less effective or completely stops working, they should reach out to their doctor or prescriber.[41]

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 safety and clinical efficacy (i.e., how well the drug works) of nemolizumab in patients with PN has been tested in three main studies:

- **OLYMPIA 1 and OLYMPIA 2**: these studies compared the safety and efficacy of nemolizumab with placebo (i.e., an inactive substance used to compare to an active ingredient). The studies ran over 24 weeks (OLYMPIA 1) and 16 weeks (OLYMPIA 2).

    - The **severity of itch** was measured using a scale known as the *PP NRS* (See section 2b)
    - The **severity of disease** was measured using the *IGA*[42] (See section 2b)

- **OLYMPIA LTE** (long-term extension): this long-term trial is still ongoing and is mainly testing the safety of nemolizumab over 196 weeks. Patients in this study have already taken part in another study where nemolizumab was being investigated, which include the OLYMPIA 1 and OLYMPIA 2 trials. No placebo arm was used in this trial. However, some patients enrolled from previous trials may have received placebo in those trials, and will be used as a comparison to those who had already received nemolizumab before starting this study to investigate the time taken for their response to nemolizumab to catch-up with those who had previously received the drug.[43]
    - To determine the **safety** of nemolizumab over the course of this study, investigators noted the different side effects that happened, as well as how severe they were, and if/how these effects resolved

OLYMPIA 1 was held at 77 sites across 10 countries in Europe and North America. OLYMPIA 2 was held at 55 study sites across 9 countries in Europe and North America, enrolling a total of 560 patients.[42] To take part, patients had to:

- Be aged ≥ 18 years
- Have a clinical diagnosis of PN for at least six months with lesions on upper limbs, trunk, and/or lower limbs
- Have at least 20 nodules across both sides of the body
- Have an Investigator's Global Assessment score of at least 3 (based on the IGA scale ranging from 0 to 4, in which 3 indicates moderate disease and 4 indicates severe disease) at both the screening visit and on the first day of the trial[42]

The OLYMPIA LTE study has a total of 510 patients and is currently being held at 120 sites across Europe and North America.[43]

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.

Understanding the OLYMPIA trials

The key measures used to show how well nemolizumab works in the clinical trials were the Peak Pruritus Numeric Rating Scale and the Investigator's Global Assessment:

- The PP NRS is used to measure the intensity of itch experienced by a patient within the previous 24-hour period (See section 2b)
- The IGA is recorded by the investigator or healthcare professional and is a measure of the severity of the disease based on the number of lesions on a patient's skin (See section 2b)

OLYMPIA 1 and OLYMPIA 2 efficacy

In both the OLYMPIA 1 and OLYMPIA 2 trials, nemolizumab reduced itch versus placebo, with 58.4% of patients treated with nemolizumab reporting a clinically meaningful reduction in itch in the OLYMPIA 1 trial versus 16.7% who received placebo, and 56.3% who received nemolizumab in OLYMPIA 2 versus 20.9% who received placebo. After 16 weeks, the proportion of itch-free or nearly itch-free patients was also much greater in those who received nemolizumab (34.2% in OLYMPIA 1 and 35.0% in OLYMPIA 2) than those who received placebo (4.2% in OLYMPIA 1 and 7.7% in OLYMPIA 2).[42] Both of these improvements were statistically significant (unlikely to be explained by chance) and clinically important findings.

Significantly more patients achieved clear or almost clear skin (defined by an IGA score of 0 or 1) following nemolizumab treatment compared to placebo (OLYMPIA 1: 26.3% vs. 7.3%, respectively; OLYMPIA 2: 37.7% vs. 11.0%, respectively)[42]

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.

Health-related QoL

The impact of nemolizumab on health-related QoL of patients was measured using the Dermatology Life Quality Index (DLQI) questionnaire.

The DLQI is a 10-question questionnaire that asks patients how their skin condition has affected certain aspects of their daily lives over the past week on a scale of 0-3. The questions cover various topics, including symptoms, shopping, wardrobe selection, social activities, work/education, and relationships. The total score, out of a maximum of 30, indicates how much of an impact PN has on patients' QoL; a score of 0 would mean that PN has had no effect on someone's QoL, whereas a score of 30 would indicate a very severe impact.

Patients who received nemolizumab in the OLYMPIA 1 and OLYMPIA 2 trials reported significantly improved QoL, as measured by the DLQI scale. At the end of the OLYMPIA 1 trial, more than twice as many patients treated with nemolizumab reported an improvement in DLQI score of four of more compared with patients who received placebo; in OLYMPIA 2, the corresponding figure for nemolizumab was nearly twice that of placebo.[42]

Sleep disturbance

The impact of nemolizumab on QoL was also measured using the Sleep Disturbance Numeric Rating Scale, where patients report the level of disturbance they experienced to their sleep because of the symptoms of PN.

Sleep disturbance was significantly reduced in patients who received nemolizumab in both clinical trials, as measured by the Sleep Disturbance Numeric Rating Scale. In OLYMPIA 1, half of the patients who received nemolizumab reported an improvement on four or more points regarding their sleep disturbance, versus 11.5% in those who received placebo, and in OLYMPIA 2 just over half (51.9%) reported the same following nemolizumab treatment versus 20.9% in those who received placebo.[42]

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.

Nemolizumab was generally well tolerated and had a safety profile comparable to that of placebo in the OLYMPIA 1 and OLYMPIA 2 trials. In OLYMPIA 1, treatment emergent adverse events (TEAEs; defined as a side-effect [adverse event] that began after starting a medical treatment) were reported in similar numbers of patients in the nemolizumab and placebo groups of the OLYMPIA 1 and OLYMPIA 2 trials. The majority of TEAEs were of mild or moderate severity, and only one TEAE was recorded as leading to the death of a patient which occurred in the placebo group of OLYMPIA 1. The most common TEAEs experienced by patients were headache, dermatitis atopic, neurodermatitis, and all were easily resolved with routine clinical practise.[42]

Over 52 weeks of follow-up in the LTE study, nemolizumab was seen to be well tolerated with no new safety concerns emerging over this time frame. Only a small proportion of the TEAEs that occurred were due to nemolizumab treatment and most of the TEAEs were mild or moderate in severity.[43]

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

There are currently no treatments recommended by NICE for use in patients with PN; therefore, a significant unmet need remains for an approved targeted treatment. This means that currently clinicians must rely on off-label treatments with limited clinical trial evidence to treat patients with PN. Furthermore, the currently available off-label treatments for patients with PN aim to relieve symptoms, rather than address the underlying pathophysiology.

Nemolizumab offers patients with PN a treatment that resolves symptoms by targeting the underlying causes of the itch they experience, rather than just relieving the symptoms. As patients only take one dose every four weeks, they benefit from the convenience of not needing to apply often oily/greasy creams and ointments several times a day, or the need to take oral solutions one or more times per day.

Unlike some off-label treatments taken by patients with PN, nemolizumab does not require regular blood tests or follow-up appointments with healthcare professionals. Likewise, these treatments often have unpleasant side effects, whereas those experienced by patients who receive nemolizumab are generally minor and can be treated, if necessary, with simple medications like painkillers.

Nemolizumab has been shown to be both safe and effective in treating PN in all clinical trials conducted,[42] which includes long-term evidence from the currently ongoing LTE trial over 52 weeks.[43]

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

Before starting nemolizumab treatment for PN, patients need to undergo a consultation with a skin care specialist. As nemolizumab is administered by a subcutaneous injection (i.e., into the layers of the skin), patients will be required to receive training to do so correctly by a healthcare professional, which generally takes 30–60 minutes.

As with all pharmaceutical treatments, patients taking nemolizumab may experience some side effects following their treatment as outlined in Section 3g. The side effects experienced by patients taking nemolizumab are generally tolerable, and mild or moderate in severity. Common side effects in patients receiving nemolizumab (that effect between 1–10% of patients) include headache (including tension headache), atopic dermatitis, eczema and eczema nummular.

It should be noted that the treatments currently used to manage PN are also associated with sometimes serious side effects. For instance, methotrexate is known to cause gut issues such as nausea and vomiting, ulcers in the mouth and throat, and is toxic to organs such as the liver, kidneys, and lungs. Therefore, it requires specific monitoring. Ciclosporin can cause high blood pressure, nausea, cholesterol dysregulation, and gum problems. Both these treatments also reduce the effectiveness of the immune system, leaving patients more prone to infection and at risk of serious problems following infection. Topical corticosteroids may also cause thinning of the skin, especially where more potent preparations are used regularly over long periods of time, which is often the case in patients with PN.

Patients who take nemolizumab may be at risk of hypersensitivity reactions, also known as an allergic reaction; 0.3% of patients who have taken nemolizumab reported a hypersensitive reaction with symptoms such as hives or facial swelling; however, these did not result in the patient stopping treatment.

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.

How does the model reflect PN

An economic model has been developed to assess the value of nemolizumab in patients with moderate to severe PN to the NHS. The economic model can estimate the long-term clinical and cost benefits (cost-effectiveness) of nemolizumab treatment compared with BSC in patients with moderate to severe PN and inform whether it offers value for the healthcare system.

The economic model includes two distinct phases, an initial evaluation over the first 16 weeks of treatment and then a subsequent long-term follow up for the remainder of the patients' life. In the initial phase of treatment, patients with PN start treatment with either nemolizumab with BSC, or BSC alone and continue treatment for 16 weeks. After 16 weeks, response to treatment is checked; patients receiving nemolizumab who respond continue treatment, while those who do not respond stop nemolizumab treatment and receive BSC alone for the remainder of their life. Patients on BSC alone do not stop treatment regardless of their response.

After the first 16 weeks of treatment, all patients enter the long-term follow up and are assigned to one of three groups (health states): 'Maintained response', 'No response' and 'Dead.' Patients who respond at Week 16 join the 'Maintained response' group, where they stay until they stop treatment for various reasons, including no longer responding to treatment. If patients stop responding to treatment, they move to the 'No response' group where they receive BSC alone. Patients who do not respond at Week 16 enter the long-term follow up in the 'No response' group and remain there until death. At any time, patients can move to the 'Dead' group.

The effect of nemolizumab treatment is based on the OLYMPIA 1 and OLYMPIA 2 trials, which included patients receiving nemolizumab with moderate to severe PN.

Modelling differences in life expectancy

PN has a large impact on patients' QoL and mental health; with higher rates of death being reported for patients with PN in England compared to the general population.[28] Therefore, increased rates of death have been included in the

economic model for patients with PN based on Clinical Practice Research Datalink (CPRD) data analysis.[28]

Modelling how much the treatment improves quality of life

The economic model measured the impact of moderate to severe PN and treatment on patients' QoL. In the economic model, QoL was dependent on treatment, response to treatment and the time from starting treatment. The QoL is based on data from the OLYMPIA 1 and OLYMPIA 2 clinical trials.

Modelling how the costs of treatment differ with new treatment

The economic model estimates the costs associated with medication, which includes nemolizumab, BSC and treatment administration. In addition, costs associated with disease management and monitoring (which are dependent on response to treatment) and adverse events (which are dependent on the treatment received) are included in the model.

Cost-effectiveness results

The economic model produces outcomes for patients as quality-adjusted life years (QALYs), which reflects the impact of a treatment on both the quantity and QoL. One QALY is worth one year of life in perfect health. For example, if a patient gained one QALY because of a new therapy compared to an existing therapy, it would be equivalent to them gaining one year of life in perfect health. Further details on the cost-effectiveness results of nemolizumab can be found in Section B.3.9 of the Company evidence submission.

Uncertainty

During the development of an economic model, you are required to make assumptions where there is a lack of available evidence. These assumptions were tested through sensitivity analysis, where alternate assumptions or values were used in the economic model to determine the impact on the economic results.

Benefits not captured in the modelling

There are a number of benefits of nemolizumab for patients and the wider healthcare system that may not be captured in the economic model based on how response to treatment is assessed. The impact of relentless and severe itch is complicated[44] and its impact on patient QoL is unlikely to be fully captured by EQ-5D (measure of patient QoL used in economic model).

The persistent itch associated with PN impacts both quality and quantity of sleep, with > 70% of patients reporting nocturnal itch.[13,37] PN-related itch can lead to sleep deprivation, with 42.5% of patients with PN experiencing sleep impairment.[45] In one study, 100% of patients with PN reported sleep disturbances as a result of their disease, with 29% reporting that this disturbed their daily life or work.[24] Poor sleep is related to depression, suicidal ideation, and anxiety, which are significantly increased in patients with PN and are observed at the highest rates amongst skin diseases.[46,47] It has also been reported that patients with PN are more prone to days off work because of their disease.[48] The wider impacts of nocturnal itch on

sleep, mental health, and missed workdays are not properly captured by EQ-5D, and therefore, the full impact of the reduction in sleep disturbance following nemolizumab treatment are not fully accounted for in the economic model.

Patients with PN also experience significant personal costs that have not been captured in the economic analysis, which are shown to increase with disease severity.[49,50] In addition, there are significant indirect costs to the wider society, relating to productivity loss due to sleep deprivation, missed workdays, and limited working capacity following episodes of insomnia.

Nemolizumab has a convenient treatment regimen, where patients can self-administer nemolizumab subcutaneously every four weeks following training. Many current treatments require daily applications or more frequent administration, and immunosuppressants, such as methotrexate, require frequent monitoring and follow-up appointments. This additional burden to the healthcare system has not been fully captured in this economic analysis. Likewise, the improved convenience of nemolizumab to patients has not been captured in the model.

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)

If recommended, nemolizumab would be the only therapy recommended by NICE in the UK to treat patients with PN. With its unique mechanism of action targeting the substance known as IL-31, nemolizumab would be the only therapy available to patients in the UK that targets the underlying cause of PN, reduces itch and skin lesions and improves patients QoL. The lack of effective treatments available leaves patients dissatisfied and frustrated, whilst also experiencing debilitating symptoms such as constant itch, skin lesions, sleep disruption, and mental health consequences.[51]

Patients would also benefit from the convenience of self-administering the treatment once every four weeks following a brief training session with a healthcare professional. This presents a stark contrast to current treatments which require application multiple times every day or may need to be taken at least every day and may require regular monitoring.

PN also impacts a patient's sleep due to itch which affects their ability to perform day-to-day activities. Lesions on the skin often lead to feelings of embarrassment, forcing patients to choose clothing specifically in an attempt to cover them, and can impact their relationships in both a social and romantic context.[24]

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

There are not expected to be any equality issues associated with using nemolizumab for the treatment of PN.

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. 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.

Further information on clinical trial data supporting nemolizumab for the treatment of PN can be found here:

- Stander S et al. Nemolizumab monotherapy improves itch and skin lesions in patients with moderate-to-severe prurigo nodularis: Results from a global Phase 3 trial (OLYMPIA 1). European Academy of Dermatology and Venerology. 2023

- Kwatra S et al. Nemolizumab monotherapy improves itch, skin lesions, and sleep disturbance in patients with prurigo nodularis: Results from a phase 3 trial (OLYMPIA 2) American Academy of Dermatology Annual Meeting. 2023

The British Association of Dermatologists has produced the following leaflet that describes PN, what it is, what causes it and how it is treated: https://www.bad.org.uk/pils/nodular-prurigo/

Further information on NICE and the role of patients**:**

- Public Involvement at NICE
- NICE's guides and templates for patient involvement in HTAs
- EFPIA – Working together with patient groups (PDF)
- National Health Council Value Initiative

4b) Glossary of terms

Dermatologist: a medical doctor specialising in treating conditions of the skin, hair and nails.

Dermatology Life Quality Index (DLQI): a 10-question questionnaire used to assess a person's quality of life, specifically in the context of skin diseases.

Efficacy: the ability of a drug to bring about an intended result or outcome.

Immune system: a network of organs, cells and substances within the body that work together to defend the body against infections.

Inflammation: a response of the body to things such as illness or injury, which may present as swelling, redness, soreness, and heat in the affected area.

Interleukin-31: a specific type of chemical produced by immune cells in the body that acts as a signal in processes regulating responses of the immune system to certain triggers.

Investigator's Global Assessment (IGA): an assessment by an investigator/doctor to rate the severity of the disease based upon the number of lesions that are present on the patient's skin.

Lesion: an area of the skin that looks different to the skin tissue around it; they often come about as a result of damage or injury to the skin.

Moderate-to-severe PN: defined as a case of PN where the patient presents with > 20 nodules in line with a scale used by skin care specialist called the Investigator's Global Assessment, and/or with an itch severity rated as 3 or more out of 10 on a scale used by skin care specialist called the Prurigo Activity Score.

Nodule: a small lump, caused by abnormal growth of skin tissue just below the surface layer of the skin that may feel hard to the touch.

Off-label: an unapproved use of an approved drug; drugs are licensed to treat specific conditions but may be effective in treating other conditions as well. In that case, a prescriber may use the drug outside the terms of its license 'off-label' in the best interests of the patient.

Peak Pruritis Numeric Rating Scale (PP NRS): a scale that measures the most intense itch experienced in the last 24-hours as reported by the patient themselves from 0 to 10.

Placebo: a substance used in clinical trials with no therapeutic value, so that it can be used as a comparator for the active drug being investigated.

Quality adjusted life year (QALY): a measure of how well a treatment improves and/or lengthens a patient's life. One QALY is worth one year of life in perfect health.

Subcutaneous: an injection route, whereby the needle penetrates and administers the drug directly into the layers of the skin.

Systemic therapy: a drug that affects the whole body, often they access the blood to be moved around the body and act at the desired organ(s).

Topical calcineurin inhibitors: a topical treatment used to treat AD.

Topical corticosteroids: a topical treatment used to treat AD.

Topical: a type of treatment that is applied to the skin, and normally only works locally on the area it is applied.

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:

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal

Nemolizumab for adults with moderate to severe prurigo nodularis [ID6451]

Clarification questions

November 2024

File name	Version	Contains confidential information	Date
[ID6451] Nemolizumab CQ 061124 [Redacted]	**1**	**Yes**	**6 November 2024**

Section A: Clarification on clinical effectiveness data

A1. PRIORITY: Document B, Section B.1.1, p.12, Table 1. Please provide an explicit rationale for not including phototherapy and antidepressants as comparators.

Response – Neither phototherapy nor antidepressants were included as comparators for this submission. During the modified Delphi panel exercise and expert interviews, UK clinicians did not consider phototherapy or antidepressants to be used commonly for best supportive care (BSC) for the treatment of prurigo nodularis (PN).[1,2] This was especially true in the case of phototherapy, which was deemed unlikely to be commonly used due to limitations in availability and practicality.[1,2] The limited availability of phototherapy means that is it not universally accessible, and therefore, should not be considered standard of care.

Furthermore, during the TA955 submission, the EAG agreed with the exclusion of phototherapy as BSC.[3] It also agreed that antidepressants are considered 'as additional treatments that might be used in UK clinical practice,' rather than as BSC commonly used in patients with PN.[3] The British Association of Dermatologists and British Photodermatology Group guidelines for UV phototherapy, published in 2022, suggest that the evidence base for the use of phototherapy in PN is weak.[4]

Neither treatment is considered to have any effect on the underlying condition of PN, but instead aim to provide symptomatic relief.[2] Antidepressants may be used to address the psychological impacts of PN, but do not have any impact on the dermatological symptoms experienced.[5] As such, they would not be prescribed by a dermatologist and were not plausibly considered as a comparator for nemolizumab in the assessment.[2]

A2. PRIORITY: Document B, Section B.2.3.2, p.55, Table 8. Please provide the full criteria that were used by the investigator to determine whether patients would benefit from study participant in the LTE study.

Response – The full eligibility criteria for the LTE study, taken from the study protocol, are provided below.[6]

Inclusion Criteria

Individuals must meet all of the following criteria at screening and baseline, as applicable, to be included in the study (individuals re-entering from the Phase 3b durability study must meet all inclusion criteria at re-entry):

1. Subjects who may benefit from study participation in the opinion of the investigator and participated in a prior nemolizumab study for PN including:

    a. Subjects who completed the treatment period in a Phase 3 pivotal study and enrol within 56 days

    OR

    b. Subjects who were previously randomised in the nemolizumab Phase 2a PN study

    OR

    c. Subjects who completed through Week 24 of the Phase 3b durability study or who exit the study due to relapse may be eligible to re-enter in the LTE study within 28 days of exiting the durability study (selected countries/ selected sites)

2. Female subjects of childbearing potential (i.e., fertile, following menarche and until becoming post-menopausal unless permanently sterile) must agree to use an adequate and approved method of contraception throughout the study and for 12 weeks after the last study drug injection.

3. Female subjects of non-childbearing potential must meet one of the following criteria:

- Absence of menstrual bleeding for 1 year prior to screening without any other medical reason, confirmed with follicle stimulating hormone (FSH) level in the postmenopausal range

  OR

- Documented hysterectomy, bilateral salpingectomy, or bilateral oophorectomy at least 3 months before the study.

4. Subject willing and able to comply with all of the time commitments and procedural requirements of the clinical study protocol, including periodic weekly recordings by the subject using an electronic handheld device provided for this study.

5. Understand and sign an informed consent form before any investigational procedure(s) are performed.

Exclusion Criteria

Individuals meeting any of the following criteria at screening or baseline are ineligible to participate in this study (individuals re-entering from the Phase 3b durability study meeting any of the following criteria at the re-entry Week R0 visit are ineligible):

1. Subjects who, during their participation in a prior nemolizumab study, experienced an AE which in the opinion of the investigator could indicate that continued treatment with nemolizumab may present an unreasonable risk for the subject.

2. Body weight < 30 kg.

3. Having received any of pre-specified prohibited treatments within the specified timeframe before the baseline visit or re-entry Week R0 visit

4. Pregnant women, breastfeeding women, or women planning a pregnancy during the clinical study.

5. Any medical or psychological condition that may put the subject at significant risk according to the investigator's judgment, if he/she participates in the clinical study, or may interfere with study assessments (e.g., poor venous access or needle-phobia).

6. Planning or expected to have a major surgical procedure during the clinical study.

7. Subjects unwilling to refrain from using prohibited medications during the clinical study.

8. History of alcohol or substance abuse within 6 months of the screening visit or re-entry Week R0 visit.

For subjects who do not rollover within 28 days from a prior nemolizumab study or who completed study visits but prematurely discontinued study drug, the following exclusion criteria also apply:

9. Subjects with a history of asthma meeting 1 or more of the following criteria:

- Had an exacerbation of asthma requiring hospitalization in the preceding 12 months.
- Reporting asthma that has not been well-controlled (i.e., symptoms occurring on > 2 days per week, nighttime awakenings 2 or more times per week, or some interference with normal activities) during the preceding 3 months.
- Asthma Control Test (ACT) ≤ 19 (only for subjects with a history of asthma) at screening and baseline.
- Peak expiratory flow (PEF) < 80% of the predicted value.

10. Subjects with a current medical history of chronic obstructive pulmonary disease and/or chronic bronchitis.

11. Cutaneous infection within 1 week before the baseline visit, any infection requiring treatment with oral or parenteral antibiotics, antivirals, antiparasitic or antifungals within 2 weeks before the baseline visit, or any confirmed or suspected coronavirus disease (COVID)-19 infection within 2 weeks before the screening or baseline visit. Subjects may be rescreened once the infection has resolved. Resolution of COVID-19 infection can be confirmed by recovery assessment methods,

12. Positive serology results (hepatitis B surface antigen [HBsAg] or hepatitis B core antibody [HBcAb], hepatitis C (HCV) antibody with positive confirmatory test for HCV (e.g., polymerase chain reaction [PCR]), or human immunodeficiency virus antibody) at screening.

13. Chronic pruritus resulting from another active condition than PN

14. History of or current confounding skin condition

15. Subjects with active atopic dermatitis (signs and symptoms other than dry skin) in the last 3 months.

16. Neuropathic and psychogenic pruritus

17. History of lymphoproliferative disease or history of malignancy of any organ system within the last 5 years, except for: (1) basal cell carcinoma, squamous cell carcinoma in situ (Bowen's disease), or carcinomas in situ of the cervix that have been treated and have no evidence of recurrence in the last 12 weeks before the screening visit, or (2) actinic keratoses that have been treated.

18. History of hypersensitivity (including anaphylaxis) to an immunoglobulin (plasma-derived or recombinant) product (e.g., monoclonal antibody) or to any of the study drug excipients.

19. Current active or latent tuberculosis (TB) infection or history of either untreated or inadequately treated active or latent TB according to the local applicable guidelines.

20. Known or suspected immunosuppression or unusually frequent, recurrent, severe, or prolonged infections as per investigator judgment.

21. Any clinically relevant laboratory abnormalities, such as but not limited to elevated alanine aminotransferase (ALT) or aspartate aminotransferase (AST) during the screening period that may put the subject at significant risk according to the investigator's judgment, if he/she participates in the clinical study.

22. Currently participating or participated in any other study of an investigational drug or device, within the past 8 weeks (or 5 half-lives of the investigational drug, whichever is longer) before the screening visit, or is in an exclusion period (if verifiable) from a previous study, other than the nemolizumab studies for PN.

A3. Document B, Section B.2.6.2, p.87 & 90, Tables 23 & 24. The total number of LTE participants reported in Tables 23 and 24 is n=[redacted]. The number of participants reported for the lead-in studies sums to n=[redacted] Phase 2a trial (n=[redacted]), OLYMPIA 1 (n=[redacted]), and OLYMPIA 2 (n=[redacted]). Please clarify whether the n=[redacted] patients who re-entered from the durability study are included in the n=[redacted] total (and please clarify which of the lead-in studies contributed patients to the durability study if this is the case) or are these patients additional to the n=[redacted] total?

Response – The [redacted] patients from the Durability study are part of the total [redacted] patients in the LTE study. These 17 participants transitioned from the Phase 2 ([redacted] participants), OLYMPIA 1 ([redacted] participants), and OLYMPIA 2 ([redacted] participants) trials to the LTE study.[7] After 52 weeks of LTE treatment, these patients moved to the Durability study and subsequently re-entered the LTE upon either completion or early termination.[8]

A4. Document B, Section B.2.6.2.2.4, p.104, Table 26. Please provide the source for Table 26.

Response – The data provided in Table 26 of Document B were sourced from the OLYMPIA LTE CSR (Table 31, Table 37, Table 39, Table 47, Table 57).[7]

A5. Document B. Section B.2.12.2. p.121. The company submission states that "*The LTE study is ongoing with data at later timepoints expected."* Please clarify whether additional data cuts will become available during this appraisal and provide the date of any new anticipated upcoming data cuts.

Response – No additional data cuts will become available during the appraisal. An additional data cut for the LTE study is anticipated mid-to-late 2025.

A6. PRIORITY. Appendix D, p.21, Table 7. For each randomised controlled trial in in Table 7, please provide the reason why this was not included in a meta-analysis or quantitative evidence synthesis.

Response – Table 1 outlines why each of the trials identified during the systematic literature review for clinical evidence were not suitable for inclusion in a meta-analysis or quantitative evidence synthesis during this submission.

In summary, the majority of studies identified did not consider populations or interventions that were relevant to the scope of this submission. Some studies were considered low quality (Phase 2 or non-RCTs with small sample sizes). Additionally, there was a lack of commonality between studies in terms of the outcome measures reported, which would make comparison between studies difficult. Overall, the variations between the trials identified meant that any meta-analysis or quantitative evidence synthesis would be associated with significant uncertainty.

Table 1. Reasons for not including identified trials in meta-analysis

Trial	Reason for not including
APREPRU[9] (EudraCT 2013-001601-85)	• Different population to the one considered in the scope of this submission (patients with antihistamine refractory PN) • Non-relevant intervention (aprepitant is not considered in the PN clinical treatment landscape in the UK) • Study design: Phase 2 clinical trial
NCT0050783[10]	• Different population to the one considered in the scope of this submission (patients with non-atopic PN) • No relevant comparator (no BSC arm) • Study design: Phase 2 clinical trial
NCT02174419[11]	• No relevant comparator (no BSC arm) • Non-relevant intervention (nalbuphine is not licensed for use in the UK) • Study design: Phase 2 clinical trial
NCT03181503[12]	• Different population to the one considered in the scope of this submission (patients with moderate to severe PN and severe pruritus) • Study design: Phase 2 clinical trial

TCP-102[13] (NCT02196324)	• Different population to the one considered in the scope of this submission (patients with chronic, treatment refractory PN) • Non-relevant intervention (serlopitant is not licensed for use in the UK) • Study design: Phase 2 clinical trial
NCT03816891[14]	• No relevant comparator (no BSC arm) • Non-relevant intervention (vixarelimab is not licensed for use in the UK) • Study design: Phase 2 clinical trial
PRISM[15] (NCT03497975)	• Non-relevant intervention (nalbuphine is not licensed for use in the UK) • No relevant comparator (no BSC arm) • Study design: Phase 2 clinical trial
LIBERTY-PN PRIME[16] (NCT04183335)	• Non-relevant intervention (dupilumab is not recommend by NICE for use in the UK) • No relevant comparator (no BSC arm)
PRIME2[16] (NCT04202679)	• Non-relevant intervention (dupilumab is not recommended by NICE for use in the UK) • No relevant comparator (no BSC arm)
NCT03677401[17]	• Non-relevant intervention (serlopitant is not licensed for use in the UK) • No relevant comparator (no BSC arm)
OLYMPIA 1[18] (NCT04501666)	• NA
OLYMPIA 2[19] (NCT04501679)	• NA
NCT03576287[20]	• Non-relevant intervention (apremilast is not licensed for use in the UK) • Study design: Phase 2 trial
NCT03540160[21]	• No relevant comparator (single arm trial) • Non-relevant intervention (serlopitant is not licensed for use in the UK)
OLYMPIA LTE[22] (NCT04204616)	• NA
Ahsan, 2018[23]	• Study design: Single arm trial • Different population to the one considered in the scope of this submission (patients with idiopathic PN) • Primary outcomes not reported
Kwatra S, 2023[24]	• Study design: Single arm trial • Non-relevant intervention (abrocitinib is not licensed for use in the UK)

Mazza M, 2013[25]	• Study design: Single arm trial • Non-relevant intervention (pregabalin is not considered BSC for PN in the UK) • Primary outcomes not reported
Zalaudek, 2006[26]	• Study design: Single arm trial • Non-relevant intervention (amitriptyline is not considered BSC for PN in the UK)

Abbreviations: BSC, best supportive care; NA, not applicable; PN, prurigo nodularis; UK, United Kingdom.

A7. Appendix D, p.49, Table 14. The EAG noted that OLYMPIA 2 is the only nemolizumab study included in this table, even though OLYMPIA 1 data are also included in Table 35 (Document B, Section B.3.3.1, p.138) using the same response definition (an improvement of ≥ 4 PP NRS and IGA success (defined as a score of 0 or 1) at 16 weeks. Both outcomes also appear to have been collected in the Phase 2 trial NCT03181503 (Ständer 2020). Please confirm that the company has access to participant-level data that enables calculation of this composite response outcome by randomised group for: a) OLYMPIA 1, b) OLYMPIA 2, c) NCT03181503 (Ständer 2020).

Response – The OLYMPIA 1 trial was excluded from Appendix D, Table 14 of the Company submission by a reporting error. The missing data for this trial can be found in Table 2. The Phase 2 trial NCT03181503 did not report the composite response outcome and was therefore, not included in the table. In Appendix D of the Company submission, the clinical strategies were inadvertently spell-checked and reported incorrectly, with US spellings being changed to UK spellings. In line with PRISMA requirements, the clinical strategies as they were run for the clinical SLR are presented in Appendix B.

Table 2. PP NRS/WI NRS improvement of ≥ 4-points from baseline and IGA score of 0 or 1 composite endpoint

Trial name/First author, year	Intervention (n)	Analysis Set	Timepoint (weeks)	Imputation Method	Proportion of Patients with improvement of ≥4-points from baseline and IGA score of 0 or 1 composite endpoint (%)	Difference (95% CI), *P* value
RCTs						
OLYMPIA 1	Nemolizumab (190)	190	16	NRI	43 (22.6)	NR
	Placebo (96)	96	16	NRI	2 (2.1)	NR

Abbreviations: CI, confidence interval; IGA, Investigator's Global Assessment; NR, not reported; PP NRS, peak pruritus numerical rating scale; RCT, randomized controlled trial; WI NRS, worst itch numerical rating scale.

Participant-level data (PLD) is available from the OLYMPIA 1 and OLYMPIA 2 trials, which enables calculation of the composite outcome of an improvement of ≥ 4 PP NRS and IGA success (defined as a score of 0 or 1) at 16 weeks. PLD is also available for the Phase 2 trial NCT03181503 (Ständer et al. 2020).[12] However, Galderma does not consider it appropriate to present the NCT03181503 (Ständer et al. 2020)[12] PLD given that Phase 3 data is available and is considered a more robust data source compared with Phase 2 trial data.

A8. <u>PRIORITY:</u> Document B, Section B.3.3.1, p.138, Table 35. Related to Question A7, for the composite outcome definition used in this table, please provide data (numerator, denominator, percentage) by randomised group separately for: a) OLYMPIA 1, b) OLYMPIA 2, c) NCT03181503 (Ständer 2020)? Please provide these data for all available response measurement time points.

Response – Data (numerator, denominator, percentage) for the composite outcome definition by randomised group for OLYMPIA 1 and OLYMPIA 2 are presented in Table 3 and Table 4, respectively. In addition, data for the composite outcome definition by randomised group for OLYMPIA 1 and OLYMPIA 2 combined are presented in Table 5.

Table 3. Data used to calculate response rates for OLYMPIA 1 for nemolizumab and placebo for PP NRS+IGA composite outcome

OLYMPIA 1	Arm	N	Responder count	Response (%)
Week 4	Nemolizumab	[redacted]	[redacted]	[redacted]
	Placebo	[redacted]	[redacted]	[redacted]
Week 8	Nemolizumab	[redacted]	[redacted]	[redacted]
	Placebo	[redacted]	[redacted]	[redacted]
Week 12	Nemolizumab	[redacted]	[redacted]	[redacted]
	Placebo	[redacted]	[redacted]	[redacted]
Week 16	Nemolizumab	[redacted]	[redacted]	[redacted]
	Placebo	[redacted]	[redacted]	[redacted]
Week 20	Nemolizumab	[redacted]	[redacted]	[redacted]
	Placebo	[redacted]	[redacted]	[redacted]
Week 24	Nemolizumab	[redacted]	[redacted]	[redacted]
	Placebo	[redacted]	[redacted]	[redacted]

Abbreviations: IGA, Investigator Global Assessment; PP NRS, peak pruritus' numerical rating scale.

Table 4. Data used to calculate response rates for OLYMPIA 2 for nemolizumab and placebo for PP NRS+IGA composite outcome

OLYMPIA 2	Arm	N	Responder count	Response (%)
Week 4	Nemolizumab	[redacted]	[redacted]	[redacted]
	Placebo	[redacted]	[redacted]	[redacted]
Week 8	Nemolizumab	[redacted]	[redacted]	[redacted]
	Placebo	[redacted]	[redacted]	[redacted]
Week 12	Nemolizumab	[redacted]	[redacted]	[redacted]
	Placebo	[redacted]	[redacted]	[redacted]
Week 16	Nemolizumab	[redacted]	[redacted]	[redacted]
	Placebo	[redacted]	[redacted]	[redacted]

Abbreviations: IGA, Investigator Global Assessment; PP NRS, peak pruritus' numerical rating scale.

Table 5. Data used to calculate response rates for OLYMPIA 1 and OLYMPIA 2 for nemolizumab and placebo for PP NRS+IGA composite outcome

OLYMPIA 1+2	Arm	N	Responder count	Response (%)
Week 4	Nemolizumab	[redacted]	[redacted]	[redacted]
	Placebo	[redacted]	[redacted]	[redacted]
Week 8	Nemolizumab	[redacted]	[redacted]	[redacted]
	Placebo	[redacted]	[redacted]	[redacted]
Week 12	Nemolizumab	[redacted]	[redacted]	[redacted]
	Placebo	[redacted]	[redacted]	[redacted]
Week 16	Nemolizumab	[redacted]	[redacted]	[redacted]
	Placebo	[redacted]	[redacted]	[redacted]
Week 20	Nemolizumab	[redacted]	[redacted]	[redacted]
	Placebo	[redacted]	[redacted]	[redacted]
Week 24	Nemolizumab	[redacted]	[redacted]	[redacted]
	Placebo	[redacted]	[redacted]	[redacted]

Abbreviations: IGA, Investigator Global Assessment; PP NRS, peak pruritus' numerical rating scale.

Section B: Clarification on cost-effectiveness data

Model baseline characteristics

B1. Document B, Section B.3.2.2, p.129 & Table 30. Please provide an estimate of mean (SD) patient weight (kg), calculated using only data from the nemolizumab arms of the OLYMPIA studies.

Response – The baseline patient weight summaries calculated from the nemolizumab arms of OLYMPIA 1 and OLYMPIA 2 is presented in Table 6.

Table 6. Patient weight summary from the nemolizumab arms of OLYMPIA 1 and OLYMPIA 2 studies

OLYMPIA 1 and OLYMPIA 2 (nemolizumab arm only)	Mean (SD)
Patient weight (kg)	83.4 (20.2)

Abbreviations: kg, kilograms; SD, standard deviation.

Economic model structure

B2. PRIORITY: Document B, Section B.3.2.3.2, p.129-131 & Figure 20. The EAG note that the decision tree model only captures trial response outcomes up to 16 weeks, but that 24-week response data are available from the OLYMPIA 1 study. Please provide:

- A justification for relying only on the 16-week data.
- A table that reports response probabilities as n/N (%) at week 16 and 24 by study arm. Please also include a measure of uncertainty for the PSA.
- A scenario analysis demonstrating the impact of using 24-week response data on cost-effectiveness results.

Response – A 16-week time frame was decided upon for the decision tree as it aligns with the primary endpoints of both the OLYMPIA 1 and OLYMPIA 2 trials.[27,28] Furthermore, both the OLYMPIA 1 and OLYMPIA 2 trials report outcomes at this time point, but only OLYMPIA 1 provides outcomes at Week 24. As such, using a 24-week time point where data is only available from one of the two Phase 3 clinical trials would be less robust than using a time point where more data was available, and would add additional uncertainty to the cost-effectiveness estimates.[27,28] Furthermore, during expert interviews conducted by Galderma, a UK health economist and a UK clinical expert validated the model structure using the 16-week time point as being appropriate.[2]

Data for the composite endpoint (PP NRS+IGA improvement) response rates are presented in Table 7.

Table 7. Composite PP NRS + IGA response data from OLYMPIA 1 + OLYMPIA 2

Week	Nemolizumab	BSC	Source
Week 16	[redacted]	[redacted]	OLYMPIA 1[27]
Week 16	[redacted]	[redacted]	OLYMPIA 2[28]
Week 16	[redacted]	[redacted]	OLYMPIA 1 and OLYMPIA 2[27,28]
Week 24	[redacted]	[redacted]	OLYMPIA 1[27]
Week 16/24	[redacted]	[redacted]	OLYMPIA 1 (Week 24) and OLYMPIA 2 (Week 16)[27,28]

Abbreviations: BSC, best supportive care; IGA, Investigator' Global Assessment; PP NRS, peak pruritus numerical rating score; SE, standard error.

The following scenario analyses were conducted, with results presented in Appendix A (Table 6, Section 1.2.4):

- Scenario 1: response rates assessed at Week 24 based on the OLYMPIA 1 trial results at Week 24
- Scenario 2: response rates assessed at Week 24 based on OLYMPIA 1 trials results at Week 24 and OLYMPIA 2 trial results at Week 16

B3. <u>PRIORITY:</u> Document B, Section B.3.2.3.2.2, p.132-133 & Figure 21. The Markov state transition diagram shows that it is not possible to regain a response once it is lost in the economic model. The EAG note however that non-responders are assumed to incur higher treatment costs due to greater use of TCS, corticosteroids, immunosuppressants and TCI treatments. This would suggest that those who have previously lost a response could feasibly regain a response using these more active BSC treatments. The EAG are concerned that the economic model structure might not fully capture the benefits of using more active BSC treatments after a response has been lost. Please provide the following information:

- A justification for assuming that a response cannot be achieved once it is lost, including where appropriate, clinical expert validation of the assumption.
- Additional discussion and scenario analyses that attempt to align the BSC non-responder costs and any anticipated QALY benefits in the economic model.

Response – Current BSC treatment options used in the management of PN are prescribed off-label, aim to address symptoms rather than the underlying disease and are not considered effective treatment options.[29] A questionnaire study conducted across 15 European dermatological centres (N = 406) found that a substantial number of patients with PN (28.7%) consider none of the therapeutic options offered to them as effective.[29] In addition, most patients with PN were not satisfied with their previous therapy (56.8%), while 9.8% did not receive any therapy despite having active disease.[29]

The assumption that response cannot be achieved once patients have stopped responding aligns with the model used during the TA955 submission.[3] Furthermore, during expert interviews, a UK clinical expert validated that the model structure used in economic model was appropriate and reflective of the patient pathway in moderate to severe PN.[2] It should also be considered that there is no clinical data available to inform whether a response can be achieved using BSC treatments once it is lost, or that quantifies the extent of this response. Therefore, the inclusion of response for non-responders would not align with UK clinical expert feedback or previous submission in moderate to severe PN and add significant uncertainty to the economic model.

Galderma considers the cost and utility values for non-responders as appropriate for inclusion in the economic model and do not consider it appropriate to update the model structure to conduct scenario analysis.

In the economic model, non-responders in the BSC arm were assumed to return to baseline utility and non-responders in the nemolizumab arm were assumed to have utility equal to responders for 6 months, after which their utility returned to the baseline value. The baseline utility value was estimated based on PLD from the full cohort of the OLYMPIA 1 and OLYMPIA 2 trials at baseline. There is no evidence to support increased long-term utility (beyond the trial duration) for non-responders compared with baseline. Furthermore, the assumption that utility for non-responders would return to baseline was validated by a UK clinical expert.[2]

Increased utility was assumed for non-responders in the nemolizumab arm for the initial 6 months to account for partial responders and any durability effect after

treatment is discontinued. This assumption was also validated by a UK clinical expert and is in line with the assumption used in TA955.[2,3] Therefore, given the lack of data for increased long-term utility for non-responders and validation with a UK clinical expert, the utility values for non-responders can be considered as appropriate and generalisable to UK clinical practice.

The disease management and monitoring costs for non-responders were estimated based on resource use from TA955.[3] In TA955, the Company state that the resource use costs for non-responders are conservative.[3] Furthermore, the resource use from TA955 may not fully capture the additional monitoring associated with BSC treatments such as methotrexate, which was not considered as part of BSC in TA955.[3] Therefore, Galderma considers the costs for non-responders used in the economic model as conservative and believes that any reduction in the costs for non-responders would not represent UK clinical practice.

Economic model comparators - BSC

B4. PRIORITY: Document B, Section B.3.2.5.2, p.136. Please provide further details regarding the distribution of the basket of treatments within the BSC arm of the model. Specifically, please provide a table that details the different types of BSC treatments (treatment name and n/N (%) of patients receiving each treatment) used in all nemolizumab studies, compared to those derived from the Delphi study.

Response – In the economic model, the distribution of the basket of treatments within both the nemolizumab and BSC arms are dependent on response to treatment (Table 8). As nemolizumab is administered with BSC, the distributions of treatments used for the nemolizumab and BSC arms of the economic model were assumed to be the same. The baskets of treatments included as BSC for responders and non-responders were determined based on clinical expert opinion in a modified Delphi panel, which included two UK clinical experts.[1] Based on the limited treatments currently available for patients with moderate to severe PN in the UK, clinical experts considered BSC for responders to consist of emollients, TCSs, TCIs and antihistamines; while BSC for non-responders was considered to consist of emollients, TCSs, TCIs, antihistamines, systemic corticosteroids and immunosuppressants.[1]

The proportions of each BSC treatment received for responders and non-responders were based on percentages provided by the clinical experts.[1] Based on the significant variation in the use of off-label treatments in moderate to severe PN and the lack of treatments recommended by NICE in this population, the distributions of the basket of treatments for responders and non-responders are considered to be appropriate and generalisable evidence to support the economic model.

Table 8 presents a comparison of the distribution of the basket of treatments for responders and non-responders sourced from the modified Delphi panel exercise results compared with the equivalent concomitant therapy not classed as rescue therapy in the pooled OLYMPIA 1 and OLYMPIA 2 trials. As discussed in the Company submission, these concomitant treatments were permitted and not classed as rescue therapy, provided that they were required for the treatment of a condition other than PN and agreed with the Investigator and medical monitor.

Table 8. Comparison of BSC in the economic model with BSC in the pooled OLYMPIA 1 and OLYMPIA 2 trials

Treatment	Economic model*		Pooled OLYMPIA 1 and OLYMPIA 2 trials**	
	Responders	Non-responders	Nemolizumab (N = 373)	Placebo (N = 187)
Emollients	100%	100%	[redacted]	[redacted]
TCSs	20%	100%	[redacted]	[redacted]
TCIs	30%	100%	[redacted]	[redacted]
Antihistamines	5%	30%	[redacted]	[redacted]
Systemic corticosteroids	0%	15%	[redacted]	[redacted]
Immunosuppressants	0%	77%	[redacted]	[redacted]

*Nemolizumab is administered with BSC; therefore, BSC was assumed to be equal between the nemolizumab and BSC arms in the economic model.
**The patients in OLYMPIA 1 and 2 received concomitant therapy which was not classed as rescue therapy provided that the therapy was required for the treatment of a condition other than PN and agreed upon with the Investigator and medical monitor.
Abbreviations: BSC, best supportive care; TCI, topical calcineurin inhibitor; TCS, topical corticosteroid.

Clinical effectiveness parameters

B5. PRIORITY: Document B. Section B.3, Tables 35-38. For all clinical effectiveness parameters used in the economic model, please provide the following information:

- updated tables that include numerators and denominators used to derive proportions and percentages.
- Estimates of uncertainty, using all available data, that can be used to inform the probabilistic sensitivity analyses.
- Please also include these data within an updated economic model file.

Response – Updated tables that include the numerators and denominators to derive the proportions and percentages for response rates, conditional discontinuation, and treatment related adverse events (TRAEs) are presented Table 9, Table 10 and Table 11, respectively. Please note that following response to the clarification questions, the values for treatment discontinuation and TRAEs in the base-case have been updated. Updated base-case cost-effectiveness results are presented in Appendix A. Additional information regarding the treatment discontinuation and TRAEs used in the updated base-case is provided in response to B7 and B16, respectively.

The inputs used for loss of response presented in Document B, Table 37 were sourced from TA955 and consequently, the numerators and denominators used to derive these values cannot be provided.[3]

Table 9. Response rate at Week 16 for nemolizumab and BSC alone

Response	Nemolizumab	BSC	Source
PP NRS + IGA	[redacted]	[redacted]	OLYMPIA 1 and OLYMPIA 2[27,28]

Abbreviations: BSC, best supportive care; IGA, Investigator Global Assessment; SE, standard error.

Table 10. Treatment discontinuation at Week 52 and year 2 onwards

Treatment	Discontinuation at Week 52 and year 2 onwards	Source
Nemolizumab	[redacted]	OLYMPIA LTE[7]
BSC	[redacted]	OLYMPIA 1[27]

Abbreviations: BSC, best supportive care; LTE, long-term extension; SE, standard error.

Table 11. TRAEs rates in economic analysis

Treatment	Nemolizumab N = 370 % (n)	BSC N = 186 % (n)	Source
AD	[redacted]	[redacted]	OLYMPIA 1 and OLYMPIA 2[27,28]
Eczema nummular	[redacted]	[redacted]	
Neurodermatitis	[redacted]	[redacted]	
Dyspnoea	[redacted]	[redacted]	
Asthma	[redacted]	[redacted]	
Headache	[redacted]	[redacted]	

Abbreviations: AD, atopic dermatitis; BSC, best supportive care; TRAE, treatment related adverse event.

Response rates, discontinuation rates and TRAEs are presented in an updated economic model, presented as n/N, instead of percentages. Standard errors were estimated based on available data and used in PSA, instead of 10% of mean value.

B6 Document B. Section B.3. There are several statements in the cost-effectiveness section of the submission where it is noted that model assumptions and parameter estimates have been validated with UK clinical experts (see page 125, 130, 144, 146, 153). However, the citation reference suggests just one UK clinical expert was consulted.

- Please clarify how many UK clinical experts have been consulted when preparing the cost-effectiveness section of the submission.

- Please comment on the generalisability of those assumptions to UK clinical practice and seek additional clinical expert opinion if required.

Response – During expert interviews, Galderma sought the opinion of one UK clinical expert and one UK-based health economic expert. During the Delphi panel exercise, Galderma sought the opinion of two UK clinical experts, one of whom was

the same clinical expert who participated in the expert interviews.[1,2] Therefore, two UK clinical experts were consulted when preparing the cost-effectiveness section of the submission.

The findings of these clinical experts can be considered generalisable to wider UK clinical practise. Both experts consulted are Consultant Dermatologists with considerable experience (20+ years) treating skin conditions, including PN in the UK. While PN is a rare condition, it was believed that Consultant Dermatologists would have the most experience with treating patients with PN, especially those with moderate to severe disease. Both experts have contributed to peer-reviewed papers and textbook chapters considering skin diseases, and therefore, are considered at the forefront of their field. Similarly, both experts have trained and treated patients across several hospitals in the UK and so would be aware of how treatment for PN varies in different settings.

B7. Document B. Section B.3.3.2, p.139, Table 36. Please provide a detailed breakdown of the reasons for treatment discontinuation, and the numbers, reported as n/N (%) discontinuing for each reason. Please clarify whether those discontinuing treatment were assumed to be non-responders in the model?

Response – A breakdown of the reasons for conditional discontinuation is presented in Table 12. In the economic model, patients who discontinued treatment were assumed to be non-responders.

As stated in the response to B5, the input for conditional discontinuation for BSC has been updated following the response to the clarification questions. The previous conditional discontinuation rate for BSC in the Company submission was an error in the economic model. The conditional discontinuation rate for BSC is based on the proportion of patients in ARCADIA 1 who responded to placebo at Week 16 but withdrew from treatment at Week 24 (the latest available time point when patients were on treatment). This data is based on OLYMPIA 1 only, as OLYMPIA 2 only included a 16-week treatment period. For both nemolizumab and placebo, response was determined based on PP NRS rather than the composite endpoint due to the low number of placebo patients who responded based on the composite endpoint.

The conditional discontinuation rate at Week 52 for BSC can be considered conservative, as it is based on 24-week data from the OLYMPIA 1 trial. To assess the uncertainty around the assumption, the following scenario analysis is presented in Appendix A:

- Scenario: discontinuation in the BSC arm converted to an annual rate
- Scenario: No discontinuation applied to the BSC arm

Table 12. Treatment discontinuation and reason at Week 52 and Year 2 onwards

Treatment	Reason for discontinuation from study	Discontinuation at Week 52 and Year 2 onwards	Source
Nemolizumab	[redacted]	[redacted]	OLYMPIA LTE[7]
BSC	[redacted]	[redacted]	OLYMPIA 1[27]

Abbreviations: BSC, best supportive care; LTE, long-term extension; SE, standard error.

B8. PRIORITY: Document B, Section B.3.3.3, p.139, Table 37. The table provides estimates of treatment effect waning over time by treatment arm, based on assumptions applied in TA955. Please provide

- A justification, based on clinical expert opinion, why the assumptions from TA955 hold for the current assessment. Please provide this for both nemolizumab and BSC arms.
- Details of the content of BSC (i.e. type of BSC treatment) used to underpin the assumptions about BSC treatment waning effect from TA955. Please clarify whether these assumptions align with the definition of BSC in the current model for “responders” or “non-responders”?
- Details of any real-world evidence the company were able to find that could be used to inform longer-term treatment waning effect assumptions for either arm of the model.
- A scenario analysis that takes an alternative approach to estimating treatment waning effect that uses all available response measurement timepoints from the OLYMPIA 1, OLYMPIA 2 and LTE studies.

Response: The treatment waning over time for nemolizumab and BSC were aligned with the assumptions from TA955 for dupilumab and BSC, respectively.[3] As dupilumab and nemolizumab are both active biologic treatments, the treatment waning assumption for dupilumab can be considered generalisable to nemolizumab in the absence of treatment waning data specifically for nemolizumab in moderate to severe PN. In line with TA955, BSC for responders is considered to consist of emollients, TCSs, and TCIs; therefore, the waning assumption for BSC can also be considered generalisable to the Company economic model.[3] Furthermore, to validate the treatment waning assumptions from TA955, the treatment waning inputs were presented to a UK clinical expert and a UK health economic expert during expert interviews.[2] The experts validated that the assumptions from TA955 were appropriate for inclusion in the Company economic model for nemolizumab and BSC, with nemolizumab expected to have a lower rate of treatment waning compared with BSC.[2]

In TA955, the treatment waning assumptions for BSC was based on the NICE Committee's assumptions from dupilumab for treating moderate to severe atopic dermatitis [TA534].[3,30] The assumption from TA534 was based on a survey of clinical experts, who stated that it is improbable that the effect of BSC alone would persist.[3,30] In TA534, BSC in atopic dermatitis (AD) was considered to be combination of emollients, low-to-mid potency TCSs, and rescue therapy (such as higher potency topical or oral corticosteroids, or TCIs).[30] Therefore, BSC in TA534 can be considered to be aligned with the definition of BSC for responders in the Company economic model. Based on the alignment of BSC between TA534 and the Company economic model, and further validation by a UK clinical expert,[2] the treatment waning assumption for BSC from TA955 and TA534 can be considered most appropriate and generalisable data for the BSC in the Company economic model.

Galderma have not identified any real-world evidence that would be suitable for inclusion in the economic model and consider the treatment waning assumptions for nemolizumab and BSC, based on TA955,[3] as suitable evidence in the absence of treatment waning data specific for nemolizumab.

Treatment waning is introduced into the model in Year 2 onwards. Therefore, based on the available data from the OLYMPIA 1, OLYMPIA 2, and OLYMPIA LTE studies, scenario analysis is not feasible using response measures from these trials.

Health state utility values

B9. PRIORITY: Document B, Section B.3.4.1, p.144. The company submission states that "The LTE study was not used in HRQoL assessment as utility estimates at week 56 and week 104 were not feasible based on low patient numbers". Please provide the following points of clarification:

- Please provide a reason why limited EQ-5D data are available from the LTE study and please provide further details about the company concerns regarding the validity of the available EQ-5D data for populating the economic model.

- Even if sample size is small, please provide full details of all available EQ-5D data from the LTE study. Please report these as mean (SD) and number of participants reporting data by nemolizumab naïve, prior nemolizumab, and both groups pooled. Please provide these data for all available time points from the LTE study.

- If the company are particularly concerned about the validity of the available EQ-5D utility data from the LTE study, the EAG suggest exploring two alternative approaches, specifically (a) conducting a literature search for any other published EQ-5D utilities (by responder status) and if no such data are available, (b) exploring an alternative approach to estimating utilities by mapping the DLQI presented within table 26 to the EQ-5D using methodology published by Ali et al., 2017.

Response – The limited availability of EuroQol-5D (EQ-5D) data in the LTE is due to the trial schedule, as patients enrol in the LTE study with varying time since the start of nemolizumab treatment.

Therefore, analysis visit dates were calculated using the lead-in study treatment start date and the analysis date of the visit in the LTE. By calculating time on treatment, patient utility values could be consistently assessed at key time points for the amount

of time that treatment was received. This approach captured the time that patients received nemolizumab more accurately but resulted the limited data around the Week 56 and Week 104 timepoints.

Galderma considers the EQ-5D data from the OLYMPIA 1 and OLYMPIA 2 trials as appropriate for inclusion in the economic model and does not have concerns about the validity of the data. In the absence of EQ-5D data from the LTE study, it was assumed that the utility value for responders in Year 2 would increase by 5% based on data from the AD LTE (ARCADIA LTE) study,[31] which demonstrated that utility values for responders would increase over time. This assumption was validated by a UK clinical expert and UK health economic expert, and considered appropriate for inclusion in the economic model.[2] The UK clinical expert supported this assumption by stating that in patients with PN, itch relief is observed shortly after treatment initiation, but it takes longer (approximately 1 year) for the skin lesions to heal.[2] In addition, the assumption that non-responders to nemolizumab at Year 1 have equal utility to responders for 6 months to account for partial responders to treatment at Week 16 was also validated by the UK clinical and health economic experts and is aligned with the assumption used in TA955.[2,3] Overall, the assumptions and data used to determine the utility values have been validated by experts and can be considered appropriate for use in the economic model.

Table 13 contains the utility data available after the previously discussed approach was applied for the composite outcome (IGA+PP NRS improvement) responders. Responders at Week 16 were considered as the relevant population, so that the economic model can best reflect any utility benefits associated with response to nemolizumab in the long-term.

Table 13. Utility data from OLYMPIA LTE Composite Outcome (IGA + PP NRS improvement) responders

Time from treatment start from lead-in	Arm	N	Mean (SD)
Week 20	Nemolizumab naïve	[redacted]	[redacted]
	Prior nemolizumab	[redacted]	[redacted]
	Nemolizumab naïve and prior nemolizumab pooled	[redacted]	[redacted]
Week 56	Nemolizumab naïve	[redacted]	[redacted]
	Prior nemolizumab	[redacted]	[redacted]
	Nemolizumab naïve and prior nemolizumab pooled	[redacted]	[redacted]
Week 80	Nemolizumab naïve	[redacted]	[redacted]
	Prior nemolizumab	[redacted]	[redacted]
	Nemolizumab naïve and prior nemolizumab pooled	[redacted]	[redacted]
Week 104	Nemolizumab naïve	[redacted]	[redacted]
	Prior nemolizumab	[redacted]	[redacted]
	Nemolizumab naïve and prior nemolizumab pooled	[redacted]	[redacted]
Week 128	Nemolizumab naïve	[redacted]	[redacted]
	Prior nemolizumab	[redacted]	[redacted]
	Nemolizumab naïve and prior nemolizumab pooled	[redacted]	[redacted]

Abbreviations: IGA, Investigator Global Assessment; LTE, long term extension; NA, not available; PP NRS, peak pruritus' numerical rating scale; SD: standard deviation.

As previously stated, the Company is not concerned with the validity of utility estimates and considers the EQ-5D data from the OLYMPIA 1 and OLYMPIA 2 trials as the most appropriate and generalisable data to support the economic model. The Company does not consider it appropriate to map Dermatology Life Quality Index (DLQI) data from the LTE to EQ-5D. Similar to EQ-5D, there is limited DLQI data available from the LTE study. Furthermore, the approach of mapping the DLQI to EQ-5D would add additional uncertainty to the utility estimates.

B10. Document B, Section B3.4.1, p.144. It is assumed in the model that utility values for responders would increase by 5% in year 2 and that these increased utilities would be sustained for the full duration of response in the economic model. Please provide further justification for the validity of this assumption, particularly given the high resultant utility value ([redacted]). Where possible, please justify the approach taken by reporting relevant EQ-5D utility data from the OLYMPIA and LTE studies.

Response – Utilities were estimated based on PLD at Week 16 from the OLYMPIA 1 and OLYMPIA 2 trials and were not available from OLYMPIA LTE based on the low patient number. In the absence of long-term utility data for nemolizumab for the treatment of PN, long-term utilities were estimated based on the trend observed in the LTE trial for nemolizumab in AD (ARCADIA LTE).[31] In this trial, a 10% increase in utility value for responders was observed between Weeks 16 and 104. In the economic model, a conservative approach was applied, which assumes a 5% instead of a 10% increase in long-term utility values for responders. This assumption was conservatively applied to both the nemolizumab and BSC arms.

The increase in utility values for responders over time was validated by a UK clinical expert, who stated that although itch relief is observed shortly after treatment initiation, it takes more time for skin lesions to heal. Therefore, it would not represent clinical practice to use the utility value observed at Week 16 for responders in the long-term, as additional quality of life (QoL) increase is observed up to at least 1 year after treatment initiation.

In addition, the regression analysis presented in response to B13 demonstrates that the utility for responders is shown to increase over time, which supports the assumption included in the economic model.

B11. PRIORITY: Document B, Section B.3.4.3, p.146 & Table 41. Please provide a table reporting EQ-5D utilities (Mean, SD, N) according to response status used in the economic model. Please provide these data separately for all available time

points from OLYMPIA 1 and OLYMPIA 2 and pooled across studies where there are common measurement time points (e.g. at week 16).

Response - EQ-5D utility summaries according to the response status at Week 16 of the composite outcome are presented in Table 14. These data are presented for OLYMPIA 1 and OLYMPIA 2 as well as the pooled population.

Table 14. EQ-5D utilities by response status of composite outcome at Week 16

		Response				Non-response			
		Nemolizumab		BSC		Nemolizumab		BSC	
Analysis visit	Study population	N	Mean (SD)	N	Mean (SD)	N	Mean (SD)	N	Mean (SD)
Baseline/Day 1	OLYMPIA 1	[redacted]							
	OLYMPIA 2	[redacted]							
	OLYMPIA 1+2	[redacted]							
Week 4	OLYMPIA 1	[redacted]							
	OLYMPIA 2	[redacted]							
	OLYMPIA 1+2	[redacted]							
Week 8	OLYMPIA 1	[redacted]							
	OLYMPIA 2	[redacted]							
	OLYMPIA 1+2	[redacted]							
Week 16	OLYMPIA 1	[redacted]							
	OLYMPIA 2	[redacted]							
	OLYMPIA 1+2	[redacted]							
Week 20	OLYMPIA 1	[redacted]							
	OLYMPIA 2	[redacted]							
	OLYMPIA 1+2	[redacted]							
Week 24	OLYMPIA 1	[redacted]							
	OLYMPIA 2	[redacted]							
	OLYMPIA 1+2	[redacted]							

Abbreviations: BSC, best supportive care; EQ-5D, EuroQoL-5 dimension; NA, not available; SD, standard deviation.

B12. Document B, Section B.3.4.3, p.146 & Table 41. The EAG note large differences in utilities between responders and non-responders, noting particularly high utilities for responders ([redacted]). This is substantially higher than what might be expected for similar age adjusted UK general population norms. Please cross-check the calculation approach taken and validate against existing known HSUVs for EQ-5D profiles (e.g. profile 33333). Assuming the calculations are correct, please then comment on any reasons why we would expect utility values that are higher than UK general population norms.

Response – The utility value for responders in year 1 ([redacted]) is based on utility data at Week 16 for patients who respond to treatment with nemolizumab. Moderate to severe PN has a significant negative impact on patient's sleep,[32] QoL, and mental health.[33] One study in patients with PN reported that 57% of patients experienced depression due to the disease; while another study in patients with PN reported that 18.5% of patients with PN experienced suicidal ideations.[34] In addition, there are currently no treatment options recommended by NICE for moderate to severe PN, and the currently available treatments are used off-label and aim solely to relieve symptoms rather than address the pathophysiology of the disease. Therefore, based on this significant burden and lack of available treatments, patients who suffer from moderate to severe PN may value their health more than the general population after itch and other symptoms are controlled, which would result in a utility value higher than the general population.

To assess the impact of capping the utility based on the general population values, a scenario analysis was conducted where the maximum health state utility value (responders in Year 2+) was equal to 0.85 (the average general population utility value for a person at the age of 54 years).[35] However, as the utility values were based on the OLYMPIA 1 and OLYMPIA 2 trials and validated by a UK clinical expert,[2] it would not be appropriate to only decrease the utility for responders in Year 2+ without applying an equivalent decrement to the other health state utility values. Therefore, an equal utility decrement was applied to all health state utility values to keep the difference between health state utility values equal to the values presented in the Company submission (Table 15). The results of this scenario analysis are presented in Appendix A.

Table 15. Utility values by response status in scenario analysis with utility capped at the general population value

Parameter	Nemolizumab (SE)	BSC (SE)
Baseline	[redacted]	
Responders		
Responder Year 1 (Week 9–52)	[redacted]	
Responder Year 2	[redacted]	
Responder Year 3+	[redacted]	
Non-responder		
Non-responder Year 1	[redacted]	[redacted]
Non-responder Year 2	[redacted]	
Non-responder Year 3+	[redacted]	

Abbreviations: BSC, best supportive care; SE, standard error.

B13. PRIORITY: Document B, Section B.3.4.3, p.146 & Table 41. Please provide an appropriately specified regression analysis (e.g. repeated measures model) using all available EQ-5D data to support the utility values reported in Table 41. In particular, please use this regression to predict the additional utility that can be achieved by responders adjusting for baseline EQ-5D utility.

Response – Using all available EQ-5D data from the OLYMPIA 1, OLYMPIA 2, and OLYMPIA LTE trials, such that each analysis visit date is noted and calculated from the start of trial and the time on treatment during lead-in studies (OLYMPIA 1 and OLYMPIA 2) are accounted for, it is possible to fit a linear mixed effects model to assess the effect of time on EQ-5D values, with repeated measures for each patient. A random intercept was included for each patient to account for the repeated measures. Only observations of those who responded at Week 16 to the composite outcome (PP NRS + IGA improvement) were included in the model.

Variables treated as fixed effects and any interaction terms used in the model are listed in Table 16. The values of these coefficients presented in Table 17 demonstrate that as the time of observations increases, the utility value will also slowly increase. This aligns with UK clinical expert input and supports the

assumption used in the economic model that utility values for responders will increase by 5% in Year 2 onwards.[2]

The values predicted by the linear mixed effects model (Table 17) demonstrate higher utility values at 1 year in responders ([redacted]) than the utility values in Document B Section B.3.4.3 (Responder 1-year: [redacted]). The predictions produced by the model are visualised in Figure 1.

Table 16. Variable coefficient values and intercept of linear mixed effects model

Variable/Intercept	Estimate (SE)
Intercept	[redacted]
Analysis week visit (weeks)	[redacted]
Model inputs summary	
Number of observations	[redacted]
Random effects groups	[redacted]

Abbreviations: SE, standard error.

Table 17. Values predicted by linear mixed effects model

Parameter	Utility EQ-5D model prediction
Baseline	[redacted]
Week 16	[redacted]
Year 1	[redacted]
Year 2	[redacted]
Year 3	[redacted]

Abbreviations: EQ-5D, EuroQoL-5-dimensions.

[redacted]Figure 1. Linear mixed effects model predictions of EQ-5D for responders of composite outcome (PP NRS + IGA improvement) at Week 16

Abbreviations: EQ-5D, EuroQoL-5-dimensions ; iGA, Investigator's Global Assessment ; PP NRS, peak pruritus numerical rating scale.

B14. Document B, Section B.3.4.3, p.146 & Table 41. Please provide further justification for applying an additional treatment specific utility benefit to responders in the nemolizumab arm at 1 year, but not to responders in the BSC arm. Please

support the chosen approach using EQ-5D utility data available from the OLYMPIA studies and LTE study where feasible. This could be achieved for example using a regression analysis with treatment by response status interaction terms to determine the validity of treatment specific utility for year 1 responders.

Response – In the economic model, equal utility values were used for responders in the nemolizumab and BSC arms. However, patients who discontinued nemolizumab treatment due to lack of response, or for any other reason, have increased utility for the initial 6 months and after that they return to baseline utility values. Whereas patients who do not respond to BSC at Week 16 or go on to lose response through discontinuation or treatment effect waning were assumed to have baseline utility.

The assumption to have higher utility for non-responders in the nemolizumab arm in Year 1 was included to align with TA955, and accounts for partial responders at Week 16 and the durability effect that is observed after effective treatment is stopped.[3] Furthermore, this assumption was validated by a UK clinical expert.[2] In the response to B11, the EQ-5D utilities for non-responders observed in the OLYMPIA 1 and OLYMPIA 2 clinical trials at Weeks 16 and 24 are greater for nemolizumab versus placebo. Therefore, this data further supports the increased utility for nemolizumab non-responders versus BSC non-responders in Year 1.

B15. Document B, Section B.3.4.3. Please provide a calculation of QALYs using the area under the curve approach, with linear extrapolation between time points for each arm of the OLYMPIA 1 and 2 studies and pooled across studies. Please report incremental QALYs over the trial follow-up period. Please comment on how the QALY calculations over trial follow up align with or contradict the clinical findings from the studies.

Response – The area under the curve approach was conducted to calculate the QALYs within trial period (24 weeks). Utility estimates for responders and non-responders and response rates at Weeks 0, 16 (based on OLYMPIA 1 and OLYMPIA 2 trials) and 24 (based on OLYMPIA 1 trial) were used to develop a linear regression model. This model was used to estimate values of these parameters at different time points from Week 0 to 24 with 2-week intervals. QALYs were estimated using data mentioned above and PN-specific mortality. QALYs for nemolizumab and BSC over 24 weeks (0.46 years) are presented in Table 18.

Table 18.Total QALYs over 24 weeks in area under the curve analysis

Source	Total QALYs over 24 weeks		
	Nemolizumab	BSC	Incremental
OLYMPIA 1 and 2	[redacted]	[redacted]	[redacted]
OLYMPIA 1	[redacted]	[redacted]	[redacted]
OLYMPIA 2	[redacted]	[redacted]	[redacted]

Abbreviations: BSC, best supportive care; QALY, quality adjusted life year.

The improved incremental QALYs for nemolizumab versus BSC over the 24-week time period aligns with the QoL data from the OLYMPIA 1 and OLYMPIA 2 clinical trials. In OLYMPIA 1, nemolizumab treatment resulted in a statistically significant improvement of ≥ 4 points in DLQI from baseline at Weeks 4, 16 and 24 versus placebo (strata adjusted [redacted] at all timepoints) and a statistically significant improvement in EQ-5D visual analogue scale (VAS) at Weeks 16 and 24 versus placebo (Week 16: strata adjusted [redacted]; Week 24: strata adjusted [redacted]). Similarly, in OLYMPIA 2, nemolizumab treatment resulted in a statistically significant improvement of ≥ 4 points in DLQI from baseline at Weeks 4 and 16 versus placebo (strata adjusted [redacted] at both timepoints) and a statistically significant improvement in EQ-5D VAS at Week 16 versus placebo (strata adjusted [redacted]).

B16. Document B. Section B.3.4.3. & B3.5.3. p.143 & 153, Tables 28 & 30. Within the economic model only atopic dermatitis, eczema nummular and neurodermatitis were included. However, Tables 28 & 30 detail several other TRAEs occurring in ≥2% of patients that do not appear to have been included in the model.

- Please provide a table which details all moderate and severe TRAEs that occurred in ≥2% of patients for nemolizumab and BSC.

- If not already included in the model, please incorporate these TRAEs into the model with relevant costs and disutilities attached.

- Within section B.3.4.3.1. it is stated that "*utility values obtained from the OLYMPIA 1 and OLYMPIA 2 clinical trial data would sufficiently capture the impact of TRAEs on QoL*". However, given that the average duration of an AE was only assumed to be 14 days, it is unlikely, in the majority of cases that AE disutilities would be adequately captured by the EQ-5D. Please provide

additional evidence to support the company's concern that including adverse event disutilities might be double counting QoL.

Response – The data provided in Tables 28 and 30 of Document B lists all treatment emergent adverse events (TEAEs) experienced by ≥ 2% of patients in either treatment group in the OLYMPIA 1 and 2 and LTE clinical trials. Table 19 details only the moderate to severe TEAEs that occurred in ≥ 2% of patients in the OLYMPIA 1, OLYMPIA 2 and LTE study.

Table 19. Moderate to severe TEAEs that occurred in ≥ 2% of patients in the OLYMPIA 1 and OLYMPIA 2 trials

	OLYMPIA 1[36]		OLYMPIA 2[37]		OLYMPIA LTE[38]
	Nemolizumab	Placebo	Nemolizumab	Placebo	Nemolizumab
n	167	95	183	91	508
Any moderate TEAE n, (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Any severe TEAE n, (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gastrointestinal disorders					
Moderate n, (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
General disorders and administration site conditions					
Moderate n, (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Infections and infestations					
Moderate n, (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Severe n, (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
COVID-19 n, (%) Moderate	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Nasopharyngitis n, (%) Moderate	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Upper respiratory tract infection n, (%) Moderate	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Injury, poisoning and procedural complications					
Moderate n, (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Investigations					
Moderate n, (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Musculoskeletal and connective tissue disorders					
Moderate n, (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Arthralgia n, (%) Moderate	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Nervous system disorders					
Moderate n, (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Headache n, (%) Moderate n, (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Respiratory, thoracic and mediastinal disorders					
Moderate n, (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Skin and subcutaneous tissue disorders					
Moderate n, (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Severe n, (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Neurodermatitis n, (%) Moderate	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Eczema n, (%) Moderate	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Eczema nummular n, (%) Moderate	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pruritus n, (%) Moderate	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Vascular disorders					
Moderate n, (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: COVID-19, coronavirus disease-2019; LTE, long term extension; TEAE, treatment emergent adverse event.

Following response to the clarification question, the TRAEs included in base-case economic model have been updated and the updated base-case results presented in Appendix A. The base-case economic model was updated to include study drug related adverse events that occurred in at least 2% of patients from any treatment group based on the OLYMPIA 1 and OLYMPIA 2 trials. The rate of TRAEs used in the economic model are presented in Table 20.

Table 20. TRAEs rates in economic analysis

Treatment	Nemolizumab N = 370 % (n)	BSC N = 186 % (n)	Source
AD	[redacted]	[redacted]	OLYMPIA 1 and OLYMPIA 2[27,28]
Eczema nummular	[redacted]	[redacted]	
Neurodermatitis	[redacted]	[redacted]	
Dyspnoea	[redacted]	[redacted]	
Asthma	[redacted]	[redacted]	
Headache	[redacted]	[redacted]	

Abbreviations: AD, atopic dermatitis; BSC, best supportive care; TRAE, treatment related adverse event.

In line with the assumption used in TA955,[3] disutilities due to adverse events were not included in the base-case, as adverse reactions observed within the trial period were not expected to cause any significant reduction in QoL and this minor impact may have already been captured in EQ-5D collected within the trial. However, scenario analysis was where disutility due to adverse events is captured is presented in Appendix A.

Resource use and costs

B17. Document B. Section B.3.5, p.150 & 151, Tables 45 & 46. Please confirm whether all components of BSC for responders and non-responders would be provided through secondary or primary care? If primary care, please ensure that all treatment acquisition costs are based on the appropriate drug tariff price. If secondary care, please provide the relevant eMIT prices. Where any branded

treatments are costed in the model, please provide a clear justification for using branded list prices instead of drug tariff (or eMIT) prices.

Response – It is anticipated that all components of BSC will be provided through primary care. In line with this assumption, the costs for BSC estimated based on drug tariff prices using BNF.[39]

B18. Document B. Section B.3.10, p.148, Table 44. The use of immunosuppressants is assumed to be 77% for non-responders based upon feedback from a modified Delphi panel exercise. Further, it is also stated on page 163 that "*Many of the off-label treatments patients currently receive require at least once daily applications or administration, with immunosuppressive treatments, such as methotrexate, requiring frequent monitoring and follow-up appointments*.". Please provide:

- Full details of the methodology used for the Modified Delphi Panel, including how many UK clinicians were consulted and how a consensus was reached. Where variability of opinion existed, how was this accounted for in the economic model (e.g. through the PSA).

- Confirmation about whether the costs within table 46 include administration and monitoring costs associated with treatments detailed within table 44 or represent the monitoring cost of the prurigo nodularis disease itself. If not, please provide a scenario analysis that includes these costs within the economic model.

- Additional information about the dosage and method of administration assumed for methotrexate and for systemic corticosteroids (Table 46).

Response – The full methods of the modified Delphi panel are provided in the Delphi protocol.[40]

The population surveyed during the Delphi panel was intended to be representative of the overall population of interest, which is clinicians with experience of treating PN in a UK or Canadian healthcare setting. It was believed that participants should be considered experts in the topic with credibility in their field;[41,42] the group should be multi-disciplinary, with a relatively heterogenous group considered more robust.[43]

Four clinicians were consulted during the modified Delphi panel exercise, two were based in the UK and two were based in Canada.

The modified Delphi panel exercise consisted of a concise online survey, containing 27 statements/questions, which was completed by the experts. The survey contained a series of questions, mostly statements with the aim of assessing consensus through the form of a five-point agreement scale (strongly agree, agree, neutral, disagree, strongly disagree). Additionally, there were questions where participants were requested to rank responses, as well as some single or multiple-choice options. In some instances, free-text boxes were provided for participants to elaborate on their answers in order to support the consensus statements.

Once the surveys were completed, the responses were consolidated and the percentage agreement for each statement was calculated. Whilst there is no accepted standard for the percentage of agreement that reflects consensus, a threshold of 70–80% is commonly reported in other consensus studies.[44,45] Therefore, given the number of participants (n = 4), statements with ≥ 75% agreement (at least three out of four participants) were considered to demonstrate consensus. Statements with < 75% agreement were retained to be explored further in the consensus conference.

The consensus conference aimed to further explore the results from the online survey, focusing on areas where there was uncertainty in the responses. During the conference, results of the online survey were presented for discussion. Where the survey found consensus, the experts were asked to validate this consensus. Where there was lack of consensus, the experts exchanged opinions in an attempt to obtain consensus.

Inputs that were calculated based on the modified Delphi panel were included in the PSA through standard approach. Mean values together with standard error and assigned distribution was used to provide probabilistic estimates.

The costs in Document B Table 46, include the treatment costs of BSC. All treatments included as BSC are either topical or oral; therefore, no administration costs are included. The monitoring costs for BSC are assumed to be captured by the disease management and monitoring costs for responders and non-responders, presented in Document B Table 47.

The resource usage for responders and non-responders in Document B Table 47 were sourced from TA955 and were validated by UK clinicians.[2,3] As discussed in response to B3, in TA955 the Company state that the resource use costs are conservative. Therefore, the resource use from TA955 may not fully capture the additional monitoring associated with treatments such as methotrexate, which was not considered as part of BSC in TA955.[3] However, Galderma does not consider it appropriate to present a scenario with additional monitoring costs for BSC as this risks double counting and would add additional uncertainty to the economic model.

Methotrexate and systemic corticosteroids were included as BSC for non-responders. Oral methotrexate was assumed at a dose of 20 mg per week based on the modified Delphi panel.[1] For systemic corticosteroids, oral prednisolone was assumed at a dose of 12.5 mg per week.

B19. Document B. Reference 5. Clinical and health economic expert interview report, p.5. The reference suggests that a second interview will have taken place: "…a second round scheduled to take place at the model implementation phase.". Please clarify whether a second round did take place, and if so, provide documentation of the methodology and findings from this interview**.**

Response – The second round of interviews took place on 31st July 2024 and involved a UK based clinical expert and a health economic expert.

The methodology and the findings from this round of interviews can be found the combined interview report.[2]

References

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal

Nemolizumab for adults with moderate to severe prurigo nodularis [ID6451]

Additional clarification questions

November 2024

File name	Version	Contains confidential information	Date
[ID6451] Nemolizumab additional CQ 291124 [Redacted]	2	Yes	29/11/2024

Additonal clarification questions

CQ1. Regarding clarification query points A7 and A8, we note that the company has chosen not to share the composite outcome data from Stander 2020 (NCT03181503). However, we believe it is important for the Committee to consider the full range of evidence available for Nemolizumab, and therefore all three studies (OLYMPIA 1, OLYMPIA 2 and NCT03181503) should ideally be included in a meta-analysis or pooled analysis. This approach would enable the inclusion of these pooled data as a scenario analysis in the economic model, potentially enhancing the Committee's decision-making process. We would like to offer the company another opportunity to reconsider sharing these data. If the company decides against providing them, we will address this in our critique and conduct "best guess" scenario analyses based on the individual outcomes from the composite measure. While we acknowledge the company's stance against using Stander 2020 data, we firmly believe that the Committee should have access to this information to inform their decision.

Response – As discussed in response to CQ A7, Galderma chose not to present the patent level data (PLD) for the composite outcome of an improvement of ≥ 4 Peak Pruritus Numerical Rating Scale (PP NRS) and Investigator Global Assessment (IGA) success (defined as a score of 0 or 1) with an improvement of ≥ 2 points from Stander 2020 (NCT03181503)[1] as more robust data is available from the phase 3 trials, OLYMPIA 1 and OLYMPIA 2.[2,3]

In addition to this justification, there are a number of differences between the Phase 2 Stander 2020 trial and phase 3 OLYMPIA 1 and OLYMPIA 2 trials, that would make a pooled analysis inappropriate. Firstly, Stander 2020 includes a 12-week treatment duration and IGA was not assessed at week 16.[1] Therefore, pooling 12-week and 16-week data would add uncertainty to the composite outcome estimate at week 16. In addition, the IGA scale used in Stander 2020 was updated for the phase 3 trials based on feedback by the Food and Drug Administration (FDA). In the phase 3, OLYMPIA 1 and OLYMPIA 2 trials the IGA scale was updated to focus only on stage rather than elements of stage and activity (Table 2).[4] Finally, the dosing of nemolizumab was different between the phase 2 and phase 3 trials. In the Stander 2020 trial, a weight-based dosing of 0.5mg/kg was implemented for nemolizumab.[1]

Whereas in the phase 3, OLYMPIA 1 and OLYMPIA 2 trials a weight-based dosing approach was implemented for nemolizumab where patients weighing less than 90 kg received a 60-mg loading dose, followed by 30 mg every 4 weeks (Q4W), and those weighing 90 kg or more received 60 mg Q4W.[2,3] Therefore, based on these differences between the phase 2 Stander 2020 trial and the phase 3 OLYMPIA 1 and OLYMPIA 2 trials, a scenario analysis using pooled data of the composite outcome would be associated with significant uncertainty compared to the base-case and should not consider it appropriate for decision making.

Table 1. Evolution of IGA from phase 2 to phase 3 nemolizumab clinical trials

Score	Category	IGA scale used in trial	
		Stander 2020 (NCT03181503)	OLYMPIA 1 and OLYMPIA 2
0	Clear	No nodules and no activity signs (erythema, excoriations and/or crusts and/or bleeding). Post-inflammatory hypo-/hyperpigmentation may be present.	No nodules
1	Almost clear	Rare single nodules, flattened and activity signs (excoriations/crusts/bleeding) may be present	Rare palpable pruriginous nodules
2	Mild	Few nodules, dome-shaped with activity signs (excoriations/crusts/bleeding) present	Few palpable pruriginous nodules
3	Moderate	Many nodules, flattened with activity signs (excoriations/crusts/bleeding)	Many palpable pruriginous nodules
4	Severe	Generalised nodules, dome-shaped with activity signs (excoriations/crusts/bleeding)	Abundant palpable pruriginous nodules

IGA, Investigator Global Assessment
Source: Galderma, CD14152.CTD2.7.3 Summary of Clinical Efficacy Prurigo Nodularis[4]

However, despite the uncertainty associated with a pooled analysis of the composite outcome data from Stander 2020, OLYMPIA 1 and OLYMPIA 2, as requested by the EAG, this data is presented in Table 2. In addition, as requested by the EAG, scenario analysis results based on the pooled analysis are presented in Table 3. These results demonstrate that inclusion of pooled composite outcome data from the phase 2 Stander 2020 does not have a significant impact on the response rates at week 16 or cost-effectiveness results.

Table 2. Response rates for composite outcome of an improvement of ≥ 4 PP NRS and IGA success (defined as a score of 0 or 1) with an improvement of ≥ 2 points

PP NRS + IGA	Nemolizumab	BSC	Source
Week 16	[redacted]	[redacted]	OLYMPIA 1 and OLYMPIA 2[2,3]
Week 12	[redacted]	[redacted]	Stander 2020[5]
Week 12/16	[redacted]	[redacted]	Stander 2020, OLYMPIA 1 and OLYMPIA 2[2,3,5]

Abbreviations: BSC, best supportive care; IGA, Investigator Global Assessment; SE, standard error.

Table 3. Scenario analysis results with PAS

Base-case assumption	Scenario	Incremental costs	Incremental LYs	Incremental QALYs	ICER (per QALYG)
Base-case		[redacted]	0.000	[redacted]	£34,523
Response at Week 16 based on OLYMPIA 1 and OLYMPIA 2	Response at week 16 based on Stander 2020, OLYMPIA 1 and OLYMPIA 2	[redacted]	0.000	[redacted]	£34,458

Abbreviations: ICER, incremental cost-effectiveness ratio; LYs, life years; PAS, patient access scheme; QALYs, quality-adjusted life years; QALYG, quality-adjusted life years gained.

CQ2. Regarding the company's response to clarification question B13, we would like the ask for further clarification. It appears there may have been a misinterpretation of our initial question. It looks like the company have included a mixed-effects repeated measures model for week 16 responders only and have used this model primarily to justify increasing utilities for responders over time. In this scenario, our view is that including an explanatory variable for time alone is not sufficient. We would also like to see the model adjusted for baseline EQ-5D age and gender as a minimum, with the inclusion of an additional explanatory term in the model (e.g. weeks squared) to account for non-linearity in utility gain over time. This would provide a more robust assessment of longer-term health state utility trajectory amongst responders. However, the main purpose of our question was to seek additional validation of the magnitude of difference in health state utility values between response and non-response health states applied in the economic model. This analysis would ideally be conducted on the full sample providing EQ-5D data (both responders and non-responders). Given that EQ-5D utilities were not

available at all time-points (see Table 14 of the response to clarification queries), we appreciate it may not be feasible to apply a repeated measures model. However, we would still appreciate it if the company could provide a simplified regression model (e.g. OLS) with adjustment for baseline EQ-5D utility score, age and gender as a minimum, with the addition of a binary explanatory variable for "response", taking a value of 1 for those who achieved a response on the composite outcome, 0 otherwise). The company may also wish to explore inclusion of indicator variables for "respond at week 16" and "treatment arm" and potentially an interaction of respond at week 16* treatment arm if they wish to further justify a treatment effect for nemolizumab amongst responders at 1 year.

Response –

A. Adjusted mixed-effects model

As requested by the EAG, the mixed-effects model for responders presented in response to CQ B13 was adjusted for EQ-5D at baseline, sex, age (continuous) and time squared to account for the non-linearity in utility gain over time. Coefficients of the adjusted mixed effects model are presented in Table 4. The coefficient for age suggests that there is minimal utility decline as age increases. For time, the linear coefficient suggests that there is an increase in utility, suggesting an increasing trend over time in line with the mixed-effects model presented in response to CQ B13. The quadratic term for analysis weeks is negative which suggests that there is a decelerating increase for the utility in the long-term. However, the inclusion of the quadratic term produces implausible long-term utility results for responders which would not reflect UK clinical practice as the predicted utility significantly decreases between week 52 and week 156 ([redacted] to [redacted] and [redacted] to [redacted] in males and females, respectively [Table 5 and Figure 1]). Therefore, based on the implausible results from the adjusted mixed-effects model an additional analysis was conducted where the mixed-effects model was adjusted for EQ-5D at baseline, sex and age (continuous) but the quadratic term was not included. The coefficients predicted by the adjusted mixed-effects model with the quadratic term removed are presented in Table 6 with the long-term EQ-5D values presented in Table 7 and Figure 2.

Table 4. Coefficients for the adjusted mixed-effects model

Variable/Intercept	Estimate (SE)
Intercept	[redacted]
Age	[redacted]
Sex (Male) [Reference: Female]	[redacted]
Analysis week visit (weeks)	[redacted]
Analysis week visit (weeks)^2	[redacted]
Baseline EQ-5D	[redacted]
Model inputs summary	
Number of observations	[redacted]
Random effects groups	[redacted]

SE, standard error
*Please note that the number of observations included in response to CQ B13 was a typographical error

Table 5. Values predicted by adjusted mixed-effects model

Time	Sex	Age	Baseline EQ-5D	Utility EQ-5D model prediction
0	Male	58.60	[redacted]	[redacted]
52	Male	58.60	[redacted]	[redacted]
104	Male	58.60	[redacted]	[redacted]
156	Male	58.60	[redacted]	[redacted]
0	Female	50.10	[redacted]	[redacted]
52	Female	50.10	[redacted]	[redacted]
104	Female	50.10	[redacted]	[redacted]
156	Female	50.10	[redacted]	[redacted]

[redacted]

Figure 1. Linear mixed-effects model predictions of EQ-5D for responders of composite outcome (PP NRS+IGA improvement) at Week 16

Table 6. Coefficients for the adjusted mixed effects model with quadratic term for weeks removed

Variable/Intercept	Estimate (SE)
Intercept	[redacted]
Age	[redacted]
Sex (Male) [Reference: Female]	[redacted]
Analysis week visit (weeks)	[redacted]
Baseline EQ-5D	[redacted]
Model inputs summary	
Number of observations	[redacted]
Random effects groups	[redacted]

SE, standard error
*Please note that the number of observations included in response to CQ B13 was a typographical error

Table 7. Values predicted by adjusted mixed-effects model with the quadratic term for weeks removed

Time	Sex	Age	Baseline EQ-5D	Utility EQ-5D model prediction

0	Male	58.60	[redacted]	[redacted]
16	Male	58.60	[redacted]	[redacted]
52	Male	58.60	[redacted]	[redacted]
104	Male	58.60	[redacted]	[redacted]
156	Male	58.60	[redacted]	[redacted]
0	Female	50.10	[redacted]	[redacted]
16	Female	50.10	[redacted]	[redacted]
52	Female	50.10	[redacted]	[redacted]
104	Female	50.10	[redacted]	[redacted]
156	Female	50.10	[redacted]	[redacted]

[redacted]

Figure 2. Linear mixed-effects model with the quadratic term removed predictions of EQ-5D for responders of composite outcome (PP NRS+IGA improvement) at Week 16

B. Simplified regression model with binary explanatory variable for response

As requested by the EAG, the coefficients and EQ-5D values of a simplified regression model (OLS [ordinary least squares]) with adjustment for baseline EQ-5D utility score, age and gender, with the addition of a binary explanatory variable for "response" are presented in Table 8 and Table 9, respectively. Based on the data from the OLYMPIA 1 and OLYMPIA 2 trial for responders and non-responders to the composite outcome, the simplified regression model presents a utility gain of [redacted] for responders versus non-responders at week 16.

Table 8. Coefficients for simplified regression model

Variable/Intercept	Estimate (SE)	Statistics	P value
Intercept	[redacted]	[redacted]	[redacted]
Baseline EQ-5D	[redacted]	[redacted]	[redacted]
Age	[redacted]	[redacted]	[redacted]
Sex (Male) [Reference: Female]	[redacted]	[redacted]	[redacted]
Composite outcome responders at week 16	[redacted]	[redacted]	[redacted]

SE, standard error

Table 9. Simplified regression model estimated marginal mean for utility value

Composite outcome at week 16	Utility EQ-5D EMM (SE)	df	Statistic	P value
Responders	[redacted]	[redacted]	[redacted]	[redacted]
Non-responders	[redacted]	[redacted]	[redacted]	[redacted]

df, degrees of freedom; EMM: Estimated marginal mean; SE, standard error

However, Galderma does not consider the utility value in the simplified regression model for non-responders at week 16 as appropriate for long-term utility for non-responders in the economic model. Firstly, in TA955 the Committee concluded that the assumption utility for non-responders would return to baseline 6 months after loss of response was appropriate for decision making.[6] In TA955, clinical experts stated that in clinical trials patients are typically more energised and adherent to the treatment regimens and that a decrease in health-related quality of life (HRQoL) is expected post-trial on return to real-world clinical practice, with patients returning to their previous worse health state post-trial.[6] In addition, the assumption that non-responders would return to baseline utility was further validated by a UK clinical expert with experience in PN consulted by Galderma.[7] Therefore, removing the assumption that non-responders return to baseline utility from the economic model would not be considered generalisable to UK clinical practice as it would contradict both UK clinical expert opinion[7] and the Committee conclusions from TA955.[6]

Finally, the relatively high utility value in the simplified regression model for non-responders at week 16 can be explained by partial responders to treatment and would not reflect long-term utility for non-responders in UK clinical practice. In the

economic model, partial responders to nemolizumab are accounted through non-responders having utility equal to responders for 6 months and then returning to baseline. This assumption was validated by a UK clinical expert[7] and in line with the approach used in TA955.[6] The utility for non-responders to nemolizumab in the first year following loss of response ([redacted]) is aligned with the utility value for non-responders at week 16 from the simplified regression model presented in Table *9* ([redacted]). Therefore, it can be considered that the economic model reflects the utility data from the OLYMPIA 1 and OLYMPIA 2 trials.

C. Interaction of response at week 16 and treatment arm

It should be noted that the economic model does not include a treatment effect for nemolizumab versus BSC on utility for responders. Equal utility values for responders are used in the nemolizumab and BSC arms in all years of the analysis. However, in the economic model a nemolizumab treatment effect is included for non-responder utility in year 1 following loss of response. Patients who do not respond to BSC at Week 16 or go on to lose response through discontinuation or treatment effect waning were assumed to have the baseline utility value until death (Table 10). Whereas patients who do not respond to nemolizumab at Week 16 or go on to lose response through discontinuation or treatment effect waning were assumed to have utility equal to responders for 6 months, after which their utility returned to the baseline value (Table 10). This assumption was included to account for partial responders to nemolizumab at week 16 and the durability effect of nemolizumab after response is lost. A UK clinical expert consulted by Galderma stated that patients receiving nemolizumab are more likely to be partial responders to treatment compared to BSC and non-responders to nemolizumab should have a higher utility value to reflect this in the economic model.[7] Furthermore, this assumption is in line with the approach used in TA955.[6]

To further justify this assumption, an additional OLS model was developed with terms for treatment arm and the interaction of treatment arm and response. The results for this model are presented in Table 11 and demonstrate that there is a statistically significant difference ([redacted]) in non-responder utility at week 16 between placebo and nemolizumab. This data therefore supports UK clinical expert

opinion and assumption of a nemolizumab treatment effect on utility for non-responders in year 1 following loss of response in the economic model.

Table 10. Utilities by response status used in base-case economic model

Parameter	Nemolizumab (SE)	BSC (SE)
Baseline	[redacted]	
Responders		
Responder year 1 (Week 9–52)	[redacted]	
Responder year 2	[redacted]	
Responder year 3+	[redacted]	
Non-responder		
Non-responder year 1	[redacted]	[redacted]
Non-responder year 2	[redacted]	
Non-responder year 3+	[redacted]	

SE, standard error

Table 11. Estimated marginal means and contrasts for non-responder utility in nemolizumab and placebo arms

Composite outcome non-responders at week 16	Utility EQ-5D EMM (SE)	Lower CL	Upper CL	Difference: Placebo – Nemolizumab	P value
Placebo	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Nemolizumab	[redacted]	[redacted]	[redacted]		

CL: 95% confidence limit; EMM: Estimated marginal mean; SE, standard error

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal

Nemolizumab for adults with moderate to severe prurigo nodularis [ID6451]

Clarification questions Appendix A: Updated base-case

November 2024

File name	Version	Contains confidential information	Date
[ID6451] Nemolizumab CQ Appendix A 061124 [Redacted]	**1**	**Yes**	**06 November 2024**

Contents

Tables and figures

Tables

Figures

1 Summary of cost-effectiveness results

Table 1 presents a summary of the changes to the Company's cost-effectiveness model at the Clarification Questions stage of the NICE health technology assessment process. These results supersede those presented in the original Company Submission.

Table 1. Summary of update to base-case cost-effectiveness

Model change	Assumption	ICER (cost/QALY)
NICE submission base case		
-	NICE submission	£34,477
Changes to company model		
1	Clinical input percentages (response, discontinuation, adverse events) were replaced with their original n/N data points	
2	Standard errors were calculated from datasets instead of applying 10% of the mean value assumption	
3	Adverse events were updated to incorporate data from both OLYMPIA 1 and OLYMPIA 2 (clarification question response, Table 11)	
4	Treatment discontinuation at week 52 and year 2 onwards for BSC updated (clarification question response, Table 10).	
Updated company base case post-clarification questions		
-	Updated base-case	£34,523

Abbreviations: ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life years.

1.1. Base-case results

1.1.1. Base-case incremental cost-effectiveness analysis results

The updated base-case cost-effectiveness analysis results for nemolizumab versus best supportive care (BSC) in patients with moderate to severe prurigo nodularis (PN), are presented in Table 2. The cost-effectiveness analysis results for nemolizumab are presented with the patient access scheme (PAS) price applied.

In the base-case analysis, there was a mean incremental improvement of [redacted] discounted quality-adjusted life years (QALYs) for nemolizumab versus BSC and a total mean incremental discounted cost of [redacted]. Therefore, the base-case incremental cost-effectiveness ratio (ICER) estimate for nemolizumab was £34,523 per QALY gained versus BSC, which is just above the willingness-to-pay (WTP) threshold of £30,000 per QALY gained.

Table 2. Updated base-case results with PAS

	Total costs	Total LYs	Total QALYs	Incremental costs	Incremental LYs	Incremental QALYs	ICER (per QALYG)
Nemolizumab	[redacted]	24.895	[redacted]	[redacted]	0.000	[redacted]	£34,523
BSC	[redacted]	24.895	[redacted]				

Abbreviations: BSC, best supportive care; ICER, incremental cost-effectiveness ratio; LYs, life years; PAS, patient access scheme; QALYs, quality-adjusted life years; QALYG, quality-adjusted life years gained.

1.1.2. Base-case long-term QALY outcomes

A breakdown of the QALYs for nemolizumab and BSC from the base-case cost-effectiveness analysis is presented in Table 3.

Table 3. Updated base-case QALY breakdown

QALY component	Nemolizumab	BSC	Incremental
Maintained response health state	[redacted]	[redacted]	[redacted]
No response health state	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]

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

1.1.3. Base-case long-term cost outcomes

A breakdown of the costs for nemolizumab and BSC from the base-case cost-effectiveness analysis is presented in Table 4.

Table 4. Updated base-case cost breakdown with PAS

Cost component	Nemolizumab	BSC	Incremental
Maintained response health state	[redacted]	[redacted]	[redacted]
No response health state	[redacted]	[redacted]	[redacted]
Disease management and monitoring	[redacted]	[redacted]	[redacted]
Adverse events	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]

Abbreviations: BSC, best supportive care; PAS, patient access scheme.

1.2. Sensitivity analysis

1.2.1. Probabilistic sensitivity analysis

In the probabilistic sensitivity analysis (PSA), the economic model samples values from distributions around the means of the input parameters. The probabilistic results are comparable to the base-case analysis and are presented in Table 5.

Scatterplots for the base case analysis, arising from 1,000 simulations of the model with all parameters sampled are presented in Figure 1 and the cost-effectiveness acceptability curves are presented in Figure 2. The PSA results show that the probability that nemolizumab is cost-effective versus BSC is [redacted] at a WTP threshold of £30,000 per QALY gained.

Table 5. PSA results with PAS

	Total costs	Total LYs	Total QALYs	Incremental costs	Incremental LYs	Incremental QALYs	ICER (per QALYG)
Nemolizumab	[redacted]	24.721	[redacted]	[redacted]	0.000	[redacted]	£34,655
BSC	[redacted]	24.721	[redacted]				

Abbreviations: BSC, best supportive care; ICER, incremental cost-effectiveness ratio; LYs, life years; PAS, patient access scheme; PSA, probabilistic sensitivity analysis; QALYs, quality-adjusted life years; QALYG, quality-adjusted life years gained.

Figure 1. ICER scatterplot with PAS

Abbreviations: ICER, incremental cost effectiveness ratio; PAS, patient access scheme; PSA, probablistic sensitivity analysis; QALY, quality adjusted life year; WTP, willingness-to-pay.

Figure 2. Cost-effectiveness acceptability curve with PAS

Abbreviations: PAS, patient access scheme; WTP, willingness-to-pay.

1.2.2. Deterministic sensitivity analysis

The deterministic sensitivity analysis (DSA) involves varying one parameter at a time and assessing the subsequent impact on the incremental costs, incremental QALYs, and ICER. Each parameter is allocated a 'low' value and a 'high' value; for all parameters apart from discount rates, the low value and high value is -/+ 20% of the mean value used in the base-case analysis and demonstrates the impact of specific parameters on ICER estimates.

The ten most influential parameters in the DSA are presented as a tornado plot in Figure 3. The results demonstrate that the parameter with the highest impact on results is the utility of non-responders in the nemolizumab arm (year 3 onwards) in which the ICER varied from [redacted] (dominated) to [redacted] (cost-effective). Overall, the results of the model economic analysis were mostly robust to parameter uncertainty.

[redacted]Figure 3. Tornado plot with PAS

Abbreviations: BSC, best supportive care; ICER, incremental cost effectiveness ratio; PAS, patient access scheme; QALY, quality adjusted life year.

1.2.3. Scenario analysis

A number of scenario analyses were performed, which explored the robustness of the base-case cost-effectiveness estimates to the key model assumptions and parameters. The scenario analysis results are presented in Table 6. With the exception of the nemolizumab dose, the results of all of the scenario analyses were comparable or improved in relation to the base-case cost-effectiveness analysis. These results demonstrate that the cost-effectiveness estimates were robust to alternate model assumptions and parameters.

A scenario with a significant impact on the cost-effectiveness estimates was variation in the assumption regarding the nemolizumab dose. In the scenario where 100% of patients in the nemolizumab arm were assumed receive the < 90 kg nemolizumab dose (30 mg Q4W), nemolizumab was associated with an ICER of £25,804 per QALY gained, which is below the WTP threshold of £30,000 per QALY gained. An additional scenario analysis with a significant impact on the cost-effectiveness estimates was the inclusion of the indirect costs associated with PN based on the productivity loss due to absenteeism and work impairment as a result of sleep

disturbance. In this scenario, nemolizumab had an ICER of £24,699 per QALY gained versus BSC, which is also below the WTP threshold of £30,000 per QALY gained.

Table 6. Scenario analyses results with PAS

Base-case assumption	Scenario	Incremental costs	Incremental LYs	Incremental QALYs	ICER (per QALYG)
Base-case		[redacted]	0.000	[redacted]	£34,523
Company submission scenarios					
Response at Week 16 based on PP NRS + IGA	Response at Week 16 based on PP NRS ≥ 4	[redacted]	0.000	[redacted]	£35,120
No indirect costs included	Inclusion of indirect costs	[redacted]	0.000	[redacted]	£24,699
Disutilities due to AEs not included	Inclusion of disutilities due to AEs	[redacted]	0.000	[redacted]	£34,538
Treatment effect waning included	No treatment effect waning	[redacted]	0.000	[redacted]	£37,054
30% of patients received ≥ 90 kg nemolizumab maintenance dose	100% of patients received ≥ 90 kg nemolizumab maintenance dose (60 mg Q4W)	[redacted]	0.000	[redacted]	£54,867
70% of patients received < 90 kg nemolizumab maintenance dose	100% of patients received < 90 kg nemolizumab maintenance dose (30 mg Q4W)	[redacted]	0.000	[redacted]	£25,804
Increased mortality for patients with PN	No increased mortality in PN patients	[redacted]	0.000	[redacted]	£34,475
Clarification question scenarios					
Response at Week 16 based on OLYMPIA 1 & OLYMPIA 2	Response at Week 24 based on OLYMPIA 1	[redacted]	0.000	[redacted]	£37,231
Response at Week 16 based on OLYMPIA 1 & OLYMPIA 2	Response based on OLYMPIA 1 (Week 24) & OLYMPIA 2 (Week 16)	[redacted]	0.000	[redacted]	£36,731
Utility inputs based on OLYMPIA 1 & OLYMPIA 2	Utility capped at general population utility with equal utility decrement applied to all health states	[redacted]	0.000	[redacted]	£34,523

Discontinuation for BSC at Week 52 and long-term based on OLYMPIA 1 at week 24	Discontinuation for BSC assumed as 0% at Week 52 and long-term	[redacted]	0.000	[redacted]	£34,647
Discontinuation for BSC at Week 52 and long-term based on OLYMPIA 1 at week 24	Discontinuation for BSC at Week 52 and long-term based on OLYMPIA 1 placebo arm at week 24 converted to annual rate	[redacted]	0.000	[redacted]	£34,400

Abbreviations: AE, adverse event; BSC, best supportive care; ICER, incremental cost effectiveness ratio; IGA, Investigator's Global Assessment; kg, kilogram; LY, life year; mg, milligram; PAS, patient access scheme; PN, prurigo nodularis; PP NRS, peak pruritus numerical rating scale; Q4W, every four weeks; QALY, quality adjusted life year; QALYG, quality adjusted life year gained; TRAE, treatment related adverse event.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal

Nemolizumab for adults with moderate to severe prurigo nodularis [ID6451]

Clarification questions Appendix B: Updated Clinical SLR strategies

November 2024

File name	Version	Contains confidential information	Date
[ID6451] Nemolizumab CQ Appendix B 061124 [noCON]	**1**	**Yes**	**06 November 2024**

In Appendix D of the Company submission, the clinical strategies were inadvertently spell-checked and reported incorrectly, with US spellings being changed to UK spellings. In line with PRISMA requirements, the clinical strategies as they were run for the clinical SLR are presented below.

Table 1. Ovid MEDLINE® ALL search strategy.

#	Search terms	Search numbers	
		05 October 2023	07 May 2024
Disease terms			
1	dermatitis, atopic/ or atopic dermatitis.ti,ab. or exp Eczema/ or eczema.ti,ab.	51,671	53,576
Interventions			
2	Cyclosporine/ or Methotrexate/ or (abrocitinib or PF-04965842 or cibinqo or baricitinib or LY3009104 or Olumiant or baricinix or c#closporin* or dupilumab or dupixent or REGN668 or SAR231893 or lebrikizumab or MILR 1444A or RG 3637 or TNX 650 or nemolizumab or CIM 331 or tralokinumab or CAT 354 or upadacitinib or rinvoq or abt 494 or abt494 or methotrexate or azathioprine or mycophenolate).ti,ab.	377,937	141,083
3	1 and 2	3,333	2,927
Trials			
4	randomized-controlled trials/	164,317	169,602
5	randomized controlled trial.pt.	601,021	612,512
6	(randomized controlled trials or random allocation or double blind method or single blind method).sh.	304,692	307,465
7	((random$ and control* and trial*) or placebo or ((single or double) adj3 (blind* or mask*)) or ((phase ii or "phase 2" or phase iii or "phase 3") and trial)).tw.	677,992	705,465
8	or/4-7	1,149,086	1,181,057
9	3 and 8	652	674
Excluded studies			
10	exp animals/ not exp humans/	5,160,452	5,218,886
11	limit 9 to (address or case reports or comment or editorial or letter or published erratum)	44	58
12	10 or 11	5,160,496	5,218,944
13	9 not 12	562	578
14	exp "Review"/	3,223,785	3,324,826
15	(meta analysis or "systematic review").pt.	324,072	346,692
16	"systematic review"/ or meta analysis/	324,072	346,692
17	(systematic or meta analysis or mixed treatment comparison or indirect treatment comparison).ti,ab.	654,491	696,193
18	or/15-17	686,284	728,887

19	14 not 18	2,984,921	3,069,198
20	13 not 19	458	481
21	limit 20 to english language	**451**	474
Updated search only			
22	limit 21 to dt=20230901-20240507	-	82

Table 2. Ovid Embase search strategy.

#	Search terms	Search numbers	
		05 October 2023	07 May 2024
Disease terms			
1	atopic dermatitis/ or atopic dermatitis.ti,ab. or exp eczema/ or eczema.ti,ab.	96,112	100,134
Interventions			
2	abrocitinib/ or baricitinib/ or cyclosporine/ or dupilumab/ or lebrikizumab/ or nemolizumab/ or tralokinumab/ or upadacitinib/ or methotrexate/ or azathioprine/ or mycophenolate mofetil/ or (abrocitinib or PF-04965842 or cibinqo or baricitinib or LY3009104 or Olumiant or baricinix or c#closporin* or dupilumab or dupixent or REGN668 or SAR231893 or lebrikizumab or MILR 1444A or RG 3637 or TNX 650 or nemolizumab or CIM 331 or tralokinumab or CAT 354 or upadacitinib or rinvoq or abt 494 or abt494 or methotrexate or azathioprine or mycophenolate).ti,ab.	741,449	419,395
3	1 and 2	9,777	9,339
Trials			
4	(random* or trial or placebo or ((single or double) adj3 (blind* or mask*)) or (phase ii or "phase 2" or phase iii or "phase 3")).ti,ab.	2,712,035	2,823,754
5	exp randomization/	98,886	99,575
6	exp single blind procedure/	51,948	54,575
7	exp double blind procedure/	211,201	218,491
8	exp placebo/	403,125	412,135
9	exp placebo/	262,914	412,135
10	or/4-9	2,972,962	2,996,193
11	3 and 10	2,631	2,385
Excluded studies			
12	limit 11 to (phase 1 clinical trial or books or chapter or editorial or erratum or letter or note or short survey or tombstone or book or book series or major reference work or report or trade journal)	198	147
13	exp animals/ not exp humans/	5,148,864	5,247,982
14	11 not (12 or 13)	2,364	2,183
15	limit 14 to english	2,312	2,134
16	"systematic review"/ or meta analysis/	560,217	597,797
17	"systematic review (topic)"/	32,794	34,779

18	(systematic or meta analysis or mixed treatment comparison or indirect treatment comparison).ti,ab.	808,513	860,149
19	or/16-18	971,431	1,030,301
20	limit 15 to "review"	580	457
21	20 not 19	443	335
22	15 not 21	1,869	1,799
23	limit 22 to (conference abstracts and yr="2021 -Current")	552	648
24	limit 22 to conference abstracts	909	973
25	24 not 23	357	325
26	22 not 25	**1,512**	1,474
Updated searches only			
27	limit 26 to dc=20230901-20240507	-	279

Table 3. Wiley Cochrane Library search strategy (original SLR).

#	Search terms	Number of records 05 October 2023
Disease terms		
1	Dermatitis, Atopic/	2,357
2	atopic dermatitis.ti,ab,kw.	5,557
3	exp Eczema/	1,466
4	eczema.ti,ab,kw.	3,911
Interventions		
5	Ciclosporin/ or Methotrexate/ or Janus Kinase Inhibitors/ or Antibodies, Monoclonal/	14,806
6	(abrocitinib or PF-04965842 or cibinqo or baricitinib or LY3009104 or Olumiant or baricinix or c#closporin* or dupilumab or dupixent or REGN668 or SAR231893 or lebrikizumab or MILR 1444A or RG 3637 or TNX 650 or nemolizumab or CIM 331 or tralokinumab or CAT 354 or upadacitinib or rinvoq or abt 494 or abt494 or methotrexate or azathioprine or mycophenolate or janus kinase inhibitor* or JAK inhibitor* or Janus tyrosine kinase inhibitor* or monoclonal antibod* or clonal antibod* or hybridoma antibod* or antibod* monoclonal).ti,ab.	35,213
7	(or/1-4) and (or/5-6)	1,275
Trials		
8	(EUCTR* or NCT* or ICTRP* or CTRI* or ISRCTN* or chictr* or actrn* or IRCT* or NTR*).tn. or (trial regist* or trial protocol).pt.	600,420

#	Search terms	Number of records 05 October 2023
9	7 not 8	884
10	conference*.pt.	224,649
11	9 not 10	275
12	limit 10 to yr=2021-Current	35,779
13	9 and 12	379
14	**11 or 13**	**654**

Table 4. Wiley Cochrane Library search strategy (updated SLR).

#	Search terms	Number of records 07 May 2024
Disease terms		
1	MeSH descriptor: [Dermatitis, Atopic] this term only	2,712
2	atopic-dermatitis:ti,ab,kw	6,009
3	MeSH descriptor: [Eczema] explode all trees	1,491
4	eczema:ti,ab,kw	5,163
Interventions		
5	MeSH descriptor: [Ciclosporin] this term only	3,352
6	MeSH descriptor: [Methotrexate] this term only	5,124
7	MeSH descriptor: [Janus Kinase Inhibitors] this term only	222
8	MeSH descriptor: [Antibodies, Monoclonal] this term only	8,083

#	Search terms	Number of records
		07 May 2024
9	(abrocitinib or PF-04965842 or cibinqo or baricitinib or LY3009104 or Olumiant or baricinix or ciclosporin* or ciclosporin* or dupilumab or dupixent or REGN668 or SAR231893 or lebrikizumab or MILR-1444A or RG-3637 or TNX-650 or nemolizumab or CIM-331 or tralokinumab or CAT-354 or upadacitinib or rinvoq or abt-494 or abt494 or methotrexate or azathioprine or mycophenolate or janus-kinase-inhibitor* or JAK inhibitor* or Janus-tyrosine-kinase-inhibitor* or monoclonal-antibod* or clonal-antibod* or hybridoma-antibod* or (antibod* next monoclonal)):ti,ab	37,143
10	3-#4 and {or #5-#9}	1,550
Excluded studies		
11	(EUCTR* or NCT* or ICTRP* or CTRI* or ISRCTN* or chictr* or actrn* or IRCT* or NTR*):SO	399,366
12	(trial-regist* or trial-protocol):pt	508,181
13	#11 or #12	509,651
14	#10 not #13	1,295
15	conference*:pt	242,579
CDSR results		
16	#14 not #15 with Cochrane Library publication date from Sep 2023 to May 2024, in Cochrane Reviews	0
CENTRAL results		
17	#14 not #15 with Cochrane Library publication date from Sep 2023 to May 2024, in Trials	80
CDSR = 0 **CENTRAL = 80**		

Table 5. GREAT.

#	Search terms	Number of records	
		05 October 2023	07 May 2024
1	abrocitinib OR azathioprine OR baricitinib OR olumiant OR dupilumab OR c?closporin* OR lebrikizumab OR methotrexate OR mycophenolate OR nemolizumab OR tralokinumab OR upadacitinib OR janus kinase inhibitor* OR JAK inhibitor* OR Janus tyrosine kinase inhibitor* OR monoclonal antibod* OR clonal antibod* OR hybridoma antibod* OR antibod* monoclonal	100	100
Updated search only			
2	Publication year 2023-2024	-	0

NICE National Institute for Health and Care Excellence

Single Technology Appraisal
Nemolizumab for treating prurigo nodularis [ID6451]
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?	With a global patient community of over 5,000, Prurigo Nodularis International is the only patient led charity (Charity Commission no: 1207110) for anyone living with the rare, debilitating and life changing neuro-immunological skin condition, Nodular Prurigo or Prurigo Nodularis. Our vision is for a world where no one suffers with Prurigo Nodularis. The mission of Prurigo Nodularis International is to create worldwide awareness of Prurigo Nodularis, including educating dermatologists in the impact of the disease. To drive efforts to develop diagnostic standards, care and treatment guidelines and pathways, as well as safe and effective treatments. A core part of our mission is to also create an engaged community of patients, so that no patient will ever face this disease in isolation, and to provide information and advice to help people living with Prurigo Nodularis improve the quality of their lives. We are volunteer led and driven.
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.]	No

If so, please state the name of the company, amount, and purpose of funding.	
4c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No
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 both patients and carers in our community of over 5,000 patients.**

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 debilitating and 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 sensations. • 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, patients are subject to trying a myriad of empirical treatments, with little to no relief, this 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 the majority of 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 might 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?	The unmet need question has already been established and acknowledged by NICE during the Dupilumab HTA (TA955). Patients in England have already been denied access to the one targeted treatment, currently approved in Scotland, the USA, Europe and a number of other countries, Dupilumab. The best supportive care available does little to nothing to help patients. The unmet need is for targeted treatments, such as Nemolizumab.

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. • Well tolerated with few side effects.

Disadvantages of the technology

10. What do patients or carers think are the disadvantages of the technology?	The technology is reported to be quite well tolerated by members of our community. Given Prurigo Nodularis has various pathways, it may not always have efficacy in all patients, while it can be life changing for others.

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?	Dupilumab, a multi-indication technology and currently the only dedicated treatment for Prurigo Nodularis has been approved by the Scottish Medicines Consortium for Prurigo Nodularis in Scotland, but not by NICE, creating a postcode lottery in the UK, as patients in England have been denied access to life changing treatment. Dupilumab has also been approved for treatment of mainstream conditions, while being denied for Prurigo Nodularis patients. Nemolizumab has the potential to also be life changing for some Prurigo Nodularis patients, once again this multi-indication technology is likely to be approved for patients of more mainstream conditions. If this is the case and the technology is denied to our community, it reflects that there isn't a level playing field for rare disease patients such as ours with patients who have mainstream conditions to access targeted treatments. The unmet need which has been established will never be met,

Other issues

13. Are there any other issues that you would like the committee to consider?	Dupilumab, a multi-indication technology and currently the only dedicated treatment for Prurigo Nodularis has been approved by the SMC for Prurigo Nodularis in Scotland, but not by NICE, creating a postcode lottery in the UK, as patients in England have been denied access to life changing treatment. Dupilumab has also been approved for treatment of mainstream conditions, while being denied for Prurigo Nodularis patients. Nemolizumab has the potential to also be life changing for some Prurigo Nodularis patients, once again this multi-indication technology is likely to be approved for patients of more mainstream conditions. If this is the case and the technology is denied to our community, it reflects that there isn't a level playing field for rare disease patients with patients who have mainstream conditions. The unmet need which has been established will never be met. Furthermore, rare disease patients in England would be at a disadvantage in being able to access innovative, targeted and effective treatments, which are available in other countries.
14: In TA955 (dupilumab for treating moderate to severe prurigo nodularis), it was noted that there is currently no established standard of care for prurigo nodularis. Which treatment options do you consider are the most appropriate comparators for nemolizumab?	Dupilumab.
15: Would treatment options vary as severity of the condition increases? What do you consider the impact of this would be for treatment with nemolizumab and where would nemolizumab be best placed in the patient pathway?	There are no targeted or dedicated treatment options, all treatments in the stepped approach are currently empirical and used off label, with limited to little or no ability to contain the disease, while exposing patients to dangerous side effects. Prurigo Nodularis patients who are candidates for systemic treatment or even once diagnosed with Prurigo Nodularis should be given access to Nemolizumab first without having to try and fail empirical treatments, as none of these are established or have been proven either anecdotally or with real data as viable treatments for Prurigo Nodularis. As already covered further above, the disease does not resolve on its own and the current empirical stepped approach is unable to arrest the spread of the disease or contain symptoms to give patients any quality of life. If left untreated the lesions will typically become widespread often in the hundreds.

Key messages

16. 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 in England 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 latest developments for this disease. • Once diagnosed patients in England do not have any dedicated treatments, there are only empirical treatments available. There is already a postcode lottery in the UK. Patients in Scotland do have access to the only approved technology – Dupilumab, denied by NICE to patients in England. • 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. • The disease if not contained and treated with a targeted technology (currently none available) spreads often to cover a significant part of the body. Patients are also at risk of developing other conditions alongside Prurigo Nodularis as a result of the long-standing inflammation.

Thank you for your time.

Please log in to your NICE Docs account to upload your completed submission.

Your privacy

The information that you provide on this form will be used to contact you about the topic above.

Please select YES if you would like to receive information about other NICE topics - YES or NO

For more information about how we process your personal data please see our privacy notice.

NICE National Institute for Health and Care Excellence

Single Technology Appraisal
Nemolizumab for treating prurigo nodularis [ID6451]
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] and [redacted], on behalf of the British Association of Dermatologists (BAD) and BAD guideline development group for managing people with 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** A specialist in the treatment of people with this condition? **Yes** A specialist in the clinical evidence base for this condition or technology? **Yes** 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.**	No.
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 people 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 – people with NP often cycle through off-licence treatments of variable (usually un-evidenced) efficacy. It is likely that effective medication with be particularly cost-effective for patients with moderate-to-severe NP.

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 a referral, or cannot access certain medications within primary care. There is no current, established practice of treating NP; however, the treatments listed in the previous draft scope are reasonable:

	• emollients • topical corticosteroids (TCS) • topical calcineurin inhibitors (TCI) • antihistamines • oral steroids • phototherapy • immunosuppressive therapies (azathioprine, ciclosporin, methotrexate or thalidomide) • antidepressants (for itch relief) In addition, intralesional steroids for localised and/or persistent lesions, cryotherapy for *highly* localised and/or persistent lesions and skin camouflage, when needed.
9a. Are any clinical guidelines used in the treatment of the condition, and if so, which?	Currently, the BAD is in the final stages of developing its *draft* guideline for managing people with NP.
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; e414-31), and American consensus guidelines (*J Am Acad Dermatol* 2021, 84: 747-760), however, 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. But there is a literature about treatments. The BAD is currently in the process of developing a clinical guideline for treating people with 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, especially as dupilumab was not approved by NICE.
10. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	Yes; other biologics are already used to treat people with atopic dermatitis (AD). There is a significant population of people with NP and concomitant eczema so this will be of particular benefit to these patients. And there is a significant population of patients who have NP without a background of AD.
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 and at least one systemic anti-inflammatory medications has been ineffective or contraindicated.
10b. In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	In secondary care, specialist medical dermatology 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 similar technologies 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 that this technology reduces pruritus (more rapidly), improves QoL (including sleep) and reduces severity of NP when used as monotherapy, or in combination with TCS (Yokozeki *et al.* BJD 2024). https://pubmed.ncbi.nlm.nih.gov/37888917/ https://pubmed.ncbi.nlm.nih.gov/32074418/ https://pubmed.ncbi.nlm.nih.gov/35766128/ https://pubmed.ncbi.nlm.nih.gov/38629497/

	https://pubmed.ncbi.nlm.nih.gov/38217530/ https://pubmed.ncbi.nlm.nih.gov/37987710/ 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?	
11b. Do you expect the technology to increase health-related quality of life more than current care?	Yes, all clinical trials for nemolizumab in prurigo nodularis showed reduction in itch, improvement of sleep disturbance, DLQI and HADS (see the evidence from Ständer *et al.* 2020 (10.1056/NEJMoa1908316), Stander *et al.* 2023 (10.1007/s13555-023-00962-8) and Kwatra *et al.* 2023 (10.1056/NEJMoa2301333) and HADS (Kwatra et al. 2023) Trial of **Nemolizumab** in Moderate-to-Severe **Prurigo** Nodularis. Ständer S, Yosipovitch G, Legat FJ, Lacour JP, Paul C, Narbutt J, Bieber T, Misery L, Wollenberg A, Reich A, Ahmad F, Piketty C.N Engl J Med. 2020 Feb 20;382(8):706-716 The Sleep Disturbance Numerical Rating Scale: Content Validity, Psychometric Validation, and Meaningful Within-Patient Change in **Prurigo** Nodularis. Ständer S, Fofana F, Dias-Barbosa C, Rodriguez D, Budhiarso I, Jabbar-Lopez ZK, Piketty C, Vernon M, Puelles J.Dermatol Ther (Heidelb). 2023 Jul;13(7):1587-1602
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 affecting patient acceptability or ease of use or additional tests or monitoring needed.)	It should be easier 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 similar technology for other 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. Nemolizumab may be used in combination with TCS or TCI, antihistamines (non-sedating; at the lowest effective dose for the shortest period of time for *sedating* antihistamines), antidepressants for itch relief (used at lower doses than those used for depression), intralesional steroids for localised and/or persistent lesions, cryotherapy for *highly* localised and/or persistent lesions and skin camouflage, when 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 similar technology that has been applied to people with AD.
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 particular unmet need of the patient population?	Yes, it addresses the unmet need for a safe, effective and approved medication, given that there are very limited, often off-licence and unevidenced, options for the effective treatment of severe NP. Moreover, the response to currently available treatments of the condition is poor.
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?	Studies on nemolizumab suggest very few adverse side effects among which the commonest are injection-site erythema/reactions, which are similar to other biologics used in standard dermatology practice.

Sources of evidence

18. Do the clinical trials on the technology reflect current UK clinical practice?	Generally no, because there are currently no published clinical guidelines on managing 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.

18a. If not, how could the results be extrapolated to the UK setting?	The BAD is currently developing a clinical guideline on managing people with NP, which is likely to be published early next year.
18b. What, in your view, are the most important outcomes, and were they measured in the trials?	Peak pruritus numerical rating scale (PPNRS) or visual analogue scale (VAS) itch scales and NP investigators global assessment (IGA) responses. 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.
18c. If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	This is untested, but clinical practice would indicate that these outcome measures are a reasonable assessment of 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. 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

21a. Are there any potential equality issues that should be taken into account when considering this treatment?	Erythema may be underestimated in those with darker skin tones, hence the severity assessment 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. Quality of life measures such as the DLQI may not adequately capture impact in older people (question about work, studying, sport) or those who are not in a relationship (question about sexual activity). It is also known to capture anxiety and depression poorly across all groups (two parameters that are commonly negatively influenced by NP). There is evidence from the US that NP may be more common in Afro-Caribbean, Asian and Hispanic patients (https://pubmed.ncbi.nlm.nih.gov/31405223/; https://pubmed.ncbi.nlm.nih.gov/29733939/). However, an NHS dataset indicated that 82.8% of patients with NP were of white background (https://pubmed.ncbi.nlm.nih.gov/35083742/) which is in alignment with the UK 2021 census.
21b. 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.

Topic-specific questions

22. In TA955 (dupilumab for treating moderate to severe prurigo nodularis), it was noted that there is currently no established standard of care for prurigo nodularis. Which treatment options do you consider are the most appropriate comparators for nemolizumab?	See response in section 9 above.
23. Would treatment options vary as severity of the condition increases? What do you consider the impact of this would be for treatment with nemolizumab and where would nemolizumab be best placed in the patient pathway?	No, treatment options tend to narrow as severity of NP increases. For milder disease, topical anti-inflammatories and/or phototherapy may be effective. For patients with moderate-to-severe disease, the topical preparations have usually been tried and failed, and so systemic medications are usually indicated. Nemolizumab is probably best indicated for patients with moderate to severe NP in whom topical treatments and antihistamines have failed and for whom at least one systemic medication has either failed or been contraindicated.

24. TA955 (dupilumab for treating moderate to severe prurigo nodularis), noted that the treatment may have a reduced effect in people who weigh over 90 kg. What do you consider the impact of weight changes would have for treatment with nemolizumab?	From the methods section of the phase 3 study (Kwatra *et al.*): On the basis of phase 2 trial findings and population pharmacokinetic–pharmacodynamic modelling, a flat dose with a body-weight adjustment was selected for the phase 3 trial to achieve systemic exposure and efficacy results similar to those observed in the phase 2 study.[20,21] Randomization was stratified according to baseline body weight (<90 kg vs. ≥90 kg). Blinded, coded trial regimen kits were used to mask the assigned regimen. In the nemolizumab group, patients weighing less than 90 kg received a 60-mg initial dose (2 injections, 30 mg each), followed by 30 mg (1 injection) every 4 weeks, and those weighing 90 kg or more received 60 mg (2 injections, 30 mg each) every 4 weeks. Patients in the placebo group received matching placebo injections according to their weight. People who weigh at least 90 kg are likely to require a higher maintenance dose of nemolizumab at 60 mg every 4 weeks as opposed to 30 mg every 4 weeks for people who weigh less than 90 kg so that they have similar systemic exposure to the drug and similarly positive outcomes (Kwatra *et al.*).

Key messages

25. In up to 5 bullet points, please summarise the key messages of your submission.	• Nodular prurigo is an underacknowledged, poorly treated and devastating disease for many patients. • 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 currently 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. • The lives of patients living with NP are often severely disabled with unremitting itch, sleeplessness, psychosocial co-morbidities (anxiety, depression and suicidal ideation), and severely impaired quality of life. Further, the lives of family members, carers, partners and loved ones are also severely affected. • Systemic medication for patients with NP is variably effective and often has untoward side effects. There is a desperate need for an effective, well-tolerated medication for patients with moderate to severe NP. • Nemolizumab has been demonstrated to be an effective and well-tolerated treatment for patients with moderate to severe NP. For a condition which has very few effective therapeutic options, nemolizumab appears to be a very welcome treatment for patients with moderate to severe NP.

Thank you for your time.

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NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Nemolizumab for treating prurigo nodularis [ID6451]

Clinical expert statement

Information on completing this form

In part 1 we are asking for your views on this technology. The text boxes will expand as you type.

In part 2 we are asking you to provide 5 summary sentences on the main points contained in this document.

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. Please type information directly into the form.

Do not include medical information about yourself or another person that could identify you or the other person.

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Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.

Please underline all confidential information, and separately highlight information that is submitted as 'confidential [CON]' in turquoise, and all information submitted as 'depersonalised data [DPD]' in pink. If confidential information is submitted, please also

send a second version of your comments with that information redacted. See Health technology evaluations: interim methods and process guide for the proportionate approach to technology appraisals (section 3.2) for more information.

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Thank you for your time.

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NICE National Institute for Health and Care Excellence

Part 1: Treating prurigo nodularis and current treatment options

Table 1 About you, aim of treatment, place and use of technology, sources of evidence and equality

1. Your name	Andrew Pink
2. Name of organisation	Guy's & St. Thomas' NHS Foundation Trust
3. Job title or position	Consultant Dermatologist
4. Are you (please tick all that apply)	☐ An employee or representative of a healthcare professional organisation that represents clinicians? ☒ A specialist in the treatment of people with prurigo nodularis? ☒ A specialist in the clinical evidence base for prurigo nodularis or technology? ☐ Other (please specify):
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☐ Yes, I agree with it ☐ No, I disagree with it ☐ I agree with some of it, but disagree with some of it ☒ Other (they did not submit one, I do not know if they submitted one etc.)
6. If you wrote the organisation submission and/or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission)	☐ Yes
7. Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None
8. What is the main aim of treatment for prurigo nodularis? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability)	- To reduce and ideally eliminate debilitating symptoms – e.g. **itch,** pain - To reduce inflammation and improve/ normalise skin appearance - To improve sleep and ability to cope

	- To improve quality of life/ enable daily function - To improve disease-associated psychological burden e.g. low mood
9. 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)	To achieve a clinically meaningful improvement in itch (e.g. peak pruritis NRS ≥4 point improvement), optimally no/ minimal itch (NRS ≤ 1) To objectively achieve clear, almost clear or mild skin (investigator global assessment 0/1/2), optimally clear/ almost clear (IGA 0/1)
10. In your view, is there an unmet need for patients and healthcare professionals in prurigo nodularis?	There is currently a very significant unmet need in the treatment of this condition with insufficient treatment options to tackle the often devastating and persistent itch, as well as the inflammation and appearance of the skin. Topical measures (*e.g.* topical and intra-lesional steroids) and basic therapeutic approaches (*e.g.* anti-histamines) are rarely sufficiently effective. Phototherapy can help some patients, but it is usually of only short term benefit and inconvenient. Traditional immunomodulatory approaches (e.g. methotrexate, ciclosporin) have no robust evidence base (no RCT evidence), are of limited and unpredictable benefit and have associated side effects. Other approaches, including neuro-modulation and low dose anti-depressants (e.g. capsaicin, gabapentin, pregabalin, doxepin, amitryptylline), are likewise not evidence based and of limited and unpredictable benefit. The use of thalidomide in severe cases, a drug with significant toxicity and permanent sequelae (including nerve damage/ paraesthesia), is testament to the unmet need in this condition. There is no approved licensed systemic treatment for prurigo nodularis in the UK. Dupilumab is licensed but not accessible/ NICE approved. In skin of colour, inflammation can leave areas of very significant hyperpigmentation and hypopigmentation (post-inflammatory pigmentary change). This can improve slowly over time but is often permanent, conferring a a profound and lasting effect on some patients. There is no proven treatment to aid resolution in this context, thus early aggressive and effective therapy for prurigo nodularis is needed, and there are currently a paucity of options.

11. How is prurigo nodularis currently treated in the NHS? • Are any clinical guidelines used in the treatment of the condition, and if so, which? • 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.) • What impact would the technology have on the current pathway of care?	There are no current UK guidelines on the management of prurigo nodularis (PN) but a British Association of Dermatology guideline is in the latter stages of development. There is an international guideline for PN management (Stander et al., Itch 2020; 5 :e42). A broad stepwise approach to care is employed in the UK : Step 1: Topical steroids, topical calcineurin inhibitors, anti-histamines Step 2: Phototherapy, occasionally intralesional steroids (if localised) Step 3: Methotrexate, ciclosporin, oral steroids, doxepin, amitryptylline, gabapentin, pregabalin Step 4: Thalidomide (rare and in specialist centres with experience) This is not uniform or consistent but represents the broad approach. Different dermatologists may adopt slightly different approaches both in terms of the exact type and order of treatments. Patients are very often cycled through multiple treatments to minimal benefit. Were this technology approved it would represent the first prescribable licensed systemic therapy for prurigo nodularis in the UK.
12. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice? • How does healthcare resource use differ between the technology and current care? • In what clinical setting should the technology be used? (for example, primary or secondary care, specialist clinic) • What investment is needed to introduce the technology? (for example, for facilities, equipment, or training)	Nemolizumab could be used at step (2 or) 3 in the above example of a treatment ladder within the existing clinic infrastructure. Given the safety profile relative to existing drugs (e.g. methotrexate and ciclosporin) this would likely require significantly less clinical input and monitoring than the existing options (e.g. no or few bloods, reduced follow up requirements etc.). This technology should be used in secondary care. No specific investment is required in terms of specific infrastructure or training.

13. Do you expect the technology to provide clinically meaningful benefits compared with current care? • Do you expect the technology to increase length of life more than current care? • Do you expect the technology to increase health-related quality of life more than current care?	The trial data (phase 3, Olympia 1 and 2 trials) demonstrated that of those with moderate-severe disease 56-59% achieved a clinically meaningful improvement in itch (peak pruritis NRS change of 4 points or more) in 16 weeks (rapid improvement demonstrated in 2 weeks) and 26-38% achieved clear or almost clear skin. This rivals data demonstrated with the only other licensed product to treat PN, dupilumab (not accessible in UK). These improvements in itch and objective signs were accompanied by up to 70% of patients achieving a clinically meaningful improvement in the QoL (DLQI) over 16 weeks
14. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	I am not aware of any specific evidence supporting greater impact in particular phenotypes, the phase III trials studied broad pure PN (i.e. not overlap AD where prurigo can arise as a secondary phenomenon). The AD/ prurigo group is an important group but can be treated using systemics approved for the treatment of AD.
15. 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 affecting patient acceptability or ease of use or additional tests or monitoring needed)	In terms of phototherapy and current systemics, nemolizumab is much easier to use as it is a once monthly injection, that can be self-administered by the patient at home. Biologic prescribing and homecare is very standard practice now in the NHS. The safety profile of this medication, with no reported impact on bloods means that there is no clear rationale for frequent follow up or monitoring blood tests, both of which could help the current capacity issues that we face (methotrexate and ciclosporin require intense 2 weekly visits at outset then 3 monthly visits when stable, nemolizumab may require annual follow up at most when effective and patient stable).
16. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	Outside of potential NICE criteria for access, none specifically. As part of standard diagnostic work up for prurigo nodularis patients often undergo a set of bloods (itch screening, to exclude any systemic driver for itching) +/- CXR +/- skin biopsy. In terms of screening for nemolizumab clinicians would follow SmPC advice around need for infection screening (if any required).
17. Do you consider that the use of the technology will result in any substantial health-related benefits that	The QoL measures (e.g. the skin -specific DLQI) utilised in the trial are not specific to PN. Whilst DLQI (and other measures e.g. EQ5D) will capture some key consequences of the itch and skin appearance in PN, the true impact of

are unlikely to be included in the quality-adjusted life year (QALY) calculation? • Do the instruments that measure quality of life fully capture all the benefits of the technology or have some been missed? For example, the treatment regimen may be more easily administered (such as an oral tablet or home treatment) than current standard of care	persistent severe itch on all facets of life will not be fully captured. The relentlessness and profound consequences of this cannot be underestimated. On a practical level, nemolizumab is a well tolerated monthly injection, versus the more regularly administered ciclosporin and methotrexate (or 3x weekly phototherapy) which can have dosing related side effects (e.g. nausea and vomiting with methotrexate). Stability on a monthly injection with potentially annual follow up would enable patients to forget about their disease far more than on a daily or weekly tablet requiring frequent monitoring.
18. 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? • Is the technology a 'step-change' in the management of the condition? • Does the use of the technology address any particular unmet need of the patient population?	This is an innovative highly targeted first in class monoclonal antibody therapy targeting the key itch cytokine, IL-31. IL-31 has long been known to be a key signal in nodular prurigo and the trial data for nemolizumab in prurigo nodularis support that role, demonstrating a rapid and meaningful improvement in itch in the majority of patients. Furthermore, the trial data demonstrate the ability of nemolizumab to improve/ clearing the objective skin signs. This proven effectiveness in robust RCTs represents a 'step-change' compared to the current poorly evidenced treatment options. The biggest unmet need in this population currently is a lack of an effective and safe option to suppress the profound associated itch. The traditional therapies are frequently inadequate at controlling this (as well as the associated skin signs).
19. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	This appears to be a very well tolerated treatment with few side effects. Rarely patients developed a mild eczema on treatment, usually manageable with topical therapy. There were also some rare cases of oedema. I do not foresee associated side effects frequently detrimentally impacting QoL but as with any new targeted therapy these will need to be monitored and carefully characterised in real world practice.
20. Do the clinical trials on the technology reflect current UK clinical practice?	The population studied in the pivotal phase III trials (Olympia 1 and 2) is frequently encountered in secondary care dermatology and can prove extremely challenging to manage. It doesn't represent all patients seen in the NHS,

• If not, how could the results be extrapolated to the UK setting? • What, in your view, are the most important outcomes, and were they measured in the trials? • If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes? • Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	whether that be because of the requirement for 20 nodules or more or a pp-NRS of 7 or more at trial outset, but I do think it represents the majority (rare for these patients to present without severe itch). There is a group of eczema patients who develop a secondary prurigo and terminology for this group has varied in the literature. They were not captured in these trials (patients with active eczema excluded) hence these data do not provide insight into the potential benefit of nemolizumab in that group. UK patients were enrolled in the Olympia 2 trial. As mentioned in the above sections, I feel the most important outcomes were captured in the OLYMPIA trials, and as primary outcomes. Thes include itch (pp-NRS, which is the most accepted validated measure) and objective disease severity (using an Investigator Global Assessment scale). Important downstream endpoints were assessed including impact on sleep, quality of life and anxiety and depression. I am not aware of any side effects that were not apparent in trials but have materialised subsequently.
21. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	I am not, but the medicine is now in routine use in the US and Japan (atopic dermatitis).
22. How do data on real-world experience compare with the trial data?	There is no real world UK data. There is limited real world data, one real world retrospective analysis of a small subset of Japanese patients on nemolizumab for atopic dermatitis demonstrated benefit and no new adverse events (doi:10.1684/ejd.2023.4551).
23. NICE considers whether there are any equalities issues at each stage of an evaluation. 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.	Inflammation is often under-scored in more pigmented skin types (as redness can be less apparent). With discreet and raised nodules this is less of a problem in terms of severity assessment that in a disease such as atopic dermatitis, but is still a very important consideration when scoring (so any potential future eligibility/ access criteria is not missed in error).

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. Please state if you think this evaluation could • exclude any people for which this treatment is or will be licensed but who are protected by the equality legislation • lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population • lead to recommendations that have an adverse impact on disabled people. Please consider whether these issues are different from issues with current care and why. 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.	In skin of colour inflammation can leave very significant post-inflammatory pigmentation (darker and lighter). This can slowly improve over time but can also be permanent and have a devastating impact on patients. There are no effective treatments to help resolve this and thus prompt and effective treatment of PN (inflammation) in this context is very important to reduce this downstream morbidity.

Part 2: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

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NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Nemolizumab for treating prurigo nodularis [ID6451]

Patient expert statement

Thank you for agreeing to give us your views on this treatment and its possible use in the NHS.

Your comments are really valued. You can provide a unique perspective on conditions and their treatment that is not typically available from other sources

Information on completing this form

In part 1 we are asking you about living with prurigo nodularis or caring for a patient with prurigo nodularis. The text boxes will expand as you type.

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Your response should not be longer than 15 pages.

The deadline for your response is **5pm** on **5pm Monday 27 January 2025.** Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

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Comments received are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

Patient expert statement

NICE National Institute for Health and Care Excellence

Part 1: Living with this condition or caring for a patient with prurigo nodularis

Table 1 About you, prurigo nodularis, current treatments and equality

1. Your name	Sailaja Maganti
2. Are you (please tick all that apply)	☒ A patient with prurigo nodularis? ☐ A patient with experience of the treatment being evaluated? ☐ A carer of a patient with prurigo nodularis? ☒ A patient organisation employee or volunteer? ☐ Other (please specify):
3. Name of your nominating organisation	Prurigo Nodularis International
4. Has your nominating organisation provided a submission? (please tick all options that apply)	☐ No (please review all the questions and provide answers when possible) ☒ Yes, my nominating organisation has provided a submission ☐ I agree with it and **do not wish to** complete a patient expert statement ☒ Yes, I authored / was a contributor to my nominating organisations submission ☐ I agree with it and **do not wish to** complete this statement ☒ I agree with it and **will be** completing
5. How did you gather the information included in your statement? (please tick all that apply)	☒ I am drawing from personal experience ☒ I have other relevant knowledge or experience (for example, I am drawing on others' experiences). Please specify what other experience: ☐ I have completed part 2 of the statement **after attending** the expert engagement teleconference

	☐ I have completed part 2 of the statement **but was not able to attend** the expert engagement teleconference ☐ I have not completed part 2 of the statement
6. What is your experience of living with prurigo nodularis? **If you are a carer (for someone with prurigo nodularis) please share your experience of caring for them**	• I have lived with Prurigo Nodularis (PN) for 20 years, the condition started with one solitary lesion, subsequently spreading top to bottom with hundreds of lesions, covering my entire body. • There is little physical, mental and emotional peace as the itch has been constant for almost 20 years. Relentless, day and night. It has been distressing and debilitating. I live with a constant itch and also have itch attacks that can last from anywhere from a few minutes to hours. Moreover, my itch has layers to it, a combination of itching, pain, burning and a stinging sensation. • Symptoms also get worse at night, which has meant I go through life very sleep deprived and constantly exhausted. The itching makes functioning in general a day-to-day challenge. My itching at night also regularly disrupts my husband's sleep. • My symptoms have been so severe that I have had to change careers, which has economic implications for me and my family. • PN is also time consuming both in terms of dealing with the itch, as well as the amount of time that it takes to constantly moisturize and tend to the skin, especially as my disease is widespread. • PN is also expensive, given the number of products and prescribed drugs as a patient I have had to try / use over the years. I have also spent resources on private Dermatologists and trying various alternative treatments, in my desperation for relief. • To sum up, the condition has had a detrimental impact on all aspects of my life: physical, mental, emotional, family (including the size), social, professional, economic etc. • Given that the majority of Dermatologists know nothing about PN, the diagnosis journey of nine years was very taxing on me. I would say that this lack of

	Dermatologist knowledge and resulting lack of any support was as equivalent a burden as the disease itself. I have also found Dermatologists will just discharge you from their clinic if you do not agree to taking empirical treatments, in effect cutting you loose, with no support at all and you are left to sink or swim on your own. • Receiving a diagnosis didn't make any difference, given the only treatment options are empirical (steroids – topical and oral, antihistamines, cancer treatments, immunosuppressants and steroid sparing agents among others). I was essentially subject to trying a myriad of empirical treatments, which had little to no effect and also exposed me to dangerous side effects for basically little to no benefit, which was all also very taxing, adding further to my distress and depleting further my resources and already poor quality of life. • There is shame and social stigma attached to such a visible skin disease, thereby making social interactions challenging. To give a few examples, I have been stopped from boarding a plane, had people move away from me at the sight of my skin, been subject to cruel comments by strangers, the list is endless. A PN patient is fair game to pretty much everyone and anyone. Aside from the discomfort, sleep deprivation and other issues outlined above, I limit social interactions, as I do not wish to subject myself to more random cruelty. The disease influences what I wear, what I eat, where I go, who I see, in effect, there is no aspect of my life that the disease has not controlled or impacted. The disease has destroyed my life as it was. I have had to build a completely new life around the disease. • I have enclosed some quotes below from members of our community, describing their experience of Prurigo Nodularis: "Terrible pain awake all night then sleeping all day no quality of life" "Additional to the physical pain and discomfort, the disease impacts many other aspects of your life. It effects your confidence and your ability to interact with people in your community. The isolation impacts your mental healrh. The condition reduces your options to work in certain industries and impacts career

	progression. It also impacts you financially with the expensive cost of medical appointments and treatments." "I have had this for 11 years of torment. Spent countless on creams and prescription meds plus all the alternative medical practitioners, nothing has made a difference. It takes over your life trying to find if not a cure at least some relief. The excess bleeding ruins clothes and bed linen because the blood stains won't come out. Many doctors are dismissive and believe we cause this by scratching and picking but this is untrue. It started with one and within months was all over my body. After two years attending an out Patient clinic I stopped going because of their lack of interest. Secondary infection is also a huge concern. I had a strain of antibiotics resistant staffilacoccus which became septic and almost cost me my life. After Two weeks in hospital I slowly recovered but it made me see this is not some benign disease but can have serious life threatening consequences. So I strongly encourage the decision makers to consider making this available to all NP sufferers." "Totally debilitating" "I had an itchy episode in front of a doctor recently. He was being dismissive and said "now what are you doing that for ?" As if I had a choice . I coolly replied "I have an inflammatory skin itching disorder called PN, that's what happens I feel intensely itchy and I scratch, if you can figure out how to stop it I'd be very grateful but otherwise I'm going to scratch. It's a skin disease doing what it says on the tin" "I feel so exhausted no energy" "My family and doctors can see the sores but can not understand the pain and burning that goes on underneath the skin. Then once they erupt it's a whole different kind of pain and itch."

	"Depressing and hopeless" "Im 32 and not married. I think to myself who's going to want me looking like this?" "Infuriating – heartbreaking" "Constant itch, non healing scars, frustrating and sad" "Never-ending incurable and miserable" "Challenging to say the least but more depressing and debilitating especially the shame that goes with it, which, hardly anyone talks about"
7a. What do you think of the current treatments and care available for prurigo nodularis on the NHS? **7b. How do your views on these current treatments compare to those of other people that you may be aware of?**	• It is difficult to find a Dermatologist who is able to quickly diagnose the disease. This meant it took nine years for me to achieve a diagnosis and I was seen by well over 100 Dermatologists and countless other medical professionals across various specialisms in an attempt to achieve a diagnosis. Lengthy diagnosis journeys are very common in our community. • As clinicians do not know or understand the disease, when I presented I was often dismissed outright, told that it was all in my head or to just stop scratching. This is the general experience of the average Prurigo Nodularis patient. There is also a tendency to send patients for 'habit reversal' treatment, which is completely incorrect and damaging for patients. This is not a habit. This is a debilitatingly itchy condition with significant unmet need. There is a culture of dismissing and blaming the patient for their disease. • Once a diagnosis had been finally achieved, it turned out that there weren't any established care or true treatment pathways available to me. In fact having the

	label 'Prurigo Nodularis' made no difference and was akin to having an unnamed condition. • There are currently no targeted treatments for Prurigo Nodularis in England in the NHS, only empirical treatments (including immunosuppressants, Thadilomide and cancer drugs, among other) which often do little to nothing to help treat Prurigo Nodularis, while at the same time exposing a patient to often quite dangerous side-effects, which can lead to developing other conditions, which they may otherwise might not during the course of their natural life. Topical steroid treatments of any strength are particularly ineffective as the lesions are too thick for topical treatments to penetrate, yet clinicians continuously reach for these. Light treatment is also often ineffective or the benefits fleeting. • Patients can find themselves often going from one ineffective and dangerous drug to another, in the hope that one may help, this often wastes time as well, as the disease continues to spread unchecked, consuming a patient's life. • There is a huge unmet need. Prurigo Nodularis patients in Scotland have access to one of the two on-label treatments available, while patients in England have been denied access to what could be life changing treatments for some of them and continue to be subject to dangerous and often ineffective empirical treatments. • As the Founder and Chair of the Trustee Board of the charity, what I have described in the points above is consistent with what our members also report.
8. If there are disadvantages for patients of current NHS treatments for prurigo nodularis (for example, how they are given or taken, side effects of treatment, and any others) please describe these	• Patients currently don't have access to any on label targeted treatments for PN under the NHS. As outlined and covered in previous answers. Like me, patients find themselves in a situation of trying one empirical treatment after another, often with little to no results, while being exposed to dangerous side effects and the risk developing other conditions as a result of these empirical treatments. To give an example, four years of empirical Prednisone treatment left me with Osteoporosis.

	• Furthermore, the lack of dedicated treatment options, alongside ineffective empirical treatments meant the disease is left unchecked and able to do as it pleases, running riot in patients systems, spreading from top to bottom. There is a dire unmet need for Prurigo Nodularis patients.
9a. If there are advantages of nemolizumab over current treatments on the NHS please describe these. For example, the effect on your quality of life, your ability to continue work, education, self-care, and care for others? **9b. If you have stated more than one advantage, which one(s) do you consider to be the most important, and why?** **9c. Does nemolizumab help to overcome or address any of the listed disadvantages of current treatment that you have described in question 8? If so, please describe these**	• It is my understanding form a number of patients in our charity's community that, as well as from my own research that Nemolizumab can lead to a reduction to complete remission from the relentless itch of Prurigo Nodularis. Which I would see as the most important advantage, as it could enable a patient to regain control over their lives and potentially live a normal and full life. Patients also often report that they see a response within weeks. There are no current treatments for Prurigo Nodularis, just empirical treatments, with poor risk profiles, with little to no impact on the disease. • Patients also report that they tolerate Nemolizumab relatively well, without side effects. • Other advantages would be to see the general appearance of the skin improve by flattening the nodules and hopefully in time enabling the skin to heal generally. • I have enclosed below quotes from a few patients in our community who have had access to treatment with Nemolizumab: " Saved my life, literally! No itch & lesions healed." " I didn't think it would work. Nothing has helped not even dupixent, but I've taken three doses and it's like my life is back. Itching is almost gone and the nodules are healing. I've been able to go back to the gym, dye my hair etc. My mother is thrilled. She says I've stopped talking about N.P. constantly and now I'm back to the happy person I was. It is very strange to he better. I was at the edge."

	" I just had my second dose and I am seeing big lesions starting to heal." " Life changing, life giving" " Saved my life, literally! No itch & lesions healed" " No itching and way less new nodules"
10. If there are disadvantages of nemolizumab over current treatments on the NHS please describe these. For example, are there any risks with nemolizumab? If you are concerned about any potential side effects you have heard about, please describe them and explain why	A number of our patient cohort who have had access to Nemolizumab have found that they tolerate it well, with limited to no side effects. There has not been any side effects reported that are of concern, unlike empirical treatments, which have very poor risk profiles, cannot be use long-term, and have no evidence as being effective for treating Prurigo Nodularis. I have enclosed below quotes from a few patients in our community who have had access to treatment with Nemolizumab: " The first dose (2 shots) gave me diarrhea and i felt a little flu-ish for a few hours .After that, there were no side effects". " I have no side effects." " No side effects at all. Works better than Dupixent".
11. Are there any groups of patients who might benefit more from nemolizumab or any who may benefit less? If so, please describe them and explain why Consider, for example, if patients also have other health conditions (for example difficulties with mobility, dexterity or cognitive impairments) that affect the suitability of different treatments	None that I am aware of.

12. Are there any potential equality issues that should be taken into account when considering prurigo nodularis and nemolizumab? Please explain if you think any groups of people with this condition are particularly disadvantage 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.	Many patients with Prurigo Nodularis fall under having a disability, as the condition is chronic and debilitating. Prurigo Nodularis patients must be treated on par with patients of mainstream conditions who have access to on-label treatments.
13. Are there any other issues that you would like the committee to consider?	Yes. The positioning of Nemolizumab is very important for Prurigo Nodularis patients. Those who are candidates for systemic treatment should have access to Nemolizumab without the requirement to fail risky empirical off-label treatments. Prurigo Nodularis patients should not be treated similar to Atopic Dermatitis patients, they are completely different conditions. There is significant unmet need, the patients desperately need access to on-label dedicated treatments.

Part 2: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

- 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, social and relationships.
- For patients the route to achieving a diagnosis is extremely challenging due to a general lack of awareness of the condition among Dermatologists, GPs and the wider medical community. Clinicians are often dismissive and blame patients for their condition.
- 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 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. Its efficacy can also wear off completely in time.
- The disease if not contained and treated with the appropriate on-label agents (currently none available to NHS patients) spreads often to cover the majority of the body. Long-standing inflammation also leads to the question as to whether patients are at an increased risk of developing other conditions alongside PN. There is a huge unmet need for Prurigo Nodularis patients. The

positioning of Nemolizumab is also very important, to meet this unmet need it must be available to patients who are candidates for systemic treatment without any requirement to “fail” empirical treatments.

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Part 1: Living with this condition or caring for a patient with prurigo nodularis

Table 1 About you, prurigo nodularis, current treatments and equality

1. Your name	Kathleen McElvogue
2. Are you (please tick all that apply)	☒ A patient with prurigo nodularis? ☐ A patient with experience of the treatment being evaluated? ☐ A carer of a patient with prurigo nodularis? ☐ A patient organisation employee or volunteer? ☐ Other (please specify):
3. Name of your nominating organisation	Prurigo Nodularis International
4. Has your nominating organisation provided a submission? (please tick all options that apply)	☐ No (please review all the questions and provide answers when possible) ☐ Yes, my nominating organisation has provided a submission ☐ I agree with it and **do not wish to** complete a patient expert statement ☐ Yes, I authored / was a contributor to my nominating organisations submission ☐ I agree with it and **do not wish to** complete this statement ☒ I agree with it and **will be** completing

5. How did you gather the information included in your statement? (please tick all that apply)	☒ I am drawing from personal experience ☒ I have other relevant knowledge or experience (for example, I am drawing on others' experiences). Please specify what other experience: My mother had Prurigo Nodularis for 25 years. Two years ago she received Dupilumab. Been clear ever since. ☐ I have completed part 2 of the statement **after attending** the expert engagement teleconference ☒ I have completed part 2 of the statement **but was not able to attend** the expert engagement teleconference ☒ I have not completed part 2 of the statement
6. What is your experience of living with prurigo nodularis? **If you are a carer (for someone with prurigo nodularis) please share your experience of caring for them**	I have lived with Prurigo Nodularis 6 years.
7a. What do you think of the current treatments and care available for prurigo nodularis on the NHS? **7b. How do your views on these current treatments compare to those of other people that you may be aware of?**	I know Dupilumab can be very good for some people. I am very reluctant to take immunosuppressants. Some people can tolerate immunosupressants. Most people I know with the disease do not like immunosuppressants**.**
8. If there are disadvantages for patients of current NHS treatments for prurigo nodularis (for example, how they are given or taken, side effects of treatment, and any others) please describe these	If immunosupressants are not tolerated well you cannot go on to try - Nemolizumab. Then the criteria for having to have eczema is nebulous in my opinion – re Dupilumab. Not sure for Nemolizumab.

9a. If there are advantages of nemolizumab over current treatments on the NHS please describe these. For example, the effect on your quality of life, your ability to continue work, education, self-care, and care for others? **9b. If you have stated more than one advantage, which one(s) do you consider to be the most important, and why?** **9c. Does nemolizumab help to overcome or address any of the listed disadvantages of current treatment that you have described in question 8? If so, please describe these**	**NA**
10. If there are disadvantages of nemolizumab over current treatments on the NHS please describe these. For example, are there any risks with nemolizumab? If you are concerned about any potential side effects you have heard about, please describe them and explain why	NA
11. Are there any groups of patients who might benefit more from nemolizumab or any who may benefit less? If so, please describe them and explain why Consider, for example, if patients also have other health conditions (for example difficulties with mobility, dexterity or cognitive impairments) that affect the suitability of different treatments	NA

12. Are there any potential equality issues that should be taken into account when considering prurigo nodularis and nemolizumab? Please explain if you think any groups of people with this condition are particularly disadvantage 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.	More than this consideration are the points made above.
13. Are there any other issues that you would like the committee to consider?	Not everyone who is eligible would respond to Nemolizumab – for those other avenues need to be tried. But my main point to make to NICE is please loosen your criteria for a person like me (severe PN 100 lesions or more) to be offered Nemolizumab without being forced to take immunosuppressants beforehand

Part 2: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

- Thank you for highlighting an alternative treatment in the market.
- Please understand the patients generally have a gut instinct as to what they can bear/tolerate. I ask NICE to review its flexibility around patients having to take immunosuppressants first, when they know they are so sick anyway it would be intolerable to do so.
- Nemolizumab offers a greatly needed treatment and has worked hard to get to this point. I was part of a meeting in London
- meeting PN sufferers and I know first-hand how helpful and how illuminating that meeting was for those suffering with PN. I would like to thank the company for that opportunity.
- Suffering PN is like this – I don’t know how anyone goes to work with it. That said, clearly if one goes to work your mind is focussed on that. Therefore, the people who do not have the diversion of work, almost bear it more in a way - with the option that you could sleep during part of the day, but then you would be awake part of the night. None of this is conducive to good health.
- Click or tap here to enter text.

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Nemolizumab for adults with moderate to severe prurigo nodularis [ID6451]

Produced by Aberdeen HTA Group

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Declared competing interests of the authors

No competing interests to disclose.

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Rider on responsibility for the 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.

This report should be referenced as follows:

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Contribution of authors

CR reviewed and critiqued the clinical effectiveness evidence presented in the company submission and drafted the background section; NS checked and critiqued the statistical analyses presented in the company submission; CK and DB reviewed and critiqued the cost-effectiveness evidence and economic model presented in the company submission; PM checked and critiqued the company's search strategies; TO provided clinical guidance and comments on the draft report. MB coordinated all aspects of this appraisal. All authors contributed to the writing of this report and approved its final version.

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List of abbreviations

BSC	Best supportive care
CPRD	Clinical Practice Research Datalink
CS	Company submission
DLQI	Dermatology Life Quality Index
EAG	External Assessment Group
EQ-5D	EuroQol 5-dimensions
HADS	Hospital Anxiety and Depression Scale
IFSI	International Forum for the Study of Itch
IGA	Investigators global assessment
IL-31	Cytokine interleukin-31
LTE	Long-term extension
NR	Not reported
PAS	Prurigo Activity Score
PN	Prurigo nodularis

PP NRS	Peak pruritus numerical rating scale
QoL	Quality of life
SD NRS	Sleep Disturbance Numerical Rating Scale
TCI	Topical calcineurin inhibitor
TCS	Topical corticosteroid
VAS	Visual analogue scale

External assessment group report executive summary

Nemolizumab for adults with moderate to severe prurigo nodularis [ID6451]

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.

All issues identified represent the EAG's view, not the opinion of NICE.

1.1 Overview of the EAG's key issues

The focus of the submission received from Galderma is nemolizumab for the treatment of adults with moderate to severe prurigo nodularis. The company's positioning of nemolizumab in the care pathway is alongside existing topical treatments, which can include topical emollients, TCSs, and TCIs, in patients with moderate to severe PN who have had an inadequate response to existing topical treatments, or where these treatments are contraindicated or not tolerated.

In the CS, the main clinical effectiveness evidence for nemolizumab is obtained from two Phase 3 randomised controlled trials (RCT), OLYMPIA 1 (NCT04501666) (n=[redacted]) and OLYMPIA 2 (NCT04501679) (n=274), and a currently ongoing long-term extension (LTE) study, OLYMPIA LTE (NCT04204616) (n=508), that included patients from the two OLYMPIA trials and a prior nemolizumab PN Phase 2 study. This Phase 2 RCT (Ständer et al., 2020, NCT03181503, n=70) was itself excluded from the CS.

Table 1 Summary of key issues

ID 6451, Issue number:	Summary of issue	Report sections
1	It is unclear whether the economic model structure reflects likely future real-world use of nemolizumab	4.2.2 & 4.2.6
2	The economic model includes costs but excludes benefits of best supportive care	4.2.2 & 4.2.8
3	Health state utility values may over-estimate the utility benefit of responders, compared to non-responders in the economic model	4.2.7

The key differences between the company's preferred assumptions and the EAG's preferred assumptions are:

- The company prefers to include an additional 5% increase in utility for treatment responders beyond year 1, whereas the EAG prefers to use the available EQ-5D data from the OLYMPIA studies for responder utility.

- The company preferred non-response utility value is to assume all non-responders have a utility equal to baseline. The EAG prefers to apply the available EQ-5D data from the OLYMPIA studies for non-responders. The company prefer to assume that the non-responder HSUV is equal to the baseline utility value.

- The company includes a utility benefit for non-responders in the first year following treatment discontinuation in the nemolizumab arm of the economic model whereas the EAG prefer to assume non-response utility values are independent of treatment.

- The company prefer to exclude adverse event disutilities whereas as the EAG prefer for them to be included in the economic model.

- The company's economic model structure assumes that treatment non-responders incur additional BSC costs, but that there is no potential for clinical or quality of life benefit of these treatments. The EAG would have preferred to model the benefits of

BSC treatment alongside costs, but in the absence of any data to inform that analysis, the EAG prefers to exclude BSC costs from the model to minimise bias.

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:

- Improving quality of life by increasing the proportion of people with moderate to severe PN who achieve a composite clinical response in terms of nodule reduction and itch improvement

Overall, the technology is modelled to affect costs by:

- Leading to an increase in treatment acquisition costs for nemolizumab whilst a treatment response is maintained
- Reducing the costs of best supportive care treatments such as TCI, TCS and immunosuppressant treatments
- Reducing the healthcare resource use associated with routine patient monitoring for non-responders.

The modelling assumptions that have the greatest effect on the ICER are:

- The assumed weight of the treated population which impacts on treatment acquisition costs for nemolizumab
- The size of the utility difference between responders and non-responders
- The impact of including BSC treatment costs for non-responders, but assuming that no clinical or quality of life benefit can be attained.

1.3 The decision problem: summary of the EAG's key issues

The company's decision problem deviated from the NICE scope by considering a more specific population and excluding comparators that are not licensed for clinical practice in the

UK. The EAG believes that including these treatments in the company's analysis could have offered valuable insights.

1.4 The clinical effectiveness evidence: summary of the EAG's key issues

No major issues were identified. The EAG was initially concerned about the exclusion of the Phase 2 trial by Ständer et al., 2020 (NCT03181503) from the company submission (CS), but after receiving further information during the clarification process, they agreed with the company that its inclusion would not make a substantial difference to the cost-effectiveness results.

1.5 The cost-effectiveness evidence: summary of the EAG's key issues

The EAG raise several key issues in relation to the cost-effectiveness modelling, discussed in Issues 1 to 3 below. These relate to

- The potential for the economic model structure to capture all the costs and benefits of nemolizumab treatment,
- Uncertainty around the generalisability of the modelling assumptions about treatment discontinuation due to lack of a composite response to how nemolizumab might be used in UK clinical practice,
- The appropriateness of an assumption that costly best supportive care treatments such as topical corticosteroids, TCIs and immunosuppressants would be prescribed indefinitely without any clinical or quality of life benefit.
- Differences in opinion between the company and EAG about how much additional quality of life benefit can be achieved for patients achieving a composite response compared to those not achieving a composite response.

These issues are discussed in further detail in the issues tables that follow.

Issue 1: It is unclear whether the economic model structure reflects likely future real-world use of nemolizumab

Report section	4.2.2
Description of issue and why the EAG has identified it as important	The company's economic model assumes that patients will discontinue treatment once a composite response has been lost. This may not reflect real world use of nemolizumab in UK clinical practice where clinicians and patients may wish to continue treatment if an improvement in symptoms can be achieved, even if the composite response has not been reached. The company attempt to include partial response utilities in the QALY calculations but have not defined what a partial response would be.
What alternative approach has the EAG suggested?	The EAG would have preferred the company to consider an appropriate definition of partial response where the cohort would remain on treatment and incur some quality-of-life benefits. The definition of partial response should be clearly described and utilities / costs / transition probabilities into any partial response health state should be informed by all available data from the OLYMPIA studies and LTE study.
What is the expected effect on the cost-effectiveness estimates?	Widening the pool of patients receiving treatment would incur additional treatment acquisition costs for nemolizumab as well as additional QALY benefits. Assuming that the utility in a partial response state is lower than the composite response, including a partial response state in the model would likely increase the ICER, but the magnitude of increase is unknown.
What additional evidence or analyses might help to resolve this key issue?	The company could have defined a partial response based on expert opinion and included it as a health state in the economic model. The model could have been updated to include a partial response health state, parameterised based on the available OLYMPIA and LTE study data.

Issue 2: The economic model includes the costs, but excludes the benefits of best supportive care

Report section	4.2.2 & 4.2.8
Description of issue and why the EAG has identified it as important	The proportion of the cohort in the "non-response" state, who fail to achieve a composite response, who discontinue treatment or who lose a composite response incur an increase in costs of intensive BSC management, but no clinical or quality of life benefit is modelled. This is an important issue as it creates a bias because non-responders remain on treatment for their remaining lifetime without benefit.
What alternative approach has the EAG suggested?	The EAG would have preferred an adapted model structure, in combination with Issue 1 above that would allow for a treatment benefit and quality of life gain in a proportion of patients treated with TCS, TCI and immunosuppressants. Whilst achievement of a composite response may be unlikely, it might be reasonable to assume some benefit for patients on lifelong treatment, even if that is just utility benefits from symptomatic control.
What is the expected effect on the cost-effectiveness estimates?	The company's assumption likely creates a bias in favour of nemolizumab by under-estimating the benefits or over-estimating the costs in the non-response BSC arm of the model.
What additional evidence or analyses might help to resolve this key issue?	The company could have updated their economic model to capture benefits in the control group, perhaps through a partial response health state. In the absence of any data provided within the company submission, the EAG removes BSC costs entirely to minimise the magnitude of bias on the ICER.

Issue 3: Health state utility values may over-estimate the utility benefit of responders, compared to non-responders in the economic model

Report section	4.2.7
Description of issue and why the EAG has identified it as important	The company's preferred analysis includes three key assumptions that may over-estimate the magnitude of QALY gains for responders compared to non-responders: A) Inclusion of a 5% utility increase for responders based on a long-term follow up of AD patients B) Assuming that nemolizumab non-responders are partial responders and receive a utility benefit in the nemolizumab non-response state for one year following loss of response, calculated as the average of baseline and response utility. C) Assuming all non-responders have a utility equal to baseline rather than the observed non-responder utility from the OLYMPIA studies.
What alternative approach has the EAG suggested?	The EAG prefers: A) To retain the response utility value observed in the OLYMPIA studies B) Remove the partial response utility benefit in the nemolizumab arm because a partial response has not been defined and including in one arm only may bias results C) To retain the non-response utility value observed in the OLYMPIA studies
What is the expected effect on the cost-effectiveness estimates?	The EAG's preferred assumptions lead to a substantial increase in the ICER compared to the company's base case analysis.
What additional evidence or analyses might help to resolve this key issue?	No further data or evidence required. A judgement is required on whether the EAG or company health state utility values are more robust and plausible.

1.6 Summary of EAG's preferred assumptions and resulting ICER

The impact of the EAG's preferred assumptions and analyses on the ICER is described in Table 2. Several minor issues were identified with the company base case calculations, therefore the EAG updated the company's preferred post clarification analysis and applied our preferred assumptions to this corrected ICER.

Table 2 Summary of EAG's preferred assumptions and ICER

Scenario	Incremental cost	Incremental QALYs	ICER
Company's base case, post clarification queries	[redacted]	[redacted]	**£34,523**
EAG corrected company base case, post clarification queries[A]	[redacted]	[redacted]	**£34,657**
Remove the 5% increase in response HSUV beyond OLYMPIA trial data EQ-5D.	[redacted]	[redacted]	£38,064
Use a non-responder HSUV ([redacted]) obtained directly from the OLYMPIA trial data	[redacted]	[redacted]	£42,068
Remove nemolizumab partial response utility from the non-response state.	[redacted]	[redacted]	£41,495
Include adverse event disutilities	[redacted]	[redacted]	£34,672
Remove all BSC costs from the non-response model health state	[redacted]	[redacted]	£37,038
EAG's preferred base case (all scenarios above combined)	[redacted]	[redacted]	**£90,712**

[A] All EAG preferred analyses applied to the EAG corrected company base case.

2 INTRODUCTION AND BACKGROUND

2.1 Introduction

The relevant health condition for the submission received from Galderma is moderate to severe prurigo nodularis (PN) in adults. The company's description of the health condition in terms of prevalence, symptoms and complications appears accurate and in line with the decision problem. The relevant intervention for this submission is nemolizumab (Nemluvio©).

2.2 Background

The company submission (CS) describes PN as a rare, chronic and debilitating neuroimmune dermatological disease that is characterised by multiple patches of thick or rough (hyperkeratotic) skin nodules and papules (raised or inflamed areas of skin) that are extremely pruritic (itchy).[1, 2] A recent retrospective analysis of 11,656 patients within the Clinical Practice Research Datalink (CPRD) (Aurum) dataset estimates that the prevalence of PN in England is 3.27 per 10,000 people, which equates to 18, 471 people, with an incidence of 2.88 per 100,000 patient-years.[3]

The primary symptom of PN is frequent severe and persistent itching that is often painful, and causes a constant urge to scratch.[2] Patients with PN report more intense itching than patients with other pruritic dermatological conditions, such as psoriasis, and many patients report associated negative impacts on their wellbeing,[4-7] such as sleep impairment and sleep disturbances,[8, 9] poor mental health and quality of life (QoL),[10] reduced participation in social activities and increased absenteeism from work.[8] PN is associated with high primary and secondary healthcare resource utilisation, which represents a significant economic burden for the NHS. Findings of a UK study into the costs associated with increased healthcare contacts found higher mean costs per annum for all healthcare contacts for patients with PN versus the control population (patients without PN): £371 versus £218 for primary care, £1,326 versus £731 for inpatient contacts, £737 versus £331 for outpatient contacts, and £97 versus £53 for accident and emergency contacts.[11, 12] Patients with PN can also face considerable 'out-of-pocket' expenses for supplementary healthcare treatments and precautionary devices.[13, 14]

The cause of PN is unknown but it is believed that it is associated with altered functioning of the immune system and nerves in the skin. Overexpression of cytokine interleukin-31 (IL-31) is associated with neuroimmune responses that promote the sensation of intense itching. This promotes a scratching response (either voluntary or involuntary), known as the itch-scratch cycle.[2, 15] The process of scratching itself also increases the release of IL-31 in the skin, which in turn induces further itching and subsequent scratching, which completes the 'itch-scratch' cycle. Patients with PN show elevated levels of IL-31 compared to patients with other pruritic skin diseases and healthy individuals.[2] In PN, the chronic scratching associated with the perpetual itch-scratch cycle, while initially relieving the itch sensation, can damage the skin and cause bleeding and persistent skin lesions.[16] Severity of PN can be assessed using several criteria. The five-point (0 to 4) Investigator's Global Assessment (IGA) scale measures the number of nodules a patient has on their body. An IGA score of 3 denotes moderate disease (approximately 20–100 palpable pruriginous nodules) and IGA 4 denotes severe disease (> 100 nodules palpable pruriginous nodules). The Prurigo Activity Score (PAS) questionnaire assesses the type, number, and distribution of lesions and the proportion of healed lesions relative to excoriated lesions. 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 < 3), moderate pruritus (≥ 3 to < 7), severe pruritus (≥ 7 to < 9) or very severe pruritus (≥ 9).[17, 18]

The treatment goals of PN are to interrupt the itch-scratch cycle and to reduce or completely heal lesions, with therapies tailored according to the patient's age, comorbidities, severity of PN, QoL and expected side effects of medications.[1] The company describes people with moderate to severe PN as the patient population with the greatest unmet need for new therapeutic options; however, there are no treatment guidelines or therapies approved by NICE for PN at the time of the CS. Current topical and systemic treatments are used off-label to provide symptomatic relief, such as improvements in itch, clearance of skin lesions, and reduction in sleep disturbance, and treatment decisions are mostly based on clinical judgment informed by the International Forum for the Study of Itch (IFSI) stepwise treatment cascade. The company provides a summary of the IFSI stepwise treatment recommendation in Figure 3 of the CS, and this is reproduced by the EAG as Figure 1.

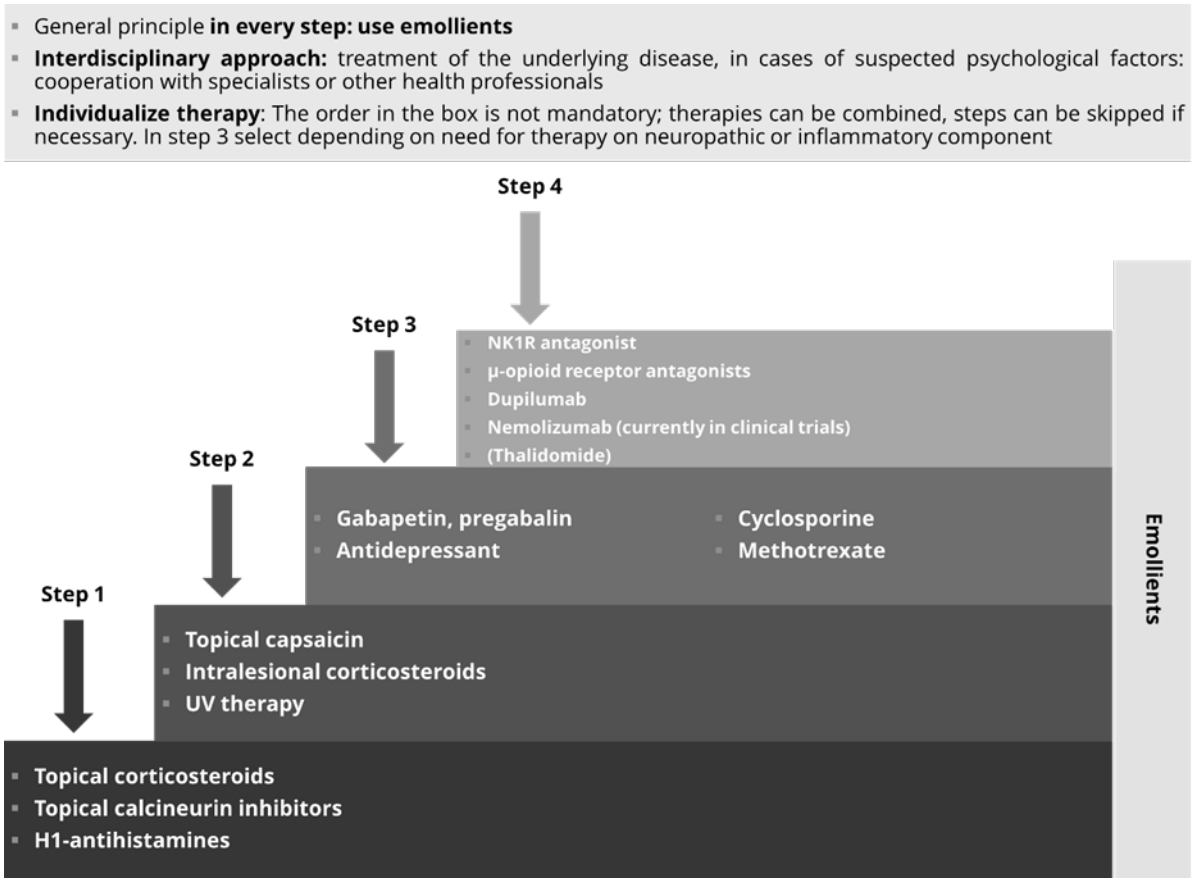

Figure 1. IFSI stepwise treatment recommendations

Source: Ständer et al. (2020)[19]

Abbreviations: IFSI, International Forum for the Study of Itch; NK1R, neurokinin-1 receptor; UV, ultraviolet.

A Delphi panel (conducted by Galderma)[20] of clinicians specialising in the treatment of PN, including clinicians from the UK, agreed that the best supportive care (BSC) for treating patients with PN includes emollients, topical corticosteroids (TCSs), and topical calcineurin inhibitors (TCIs), and that while not considered BSC, antihistamines, systemic corticosteroids, and immunosuppressants (e.g. methotrexate and ciclosporin) are occasionally used for symptomatic relief. TCSs were reported as the most frequently used first-line treatment for patients with moderate to severe PN. Phototherapy, while recognised as a potential treatment option for patients with PN was rarely recommended as a therapy option by the UK clinicians. The company reports that this is likely due to its limited effectiveness, inconvenience to patients, and concerns regarding the increased risk of melanoma from exposure to ultraviolet light.[21]

Of the currently available treatment options in the UK, topical therapies can be time-consuming and messy to apply and can cause localised skin reactions, while systemic therapies can cause significant adverse events associated with their toxicity profiles, which can contribute towards patient dissatisfaction with their treatment.[18, 22] Of those patients with moderate to severe PN, 26.8% are reported to have inadequately controlled disease,[23] and most (56.8%) respondents in a European cross-sectional survey of patient perspectives of their treatment were not satisfied with their previous therapy, and 28.7% thought that none of the therapies they received were effective, although most of the respondents in this survey were not treated with potent systemic treatments.[24]

The company anticipates that nemolizumab will be used alongside existing topical treatments, which can include topical emollients, TCSs, and TCIs, in patients with moderate to severe PN who have had an inadequate response to existing topical treatments, or where these treatments are contraindicated or not tolerated. The company states that any use of TCSs or TCIs should aim to be tapered and subsequently discontinued when the disease has sufficiently improved. The company provides a summary of the anticipated positioning of nemolizumab in the care pathway in Figure 4 of the CS, and this is reproduced by the EAG as Figure 2. The EAG clinical expert agrees with the company's description of the current treatment landscape for PN in the UK and the positioning of nemolizumab in the care pathway.

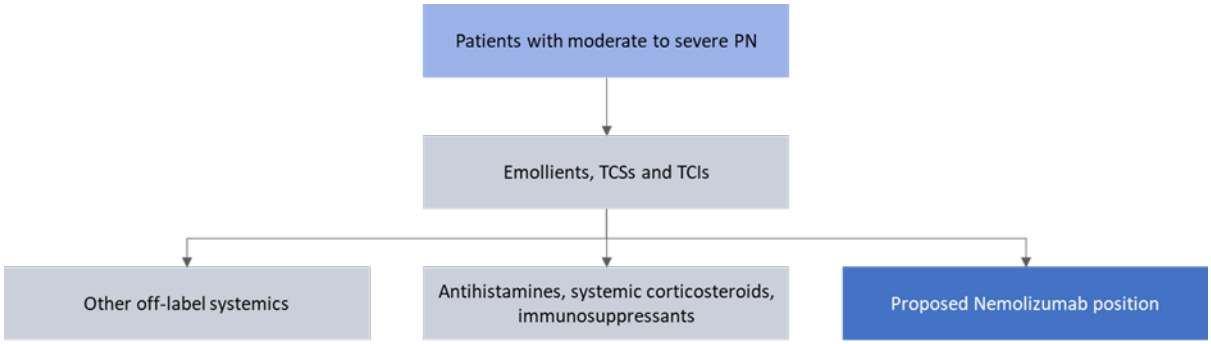

Figure 2. Anticipated positioning of nemolizumab

Abbreviations: PN: prurigo nodularis; TCIs: topical calcineurin inhibitors; TCSs: topical corticosteroids.

2.3 Critique of company's definition of decision problem

A summary of the company's decision problem in relation to the NICE final scope is presented in Table 3 below. A critique of the adherence of the company's economic modelling to the NICE reference case is presented in Chapter 4.

Table 3 Summary of the company's 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 PN	Adults with moderate to severe PN	Adults with moderate to severe PN are those with the greatest unmet need for new safe and effective therapeutic options. Furthermore, this population aligns with the patient population included in the clinical evidence,[25-27] the economic analysis and is considered the population most likely to receive nemolizumab by UK clinical experts.[20, 28]	The company's target population is more specific than that of the final scope and aligns with the company's proposed positioning of nemolizumab in the care pathway. The EAG clinical expert agrees that adults with moderate to severe PN are the patient population that are most likely to receive nemolizumab in the UK.
Intervention	Nemolizumab	Nemolizumab with BSC	It is anticipated that nemolizumab will be used with existing BSC, which can include topical emollients, TCSs, and TCIs, in patients with moderate to severe PN. This is aligned with the anticipated use of nemolizumab in clinical practice and has been validated by UK clinical experts.[28]	The intervention described in the CS matches that described in the NICE final scope. Nemolizumab is is a humanised monoclonal antibody that targets the interleukin-31 receptor alpha (IL-31RA). Interleukin-31 (IL-31) is a key mediator of itch, known as a pruritogen, in PN. Nemolizumab inhibits IL-31 signalling and suppresses pruritus by competitively preventing IL-31 from binding to IL-31RA.[29] Nemolizumab is indicated for the treatment of PN and the treatment of moderate to severe atopic dermatitis

				(AD) in patients aged 12 years and older who are candidates for systemic therapy. Only nemolizumab for the treatment of PN is considered in this submission. Nemolizumab is administered by subcutaneous injection, with dosage dependent on patient's weight: patients weighing ≥ 90 kg receive 60 mg Q4W, while patients < 90 kg receive 60 mg loading dose at Week 0, followed by 30 mg Q4W thereafter. Treatment continues for as long as patients are responding to treatment. The company reports that UK MAA submission via Access Consortium NASWSI (New Active Substance Work Sharing Initiative) was performed [redacted]. The anticipated UK marketing authorisation date is [redacted].
Comparator(s)	Established clinical management, including: • Topical emollients • TCS • TCI • Antihistamines • Oral corticosteroids • Phototherapy	Established clinical management, including: • Topical emollients • TCS • TCI • Antihistamines • Systemic corticosteroids	Treatment options for patients with PN are limited, as there are currently no guidelines published nor any treatments recommended by NICE for the treatment of PN. During a Delphi panel conducted by Galderma, UK clinicians agreed that the BSC landscape for treating patients with PN includes emollients, TCSs, and TCIs. The	The company have not considered phototherapy or antidepressants as comparators for nemolizumab in the CS. The company states that the UK clinicians who participated in their Delphi panel exercise did not consider either of these treatments to be commonly used for the best supportive care for PN. The company further states that phototherapy and antidepressants

	• Immunosuppressive therapies (azathioprine, ciclosporin, methotrexate, or thalidomide) • Antidepressants including selective serotonin reuptake inhibitors (SSRIs) and serotonin norepinephrine reuptake inhibitors (SNRIs)	• Immunosuppressive therapies (azathioprine, ciclosporin, methotrexate, or thalidomide)	UK clinicians stated that there is significant variation in the subsequent systemic treatments provided. While not considered BSC, antihistamines, systemic corticosteroids and immunosuppressants were treatments used on occasion to manage the symptoms experienced by patients with PN.[20] Therefore, this submission considers topical emollients, TCSs, and TCIs as BSC and the most relevant comparators for nemolizumab.	are considered as additional treatments that provide symptomatic relief but do not have any effect on the underlying condition of PN. The company also states that the evidence for the use of phototherapy in PN is weak and that the treatment is not universally accessible by NHS patients. The company, therefore, does not consider phototherapy and antidepressants as plausible comparators for this submission. The EAG clinical expert agrees that antidepressants do not treat the underlying PN condition. The EAG clinical expert also agrees that, while phototherapy should be available in most UK hospital settings, issues such as getting clinic appointments, travelling to hospital and time off work, could create access problems for patients.
Outcomes	The outcome measures to be considered include: • Measures of disease severity • Measures of symptom control including improvement in itch • Time to relapse/prevention of relapse • Adverse effects of treatment • HRQoL	The outcome measures to be considered include: • Measures of disease severity • Measures of symptom control including improvement in itch	During TA955, disease-free period/maintenance of remission and time to relapse/prevention of relapse were not considered relevant in PN.[23] Furthermore, the OLYMPIA 1[25] and OLYMPIA 2[26] clinical trials include a placebo-controlled 24-week and 16-week treatment duration, respectively; while the subsequent LTE study is no longer placebo controlled.	The EAG accepts the company have limited long-term data comparing nemolizumab and placebo for relapse/prevention of relapse and disease-free period/maintenance of remission outcomes; however, in the EAG clinical expert's opinion, these outcomes are relevant to PN. The EAG would have welcomed a comparative analysis of off-treatment patients with those who continued to receive

	• Disease-free period/maintenance of remission	• Adverse effects of treatment • HRQoL	Therefore, there is limited long-term comparative data that would allow for a meaningful comparative analysis of disease-free period/maintenance of remission or time to relapse/prevention of relapse in patients with PN.	nemolizumab in the long-term follow-up studies.
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 treatment technologies will be considered. The availability and cost of biosimilar and generic products should be considered.	As per NICE scope	N/A	The company's economic evaluation model is broadly aligned with the NICE reference case. However, the company has not always used the cheapest available generic alternative for BSC treatments, potentially over-costing the BSC comparator arm. This, and further key points of critique of the company's modelling assumptions are discussed in Chapter 4.
Subgroups	If evidence allows the following subgroups will be considered: • Skin colour subgroups	Subgroups of interest for nemolizumab in moderate to severe PN include: • Skin colour subgroups	The dose of nemolizumab in PN is dependent on the patient's weight. Patients weighing ≥ 90 kg receive 60 mg Q4W, while patients < 90 kg to receive a 60	The EAG accepts the company's justification for the additional subgroup analyses.

		• Patients weighing < 90kg and ≥ 90kg	mg loading dose at Week 0, followed by 30 mg Q4W thereafter.[30]	
Special considerations including issues related to equity or equality				The company states that nemolizumab is not anticipated to raise any specific equality issues or differential impact on individuals protected by equality legislation or those with disabilities, compared with the wider population. The company notes that patients with skin of colour may be more likely to receive suboptimal treatment due to the challenges in assessing skin disorders in these patients compared with people with white skin. Patients with skin of colour have a greater propensity for papulation, lichenification, PN, pigmentary changes, and extensor surface involvement than patients with white skin and erythema is more difficult to detect in highly pigmented patients and can lead to an underestimation of disease severity.[31, 32] The EAG clinical expert agrees that nemolizumab is unlikely to be associated with any issues relating to equity or equality. The EAG clinical expert agrees that PN patients with skin of colour may be more likely to receive suboptimal treatment than patients with white skin.

3 CLINICAL EFFECTIVENESS

3.1 Critique of the methods of review(s)

Full details of the methods used by the company to identify and select the clinical evidence relevant to this appraisal are reported in Appendix D of the CS. The EAG's appraisal of the company's systematic literature review (SLR) methodology is summarised in Table 4.

Table 4 EAG's appraisal of the literature review methods presented in the CS

Review process ERG	ERG response	Comments
Were appropriate searches (e.g., search terms, search dates) performed to identify all relevant clinical and safety studies?	YES	The CS provides full details of the searches used to identify the studies for the clinical effectiveness review. The search strategies include relevant controlled vocabulary and text terms with appropriate use of Boolean operators and are fully reproducible. Details are provided in Appendix D of the CS.
Were appropriate bibliographic databases/sources searched?	YES	Sources included Embase, Medline, and CENTRAL for primary research. Relevant conference proceedings, trial registers and HTA organisations were also searched. Bibliographies of recent SLRs were examined to identify relevant studies not captured by the literature searches. Searches were not restricted by any eligibility criteria, so all results were discovered and only those relevant to the scope were selected. Full details are provided in Appendix D of the CS.
Were eligibility criteria consistent with the decision problem outlined in the NICE final scope?	YES	The eligibility criteria outlined in Appendix D, section D.1.7 are consistent with the decision problem outlined in the NICE final scope.
Was study selection conducted by two or more reviewers independently?	YES	Appendix D, section D.1.8 "*Titles and abstracts identified by the search strategy were independently assessed for possible eligibility by two reviewers in line with the PICOS criteria. Those studies that did not meet eligibility criteria were excluded. For those citations that could potentially meet*

		the eligibility criteria, full texts were retrieved, and eligibility criteria were applied by two independent reviewers."
Was data extraction conducted by two or more reviewers independently?	PARTIALLY	Appendix D, section D.1.9 "*Data were extracted by one reviewer and quality checked against the original source by a second reviewer. Any discrepancies between the two reviewers were resolved by discussion*."
Were appropriate criteria used to assess the risk of bias of identified studies?	PARTIALLY	Randomised controlled trials were appropriately assessed using the Cochrane Risk of Bias (RoB) Assessment Tool 2.0. The EAG notes that the Cochrane RoB 2.0 was also used to assess the risk of bias of the LTE study, as presented in Table 11 of the CS. Participants were not randomised in the LTE study, therefore a tool for assessing risk of bias in non-randomised studies would have provided more appropriate risk of bias criteria for the LTE study.
Was the risk of bias assessment conducted by two or more reviewers independently?	PARTIALLY	Appendix D, section D.3 "*Quality assessment of included studies was undertaken by one reviewer and checked by a second reviewer. Any discrepancies between the two reviewers were resolved by consensus or involvement of a third reviewer.*"
Was identified evidence synthesised using appropriate methods?	SOME CONCERNS	No formal meta-analysis was conducted; instead, data from the OLYMPIA 1 and 2 trials were simply pooled. The EAG has some concerns about the transparency of the selection process for inclusion of studies in the CS (see sections 3.2 and 3.3)

The EAG conducted a quality assessment of the methods used by the company for the SLR of clinical evidence based on the Centre for Reviews and Dissemination (CRD) criteria. The results are presented in Table 5.

Table 5 Quality assessment of the company's systematic literature review of clinical effectiveness evidence

CRD quality item	Yes/No/Unclear
1. Are any inclusion/exclusion criteria reported relating to the primary studies, which address the review question?	Yes
2. Is there evidence of a substantial effort to search for all of the relevant research?	Yes
3. Is the validity of included studies adequately assessed?	Yes
4. Are sufficient details of the individual studies presented?	Yes
5. Are the primary studies summarised appropriately?	Yes

3.2 Critique of trials of the technology of interest, the company's analysis and interpretation (and any standard meta-analyses of these)

3.2.1 Identified studies

Details of the key clinical effectiveness evidence are presented in Section B.2 of the CS. The company's main evidence for nemolizumab is obtained from two Phase 3 clinical trials, OLYMPIA 1 (NCT04501666) (n=[redacted]) and OLYMPIA 2 (NCT04501679) (n=274) and a currently ongoing long-term extension (LTE) study, OLYMPIA LTE (NCT04204616) (n=508), that included patients from the two OLYMPIA trials and a prior nemolizumab PN Phase 2a study (NCT03181503). Of the 508 participants enrolled in OLYMPIA LTE, [redacted] had treatment exposure to nemolizumab from the previous study.

Summaries of the methodologies and baseline participant and disease characteristics of the OLYMPIA 1 and OLYMPIA 2 trials, and the LTE study are presented in Tables 6, 7 and 8. Both OLYMPIA 1 and OLYMPIA 2 were multicentre, double-blind, placebo-controlled, randomised, parallel-group trials with similar PICO (population, intervention, comparators, outcomes) eligibility criteria; however, the trials differed in their follow-up duration and the number of administrations of nemolizumab and placebo treatments: 24 weeks duration for OLYMPIA 1 (with five treatment doses at weeks 4, 8, 12, 16 and 20) and 16 weeks duration for OLYMPIA 2 (with four treatment doses at weeks 4, 8, 12 and 16). The trials were designed to

evaluate the efficacy and safety of nemolizumab in patients with moderate to severe PN.

The baseline characteristics of participants are broadly similar across the study treatment groups; however, the EAG notes that slightly more patients with severe PN (IGA category 4) were randomised to the nemolizumab arm compared with the placebo arm ([redacted]% versus [redacted]%) in OLYMPIA 1. Patients with severe PN are more likely to achieve a change of ≥2-point difference from baseline in the investigators' global assessment (IGA) but are less likely to achieve an IGA score of 0/1. *The EAG clinical advisor is of the opinion that the participants in the OLYMPIA 1, OLYMPIA 2 and OLYMPIA LTE studies are broadly representative of patients with PN seen in NHS clinical practice.*

The EAG generally agrees with the company's quality assessment of the three OLYMPIA studies and regards them as being of good methodological quality.

In addition to the OLYMPIA trials and the LTE study, the EAG considers the nemolizumab phase 2, placebo-controlled RCT conducted by Ständer et al. (2020) (NCT03181503)[33] potentially relevant to the scope of this assessment. This trial was identified through the company's SLR; however, its data were not included in the CS. This trial will be discussed in Section 3.2.6, so the EAG has included a summary of its methods and baseline participant characteristics in Tables 6, 7 and 8.

Table 6 Study methods of OLYMPIA 1, OLYMPIA 2, OLYMPIA LTE and NCT03181503

Study	OLYMPIA 1 (NCT04501666)	OLYMPIA 2 (NCT04501679)	LTE study (NCT04204616)	Ständer et al., 2020 (NCT03181503)
Study design	Phase 3, multicentre, double-blind, placebo-controlled, randomised, parallel-group study		Phase 3 prospective, multicentre, long-term extension study	Phase 2, multicentre, double-blind, placebo-controlled, randomised, parallel-group study
Location	77 sites across 10 countries: Austria, Canada, Denmark, Germany, Hungary, Italy, Poland, Sweden, UK and US	55 sites across 9 countries: Belgium, Canada, France, Netherlands, Poland, South Korea, Spain, Switzerland and US	Approximately 160 sites across 15 countries: Austria, Belgium, Canada, Denmark, France, Germany, Hungary, Italy, Netherlands, Poland, South Korea, Spain, Switzerland, UK and US	Five countries: Austria, France, Germany, Poland, and the United States (no patients were enrolled in the US)
Duration	24 Weeks	16 Weeks	196 Weeks	12 weeks
Population	Adult patients with a clinical diagnosis of PN for at least six months with pruriginous nodular lesions on upper limbs, trunk, and/or lower limbs with at least 20 nodules on the entire body with a bilateral distribution, Investigator's Global Assessment score ≥3 (based on the IGA scale ranging from 0 to 4, in which 3 was moderate and 4 was severe) at both the screening and baseline visits. Eligibility criteria for participants: 1. Male or female aged ≥ 18 years at the time of screening 2. Clinical diagnosis of PN for at least six months with:		Adult patients who had been enrolled in prior nemolizumab PN Phase 2a or Phase 3 studies. Eligibility criteria for participants: 1.Patients who may benefit from study participation in the opinion of the investigator and participated in a prior nemolizumab study for PN, including: a. Patients who completed the treatment period in a phase 3 pivotal study (OLYMPIA 1 or OLYMPIA 2) and enrol within 56 days	Adult patients who had had PN with severe pruritus for at least 6 months. Severe pruritus was defined as a mean score of at least 7 points over the previous week for the worst daily intensity of pruritus on the numerical rating scale (scores range from 0 [no itch] to 10 [worst itch imaginable]; a change of 4 points indicates a clinically important difference). Patients had to have moderate-to-severe PN, which was defined as prurigo nodular lesions on the upper limbs, with or without lesions on the trunk or lower limbs, and at least 20 nodules on the body, with lesions present on both sides of the body. Eligibility criteria for participants: Male or female of at least 18 years at screening

Study	OLYMPIA 1 (NCT04501666)	OLYMPIA 2 (NCT04501679)	LTE study (NCT04204616)	Ständer et al., 2020 (NCT03181503)
	a. Pruriginous nodular lesions on upper limbs, trunk, and/or lower limbs b. At least 20 nodules on the entire body with a bilateral distribution c. IGA score ≥ 3 (based on the IGA scale ranging from 0 to 4, in which 3 was moderate and 4 was severe) at both the screening and baseline visits 3. Severe pruritus, defined as follows on the PP NRS: • At the screening visit (Visit 1): PP NRS score was ≥ 7.0 for the 24-hour period immediately preceding the screening visit. • At the baseline visit (Visit 2): mean daily intensity of the PP NRS score was ≥ 7.0 over the previous week. 4. Female patients of childbearing potential must have agreed to use at least one adequate and approved method of contraception throughout the study and for 12 weeks after the last study drug injection. 5. Female patients of non-childbearing potential must have met one of the following criteria: • Absence of menstrual bleeding for 1 one year prior to screening without any other medical reason, confirmed with a follicle-stimulating hormone level in the postmenopausal range		b. Or patients who were previously randomised in the nemolizumab phase 2a PN study c. Or patients who completed through week 24 of the Phase 3b durability study or who exit the study due to relapse may be eligible to re-enter the LTE study within 28 days of exiting the durability study 2.Female patients of childbearing potential must agree to use an adequate method and approved method of contraception throughout the study and for 12 weeks after the last study drug injection 3.Female patients of non-childbearing potential must meet one of the following criteria: absence of menstrual bleeding for one year prior to screening without any other medical reason, confirmed with follicle stimulating hormone level in the postmenopausal range, or documented hysterectomy,	2. Clinical diagnosis of PN for at least 6 months with: • Prurigo lesions on upper limbs with or without lesions on the trunk or lower limbs • At least 20 nodules on the entire body with a bilateral distribution 3. Severe pruritus defined as follows on a Numerical Rating Scale (NRS) • At the Screening visit 1: Mean of the worst daily intensity of the NRS score is ≥ 7 over the previous 3 days • At the Baseline visit: Mean of the worst daily intensity of the NRS score is ≥ 7 over the previous week 4. Female subjects must have: • Absence of menstrual bleeding for 1 year prior to screening, without any other medical reason], hysterectomy or bilateral oophorectomy • Or, participants of childbearing potential agreed to a true abstinence or to use an effective method of contraception throughout the clinical trial and for 120 days after the last study drug administration: 5. Willing and able to comply with all the time commitments and procedural requirements of the clinical trial protocol 6. Willing and able to use electronic devices for patient reported outcomes and actigraphy devices during the study or living with someone who can ensure that the devices were properly used.

Study	OLYMPIA 1 (NCT04501666)	OLYMPIA 2 (NCT04501679)	LTE study (NCT04204616)	Ständer et al., 2020 (NCT03181503)
	• Documented hysterectomy, bilateral salpingectomy, or bilateral oophorectomy at least three months before the study 6. Patient was willing and able to comply with all of the time commitments and procedural requirements of the clinical study protocol, including daily diary recordings by the patient using an electronic handheld device provided for this study 7.Read, understood, and signed an ICF before any investigational procedure(s) were performed.		bilateral salpingectomy, or bilateral oophorectomy at least three months before the study 4.Patient is willing and able to comply with all of the time commitments and procedural requirements of the clinical study protocol, including periodic weekly recordings by the patient using an electronic handheld device provided for by the study 5.Understand and sign an informed consent form before any investigational procedure(s) are performed	7. Apprised of the Health Insurance Portability and Accountability Act (HIPAA), if in the US., as verified by signing a written authorization 8. Understand and sign an Informed Consent Form (ICF) prior to any investigational procedures being performed and agreed to collection, storage and analysis of blood and skin samples.
Intervention(s)	Nemolizumab 30 mg/60mg SC Q4W: • if patient weighs < 90 kg at baseline; 60 mg loading dose followed by 30 mg administered SC Q4W at weeks 4, 8, 12 and 16 (and 20 for OLYMPIA 1) • if patient weighs ≥ 90kg at baseline; 60 mg loading dose followed 60 mg (2 x 30 mg injections) administered SC Q4W at weeks 4, 8, 12 and 16 (and 20 for OLYMPIA 1)		Nemolizumab 30 mg/60 mg SC Q4W: • Patients weighing < 90 kg at baseline received open-label 30 mg nemolizumab every 4 weeks (Q4W), with 60 mg loading dose at baseline • Patients weighing ≥ 90 kg at baseline received 60 mg nemolizumab Q4W via two 30 mg injections • Beginning at Week 56, nemolizumab dosage will be	Nemolizumab 0.5mg/kg of body weight administered as three subcutaneous injections at baseline, Week 4 and Week 8

Study	OLYMPIA 1 (NCT04501666)	OLYMPIA 2 (NCT04501679)	LTE study (NCT04204616)	Ständer et al., 2020 (NCT03181503)
			adjusted every 6 months for patients with a documented weight change above or below the 90 kg threshold at 2 consecutive designated visits	
Comparator(s)	Placebo administered SC Q4W at weeks 4, 8, 12 and 16 (and 20 for OLYMPIA 1)		N/A	Placebo administered as three subcutaneous injections at baseline, Week 4 and Week 8
Primary outcomes	• The proportion of patients with an improvement of ≥ 4 from baseline in PP NRS at Week 16 (and Week 24 for OLYMPIA 1) • The proportion of patients with an IGA success (defined as an IGA of 0 [clear] or 1 [almost clear] and a ≥ 2-grade improvement from baseline) at Week 16 (and Week 24 for OLYMPIA 1)		• Incidence and severity of adverse events (AEs), including AEs of special interest, treatment-emergent AEs, and serious AEs	• The percent change from baseline in the peak pruritus score on the numerical rating scale at week 4
Secondary outcomes	• The proportion of patients with an improvement of ≥ 4 from baseline in PP NRS at Week 4 • The proportion of patients with a PP NRS < 2 at Week 4 • The proportion of patients with IGA success and an improvement of ≥ 4 from baseline in PP NRS at Week 16 (and 20 and 24 for OLYMPIA 1) • The proportion of patients with ≥ 4-point improvement from baseline in weekly		• The proportion of patients with an IGA success at Week 52 • The proportion of patients with an improvement of ≥ 4 from baseline in PP NRS at Week 52 • The proportion of patients with a PP NRS < 2 at Week 52 • The proportion of patients with ≥ 4-point improvement from baseline in weekly average SD NRS at Week 52	• Change from baseline in the peak and mean pruritus scores on the numerical rating scale at Week 12 • Change from baseline in the verbal rating scale score for itch (0 [no pruritus] to 4 [very severe pruritus]) at Week 12 • Change from baseline in the dynamic pruritus score for the change in itch (0 [strongly worsened pruritus] to 8 [almost no pruritus or no pruritus], with a score of 4 indicating no change) at 24 hours, 48 hours and 72 hours after the first injection and at Week 4

Study	OLYMPIA 1 (NCT04501666)	OLYMPIA 2 (NCT04501679)	LTE study (NCT04204616)	Ständer et al., 2020 (NCT03181503)
	average SD NRS at Week 4, 16 (and 24 for OLYMPIA 1) • The proportion of patients with an improvement of ≥ 4-points from baseline in DLQI total score at Week 4, 16 (and 24 for OLYMPIA 1) • Change from baseline in EQ-5D total score at Week 4, 16 (and 24 for OLYMPIA 1) • Change from baseline in HADs score at Week 4, 16 (and 24 for OLYMPIA 1)		• The proportion of patients with an improvement of ≥ 4-points from baseline in DLQI total score at Week 52	• Change from baseline in the investigator's global assessment of disease severity based on the appearance of lesions (on a scale from 0 [clear] to 4 [severe]) at Weeks 4, 8 and 12 and at the follow-up visit at Week 18 • Change from baseline in a multidimensional, 7-item prurigo activity score[34] to monitor the stage of disease (number, distribution, and activity of prurigo lesions) at Week 12 • Change from baseline in DLQI total score at Weeks 4 and 12 • Change from baseline in the NRS for sleep disturbance (from 0 to 10, with higher scores indicating worse sleep quality). • Patients' assessments of the numerical rating
All other reported outcomes	• Safety		• Safety	• Safety
Concomitant therapy	• Drugs/therapies included, but were not limited to, prescription, over the counter, birth control pills/patches/hormonal devices, vitamins, moisturisers, sunscreens, herbal medicines/supplements, and homeopathic preparations • Medical and surgical procedures (e.g., phototherapy, exodontia): procedures whose sole purpose was diagnosis (non-therapeutic) were not included • Where patients received treatments other than the study drug, reassessment of these patients was necessary before the patient could continue in the study. If a patient received a prohibited therapy during the clinical study the Investigator was to notify			• Drugs/therapies including but not limited to, prescription, over-the-counter (OTC), birth control pills/patches/hormonal devices, vitamins, moisturisers, sunscreens, herbal medicines/supplements, and homeopathic preparations • Sedatives and antidepressants were allowed if they had been administrated for at least 3 months at a

Study	OLYMPIA 1 (NCT04501666)	OLYMPIA 2 (NCT04501679)	LTE study (NCT04204616)	Ständer et al., 2020 (NCT03181503)
	the medical monitor and discuss whether or not it was acceptable for the subject to continue receiving study drug			stable dose before screening and dose changes were not planned during the study • Possible alternatives should be discussed prior to the administration of a prohibited therapy and to decide whether or not it was acceptable for the patient to continue in the study.

Abbreviations: AE, adverse event; IGA, Investigator's Global Assessment Score; DLQI, Dermatology Life Quality Index; EQ-5D, EuroQol five dimension; kg, kilogram; LTE, long term extension; mg, milligram; N/A, not applicable; PN, prurigo nodularis; PP NRS, Peak Pruritis Numerical Rating Scale; Q4W, every four weeks; SC, subcutaneous; SD NRS, Sleep Disturbance Numerical Rating Scale; TBC, to be confirmed.

Source: OLYMPIA 1 CSR,[25] OLYMPIA 2 CSR[26], LTE CSR,[27] Ständer 2020[33]

Table 7 Baseline characteristics of patients in OLYMPIA 1, OLYMPIA 2, OLYMPIA LTE and NCT03181503

	OLYMPIA 1 (NCT04501666)		OLYMPIA 2 (NCT04501679)		LTE study (NCT04204616)	Ständer et al., 2020 (NCT03181503)	
	Nemolizumab N=190	Placebo N=96	Nemolizumab N=183	Placebo N=91	Nemolizumab N=508	Nemolizumab (N = 34)	Placebo (N = 36)
Male, n (%)	80 (42.1)	40 (41.7)	70 (38.3)	36 (39.6)	[redacted]	15 (44)	14 (39)
Female, n (%)	110 (57.9)	56 (58.3)	113 (61.7)	55 (60.4)	[redacted]	19 (56)	22 (61)
Age, years, Mean (SD)	57.5 (12.8)	57.6 (13.4)	53.7 (14.4)	50.8 (15.0)	[redacted]	59.7 (13.2)	52.4 (17.5)
Weight (kg) at baseline							
Mean (SD)	87.1 (21.8)	80.8 (17.8)	79.7 (17.8)	80.8 (22.3)	[redacted]	81.6 (21.8)	80.3 (20.7)
BMI (kg/m^2)							
Mean (SD)	30.0 (6.5)	28.2 (5.2)	28.2 (5.3)	28.5 (5.9)	[redacted]	NR	NR
Height (cm) at baseline					[redacted]		
Mean (SD)	170.0 (9.5)	168.9 (9.9)	167.9 (8.5)	167.7 (10.8)	[redacted]	NR	NR
Region							
Europe	141 (74.2)	71 (74.0)	122 (66.7)	61 (67.0)	[redacted]	NR	NR
North America	49 (25.8)	25 (26.0)	47 (25.7)	22 (24.2)	[redacted]	NR	NR
Asia Pacific	NA	NA	NR	NR	[redacted]	NR	NR
Ethnicity							
Hispanic or Latino	4 (2.1)	5 (5.2)	5 (2.7)	7 (7.7)	[redacted]	NR	NR
Not Hispanic nor Latino	184 (96.8)	88 (91.7)	173 (94.5)	79 (86.8)	[redacted]	NR	NR
Unknown	1 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)	[redacted]	NR	NR
Not reported	1 (0.5)	3 (3.1)	5 (2.7)	5 (5.5)	[redacted]	NR	NR

	OLYMPIA 1 (NCT04501666)		OLYMPIA 2 (NCT04501679)		LTE study (NCT04204616)	Ständer et al., 2020 (NCT03181503)	
	Nemolizumab N=190	Placebo N=96	Nemolizumab N=183	Placebo N=91	Nemolizumab N=508	Nemolizumab (N = 34)	Placebo (N = 36)
Race							
White	160 (84.2)	81 (84.4)	147 (80.3)	68 (74.7)	[redacted]	33 (97)	35 (97)
Black or African America	18 (9.5)	10 (10.4)	5 (2.7)	7 (7.7)	[redacted]	1 (3)	1 (3)
Asian	10 (5.3)	2 (2.1)	23 (12.6)	14 (15.4)	[redacted]	0 (0.0)	0 (0.0)
American Indian or Alaska native	1 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)	[redacted]	0 (0.0)	0 (0.0)
Other	1 (0.5)	2 (2.1)	5 (2.7)	2 (2.2)	[redacted]	0 (0.0)	0 (0.0)
Not reported	0 (0.0)	1 (1.0)	1 (0.5)	0	[redacted]	0 (0.0)	0 (0.0)
Multiple	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	[redacted]	0 (0.0)	0 (0.0)
Hawaiian or Other Pacific Islander	0 (0.0)	0 (0.0)	2 (1.1)	0 (0.0)	[redacted]	0 (0.0)	0 (0.0)
Smoking status							
Never	109 (57.4)	44 (45.8)	109 (59.6)	61 (67.0)	[redacted]	NR	NR
Former	49 (25.8)	28 (29.2)	45 (24.6)	20 (22.0)	[redacted]	NR	NR
Current	32 (16.8)	24 (25.0)	29 (15.8)	10 (11.0)	[redacted]	NR	NR
Missing	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	[redacted]	NR	NR

Abbreviations: cm, centimetre; kg, kilogram; NR, not reported; Q1, quarter one; Q3, quarter three; SD, standard deviation

Source: Stander et al. (2023);[35] OLYMPIA 1 CSR;[25] OLYMPIA 2 CSR;[26] OLYMPIA LTE CSR[27] Ständer 2020[33]

Table 8 Baseline disease characteristics from OLYMPIA 1, OLYMPIA 2, OLYMPIA LTE and NCT03181503

	OLYMPIA 1		OLYMPIA 2		OLYMPIA LTE	Ständer et al., 2020 (NCT03181503)	
	Nemolizumab	Placebo	Nemolizumab	Placebo	Nemolizumab N=508	Nemolizumab	Placebo
IGA category, n (%)							
Clear (0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)		0 (0.0)	0 (0.0)
Almost clear	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)		0 (0.0)	0 (0.0)
Mild (2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)		0 (0.0)	0 (0.0)
Moderate (3)	107 (56.3)	62 (64.6)	108 (59.0)	48 (52.7)		16 (47)	22 (61)
Severe (4)	83 (43.7)	34 (35.4)	75 (41.0)	43 (47.3)		18 (53)	14 (39)
Missing	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)		0 (0.0)	0 (0.0)
Weekly average	n = 184	n = 96					
Mean (SD)	8.5 (0.9)	8.4 (1.0)	8.47 (0.90)	8.37 (0.99)		8.4 (1.2)	8.4 (1.2)
Weekly average	n = 184	n = 94	n = 178	n = 90			
Mean (SD)	8.2 (1.1)	8.2 (1.1)	8.29 (0.95)	8.21 (1.09)		7.8 (1.7)	7.9 (1.3)

	OLYMPIA 1		OLYMPIA 2		OLYMPIA LTE	Ständer et al., 2020 (NCT03181503)	
	Nemolizumab	Placebo	Nemolizumab	Placebo	Nemolizumab N=508	Nemolizumab	Placebo
Weekly average SD NRS			n = 182	N = 91			
Mean (SD)	7.0 (2.4)	6.9 (2.3)	7.19 (2.21)	7.3066 (2.23)	[redacted]	NR	NR
Pain frequency, n (%)							
Never	15 (7.9)	3 (3.1)	7 (3.8)	2 (2.2)	[redacted]	NR	NR
Less than	11 (5.8)	3 (3.1)	9 (4.9)	9 (9.9)	[redacted]	NR	NR
1-2	6 (3.2)	11	11 (6.0)	3 (3.3)	[redacted]	NR	NR
3-4	25 (13.2)	7 (7.3)	24 (13.1)	8 (8.8)	[redacted]	NR	NR
5-6	19 (10.0)	4 (4.2)	16 (8.7)	5 (5.5)	[redacted]	NR	NR
Everyd	114 (60.0)	68	116 (63.4)	64	[redacted]	NR	NR
Missin	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	[redacted]	NR	NR
Pain intensity							
Mean (SD)	7.1 (2.9)	7.6 (2.5)	7.7 (2.37)	7.8 (2.32)	[redacted]	NR	NR
Prurigo Activity Score item 4: number of lesions in							
Mean (SD)	23.0 (18.4)	17.7 (13.3)	21.7 (18.52)	25.5 (22.00)	[redacted]	NR	NR
Prurigo Activity Score item 5a: excoriation/crusts n, (%)							

	OLYMPIA 1		OLYMPIA 2		OLYMPIA LTE	Ständer et al., 2020 (NCT03181503)	
	Nemolizumab	Placebo	Nemolizumab	Placebo	Nemolizumab N=508	Nemolizumab	Placebo
0%	0 (0.0)	0 (0.0)	1 (0.5)	0 (0.0)	[redacted]	NR	NR
1-25%	9 (4.7)	7 (7.3)	11 (6.0)	11 (12.1)	[redacted]	NR	NR
26-50%	39 (20.5)	17 (17.7)	34 (18.6)	20 (22.0)	[redacted]	NR	NR
51-75%	54 (28.4)	23 (24.0)	64 (35.0)	29 (31.9)	[redacted]	NR	NR
76-100%	88 (46.3)	49 (51.0)	73 (39.9)	31 (34.1)	[redacted]	NR	NR
Missing	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	[redacted]	NR	NR
Prurigo Activity Score item 5b: healed lesion stages n, (%)							
100%	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	[redacted]	NR	NR
76-99%	1 (0.5)	2 (2.1)	3 (1.6)	0 (0.0)	[redacted]	NR	NR
51-75%	22 (11.6)	12 (12.5)	23 (12.6)	13 (14.3)	[redacted]	NR	NR
26-50%	41 (21.6)	23 (24.0)	47 (25.7)	26 (28.6)	[redacted]	NR	NR

	OLYMPIA 1		OLYMPIA 2		OLYMPIA LTE	Ständer et al., 2020 (NCT03181503)	
	Nemolizumab	Placebo	Nemolizumab	Placebo	Nemolizumab N=508	Nemolizumab	Placebo
0-25%	126 (66.3)	59 (61.5)	110 (60.1)	52 (57.1)	[redacted]	NR	NR
Missing	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	[redacted]	NR	NR
DLQI total score at baseline					[redacted]		
Mean (SD)	17.1 (7.0)	16.9 (6.7)	16.5 (6.79)	17.1 (6.60)	[redacted]	16.9 (7.5)	15.8 (6.0)
Atopy background n, (%)					[redacted]		
Yes	60 (31.6)	33	57 (31.1)	31	[redacted]	5 (15)	6 (17)
No	130 (68.4)	63	126 (68.9)	60	[redacted]	29 (85)	30
Time since PN diagnosis (months)					[redacted]		
Mean (SD)	86.9 (85.3)	100.6 (98.6)	104.16 (100.715)	108.60 (114.92	[redacted]	NR	NR

Abbreviations: AP NRS, Average Pruritis Numerical Rating Scale; DLQI: Dermatology life quality index; IGA, Investigator Global Assessment; LTE; long-term extension, N, number of patients in the population; NR, not reported; PP NRS, Peak Pruritus Numerical Rating Scale; SD, standard deviation; SD NRS, Sleep Disturbance Numerical Rating Scale.

Source: Stander et al. (2023);[35] OLYMPIA 1 CSR;[25] OLYMPIA 2 CSR;[26] OLYMPIA LTE CSR[27] Ständer 2020[33]

3.2.2 Primary and secondary efficacy endpoints

Primary efficacy endpoints

The co-primary efficacy outcomes for OLYMPIA 1 and OLYMPIA 2 were peak pruritus numerical rating scale (PP NRS) (a change of ≥4-points from baseline) and IGA success (defined as a combined change of ≥2-points from baseline and a score of 0/1).

Significantly more patients in the nemolizumab treatment arms reported a PP NRS improvement of ≥4 points from baseline compared with patients in the placebo arms of both OLYMPIA 1 and OLYMPIA 2: 58.4% vs. 16.7% (strata adjusted p[redacted]) at week 16 and [redacted]% vs. [redacted]% (strata adjusted p[redacted]) at week 24 in OLYMPIA 1, and 56.3% vs. 20.9% (strata adjusted p[redacted]) at week 16 in OLYMPIA 2. Similarly, significantly more nemolizumab patients achieved IGA success compared with placebo patients in both trials: 26.3% vs. 7.3% (strata adjusted p[redacted]) at week 16 and [redacted]% vs.[redacted]% (strata adjusted p=[redacted]) at week 24 in OLYMPIA 1, and 37.7% vs. 11.0% (p[redacted]) at week 16 in OLYMPIA 2.

Secondary efficacy endpoints

The secondary efficacy endpoints considered in OLYMPIA 1 and OLYMPIA 2 are presented in section B.2.6.1.4 and include: improvement in itch, improvement in skin clearance, reduction in sleep disruption and improvement in QoL. All secondary outcomes favoured treatment with nemolizumab.

3.2.3 Subgroup analyses

The company reports that it conducted a pooled analysis of subgroup data in OLYMPIA 1 and OLYMPIA 2 due to the limited population in each subgroup. Results of the subgroup analyses are presented in Figures 18 and 19 of the CS. Nemolizumab treatment resulted in statistically significant improvements of ≥4 points in PP NRS and IGA success regardless of participant weight (<90 kg or ≥90 kg) at baseline. Analyses by ethnic subgroups indicate that nemolizumab is associated with improvements for both primary efficacy outcomes. *However, the EAG agrees with the company that the small numbers of patients in the Black or African American, Asian and Other Ethnic subgroups preclude meaningful interpretations of these data.*

3.2.4 Adverse events

The company reports adverse events (AE) data for nemolizumab from OLYMPIA 1, OLYMPIA 2, and OLYMPIA LTE in section B.2.10 of the CS. The EAG presents a summary of the AE data in Tables 9 and 10, including information for the NCT03181503 trial that was not included by the company in the main text of the submission.

Serious adverse events (SAEs) were experienced by [redacted] of patients in the nemolizumab arm and [redacted] in the placebo arm in OLYMPIA 1; of these, [redacted] and [redacted] were considered related to the study drug in the nemolizumab and placebo arms, respectively. In OLYMPIA 2: [redacted]%) nemolizumab patients and [redacted]%) placebo patients experienced SAE, of which [redacted]%) and [redacted]%) were considered related to the study drug in the respective nemolizumab and placebo treatment arms. [redacted]%) of the nemolizumab patients in the LTE study experienced SAE of which [redacted]%) were considered related to the study drug. [redacted] death occurred in the placebo arm of OLYMPIA 1 and [redacted] deaths occurred in the LTE study. [redacted] were considered related to the study drug. Severity of AE and number of deaths were not reported in study NCT03181503.

TEAEs leading to study drug withdrawal occurred in [redacted] nemolizumab vs. [redacted] placebo patients in OLYMPIA 1; [redacted]% nemolizumab vs. [redacted]% placebo patients in OLYMPIA 2; NCT03181503; 2 (6%) vs. 2 (6%); and [redacted]% of LTE patients.

TEAEs leading to study drug discontinuation occurred in [redacted] nemolizumab vs. [redacted] placebo patients in OLYMPIA 1; [redacted]% nemolizumab vs. [redacted]% placebo patients in OLYMPIA 2; and [redacted]% of LTE patients.

The proportions of nemolizumab and placebo patients who experienced at least one treatment-emergent adverse events (TEAEs) were: OLYMPIA 1: [redacted]% vs. [redacted]%, respectively; OLYMPIA 2: 61.2% vs. 53.8%, respectively; and [redacted]% of the nemolizumab patients in the LTE study experienced at least one TEAE. The numbers of patients who experienced severe TEAEs were low: OLYMPIA 1: [redacted]% nemolizumab vs. [redacted]% placebo; OLYMPIA 2: [redacted]% nemolizumab vs. [redacted]% placebo; and [redacted]% of the nemolizumab patients in the LTE study. Commonly

observed TEAEs in ≥5% of patients are presented in Table 10. *The EAG has inspected the safety data and has no concerns about the rates of reported AEs or SAEs in the OLYMPIA trials or the NCT03181503 trial.*

Table 9 Overall summary of TEAE incidence in OLYMPIA 1, OLYMPIA 2, OLYMPIA LTE and NCT03181503

	OLYMPIA 1		OLYMPIA 2		LTE	Ständer et al., 2020 (NCT03181503)	
	Nemolizumab N=190	Placebo N=96	Nemolizumab N=183	Placebo N=91	Nemolizumab N=508	Nemolizumab N=34	Placebo N=36
TEAE (any)	134 (71.7)	62 (65.3)	112 (61.2)	49 (53.8)	[redacted]	23 (68)	24 (67)
TEAE by maximum severity[a]							
Mild	58 (31.0)	32 (33.7)	70 (38.3)	29 (31.9)	[redacted]	NR	NR
Moderate	66 (35.3)	22 (23.2)	39 (21.3)	16 (17.6)	[redacted]	NR	NR
Severe	10 (5.3)	8 (8.4)	3 (1.6)	4 (4.4)	[redacted]	NR	NR
Study drug related TEAE[b]	46 (24.6)	18 (18.9)	46 (25.1)	16 (17.6)	[redacted]	NR	NR
Study drug related TEAE by maximum severity							
Mild	23 (12.3)	11 (11.6)	31 (16.9)	9 (9.9)	[redacted]	NR	NR
Moderate	22 (11.8)	4 (4.2)	14 (7.7)	6 (6.6)	[redacted]	NR	NR
Severe	1 (0.5)	3 (3.2)	1 (0.5)	1 (1.1)	[redacted]	NR	NR
TEAE related to protocol procedure	8 (4.3)	3 (3.2)	4 (2.2)	3 (3.3)	[redacted]	NR	NR
SAE	21 (11.2)	10 (10.5)	4 (2.2)	6 (6.6)	[redacted]	NR	NR
SAE related to study drug	2 (1.1)	1 (1.1)	1 (0.5)	1 (1.1)	[redacted]	NR	NR
Severe TEAE	10 (5.3)	8 (8.4)	3 (1.6)	4 (4.4)	[redacted]	NR	NR

TEAE leading to study drug interruption	10 (5.3)	7 (7.4)	4 (2.2)	2 (2.2)	[redacted]	NR	NR
TEAE leading to study drug withdrawal	10 (5.3)	3 (3.2)	5 (2.7)	2 (2.2)	[redacted]	2 (6)	2 (6)
TEAE leading to study discontinuation	11 (5.9)	4 (4.2)	4 (2.2)	2 (2.2)	[redacted]	NR	NR
AESIs by categories	32 (17.1)	19 (20.0)	21 (11.5)	9 (9.9)	[redacted]	NR	NR
Injection-related reactions	2 (1.1)	0 (0.0)	0 (0.0)	0 (0.0)	[redacted]	1 (3)	0 (0)
Newly diagnosed asthma or worsening of asthma,	7 (3.7)	4 (4.2)	5 (2.7)	1 (1.1)	[redacted]	NR	NR
Infections	21 (11.2)	16 (16.8)	10 (5.5)	6 (6.6)	[redacted]	10 (29)	12 (33)
Peripheral oedema: limbs, bilateral, facial oedema	5 (2.7)	1 (1.1)	6 (3.3)	2 (2.2)	[redacted]	1 (2.8%)	1 (2.9%)
Elevated ALT or AST (>3 x ULN) in combination with elevated bilirubin	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	[redacted]	NR	NR
TEAE leading to death	0 (0.0)	1 (1.1)	0 (0.0)	0 (0.0)	[redacted]	NR	NR
TEAE related to study drug leading to death	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	[redacted]	NR	NR

Abbreviations: AESI: adverse event of special interest; ALT: alanine transaminase; AST: aspartate aminotransferase; NR, not reported; ULN: upper limit of normal; SAE: serious adverse event; TEAE: treatment emergent adverse event.

Note: The company reports in the CS that percentages were based on the number of subjects. Adverse events were coded using the Medical Dictionary for Regulatory Activities Version 25.0. The TEAEs during the overall study period were defined as AEs with onset date on or after the first dose to the follow-up visit date. For each row category, a subject with 2 or more AEs in that category was counted only once.

[a] In the LTE study, if subjects experienced multiple events, the subjects were counted once at the event with maximum severity

[b] In the LTE study, study drug-related TEAEs were those for which a reasonable possibility of relationship was reported (or with a missing relationship).

Source: OLYMPIA 1 CSR,[25] OLYMPIA 2 CSR,[26] LTE CSR,[27] Ständer 2020[33]

Table 10 Treatment-emergent adverse events experienced by ≥ 5.0% of patients in OLYMPIA 1, OLYMPIA 2, OLYMPIA LTE and NCT03181503

	OLYMPIA 1		OLYMPIA 2		LTE	Ständer et al., 2020 (NCT03181503)	
	Nemolizumab	Placebo	Nemolizumab	Placebo	Nemolizumab	Nemolizumab N=34	Placebo N=36
Patients ≥1 TEAE	134 (71.7)	62 (65.3)	112 (61.2)	49 (53.8)	[redacted]	23 (68)	24 (67)
Gastrointestinal Disorders	12 (6.4)	11 (11.6)	11 (6.0)	5 (5.5)	[redacted]	7 (21)	5 (14)
Infections and infestations	58 (31.0)	28 (29.5)	40 (21.9)	19 (20.9)	[redacted]	10 (29.4)	12 (33.3)
COVID-19	15 (8.0)	14 (14.7)	9 (4.9)	3 (3.3)	[redacted]	NR	NR
Nasopharyngitis	12 (6.4)	8 (8.4)	5 (2.7)	4 (4.4)	[redacted]	5 (14.7)	4 (11.1)
Upper respiratory tract infection	4 (2.1)	3 (3.2)	NR	NR	[redacted]	NR	NR
Investigations	12 (6.4)	8 (8.4)	8 (4.4)	1 (1.1)	[redacted]	NR	NR
Musculoskeletal and connective tissue disorders	22 (11.8)	7 (7.4)	21 (11.5)	7 (7.7)	[redacted]	6 (17.6)	5 (13.9)
Arthralgia	3 (1.6)	2 (2.1)	-	-	[redacted]	1 (2.9)	2 (5.6)
Nervous system disorders	21 (11.2)	9 (9.5)	17 (9.3)	9 (9.9)	[redacted]	2 (5.9)	1 (2.8)
Headache	13 (7.0)	2 (2.1)	12 (6.6)	4 (4.4)	[redacted]	0 (0.0)	1 (2.8)
Psychiatric disorders	1 (0.5)	3 (3.2)	0 (0.0)	0 (0.0)	[redacted]	0 (0.0)	2 (5.6)
Renal and urinary disorders	2 (1.1)	3 (3.2)	-	-	[redacted]	2 (5.9)	2 (5.6)

	OLYMPIA 1		OLYMPIA 2		LTE	Ständer et al., 2020 (NCT03181503)	
	Nemolizumab	Placebo	Nemolizumab	Placebo	Nemolizumab	Nemolizumab N=34	Placebo N=36
Respiratory, thoracic and mediastinal disorders	21 (11.2)	12 (12.6)	13 (7.1)	5 (5.5)	[redacted]	0 (0.0)	3 (8.3)
Cough	9 (4.8)	5 (5.3)	5 (2.7)	2 (2.2)	[redacted]	0 (0.0)	2 (5.6)
Dyspnoea	6 (3.2)	5 (5.3)	-	-	[redacted]	0 (0.0)	1 (2.8)
Skin and subcutaneous tissue disorders	59 (31.6)	28 (29.5)	44 (24.0)	21 (23.1)	[redacted]	10 (29.4)	12 (33.3)
Neurodermatitis	18 (9.6)	19 (20.0)	7 (3.8)	10 (11.0)	[redacted]	5 (14.7)	5 (13.9)
Eczema	10 (5.3)	1 (1.1)	4 (2.2)	3 (3.3)	[redacted]	1 (2.9)	0 (0)
Eczema nummular	7 (3.7)	0 (0.0)	6 (3.3)	0 (0.0)	[redacted]	1 (2.9)	0 (0)
Dermatitis atopic	7 (3.7)	1 (1.1)	10 (5.5)	0 (0.0)	[redacted]	NR	NR
Contact dermatitis	NR	NR	NR	NR	[redacted]	2 (5.9)	0 (0)
Pruritus	-	-	2 (1.1)	3 (3.3)	[redacted]	0 (0.0)	2 (5.6)
Vascular disorders	7 (3.7)	3 (3.2)	6 (3.3)	2 (2.2)	[redacted]	0 (0.0)	2 (5.6)
Hypertension	4 (2.1)	2 (2.1)	5 (2.7)	2 (2.2)	[redacted]	NR	NR

Abbreviations: COVID-19: coronavirus disease; NR, not reported; TEAE: treatment-emergent adverse event.

Note: The company reports that percentages were based on the number of patients. Adverse events were coded using the Medical Dictionary for Regulatory Activities Version 25.0. The TEAEs during the overall study period were defined as adverse events with onset date on or after the first dose to the follow-up visit date

Source: OLYMPIA 1 CSR;[25] OLYMPIA 2 CSR;[26] OLYMPIA LTE CSR,[27] Ständer 2020[33]

3.2.5 Evidence synthesis methodology

No formal meta-analyses were conducted in the CS. Instead, simple pooling of binary data from OLYMPIA 1 and OLYMPIA 2 was used to derive estimates for the proportions of those receiving nemolizumab and placebo achieving a composite response outcome. This used data at 16 weeks and was defined as having an improvement of ≥ 4 on the PP NRS and having IGA success of 0 or 1 (with an improvement of ≥ 2 points). If patients received rescue therapies before Week 16, they were automatically classified as non-responders.

The pooled response rates from OLYMPIA 1 and 2 were reported in Table 35 of the CS and Table 9 of the response to clarification as [redacted] for nemolizumab and [redacted] for placebo (best supportive care). At clarification, the company also reported data for the composite outcome at six time points (Weeks 4, 8, 12, 16, 20 and 24) for OLYMPIA 1, for four time points (Weeks 4, 8, 12, 16) for OLYMPIA 2 and at Week 12 for the Phase 2 trial (NCT03181503). Combined results including data for more than one trial were also presented, assuming that data from the last available time point was carried over if not available. The EAG has summarised these results below and has highlighted the results used in the cost-effectiveness modelling (Table 11). For two of these scenarios, the EAG changed the numerator in the table as this appeared to be an error.

Table 11 Possible data for the PP NRS+IGA composite response outcome [Derived from Tables 3, 4 and 5 of the first clarification response and Table 2 of the third clarification response]

Studies (time points)	n (Nem)	N (Nem)	n (BSC)	N (BSC)	% (Nem)	% (BSC)	% Diff	Comment
OLYMPIA 1 (w4)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
OLYMPIA 1 (w8)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
OLYMPIA 1 (w12)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
OLYMPIA 1 (w16)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
OLYMPIA 1 (w20)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
OLYMPIA 1 (w24)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
OLYMPIA 2 (w4)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
OLYMPIA 2 (w8)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
OLYMPIA 2 (w12)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
OLYMPIA 2 (w16)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
NCT03181503 (w12)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
OLYMPIA 1&2 (w4)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
OLYMPIA 1&2 (w8)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
OLYMPIA 1&2 (w12)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
OLYMPIA 1&2 (w16)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**Used in model**
OLYMPIA 1&2 (w20/16)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
OLYMPIA 1&2 (w24/16)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
OLYMPIA 1&2/ NCT03181503 (w16/16/12)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	

BSC: best supported care; Nem: nemolizumab, n: numerator (number of participants achieving a response); N: denominator (total number of participants); % Diff: difference in percentages (nemolizumab group minus BSC group); * Changed by the EAG as the company's numerators appear to be incorrect

Although formal meta-analysis could have been performed, the EAG agree that simple pooling is a reasonable approach as OLYMPIA 1 and OLYMPIA 2 have an almost identical design.

The EAG noted that using Week 16 data from OLYMPIA 1 and 2 resulted in one of the largest effect sizes in favour of nemolizumab, although this is the latest time point where data from both OLYMPIA 1 and 2 are available (Table 11). Using Week 16 data from both trials seems appropriate, but using the later (Week 24) available data for OLYMPIA 1 might also have been a reasonable choice. The EAG also noted that the results may be sensitive to the relatively small number of participants in the BSC arms achieving response.

3.2.6 Selection of studies for inclusion in the synthesis of clinical evidence

The main CS discussed only two RCTs of nemolizumab (OLYMPIA 1 and 2), but as mentioned earlier, a third RCT was identified in the company's systematic literature review and listed in Table 7 of Appendix D (NCT03181503 by Ständer et al., 2020).[33] This published Phase 2 randomised trial of nemolizumab versus placebo, was not included within the main CS, although its participants were eligible to be enrolled in the included OLYMPIA LTE study.

At clarification, the EAG inquired why NCT03181503 was not included in the formal meta-analyses. In response, the company provided the following explanations:

- *NCT03181503 has a different population to the one considered in the scope of the CS (patients with moderate to severe PN and severe pruritus).*
- *It is a Phase 2 clinical trial and Phase 3 data are more robust.*
- *It has a 12-week treatment duration and IGA was not assessed at week 16.*
- *The IGA scale used in NCT03181503 was updated for the phase 3 trials based on feedback from the FDA.*
- *NCT03181503 used a different dosing approach*

NCT03181503 does have different entry criteria from OLYMPIA 1 and OLYMPIA 2. In addition to having moderate to severe PN (defined as in the OLYMPIA trials), participants in NCT03181503 had to have a score of at least 7 on the NRS, whereas in the OLYMPIA trials participants had to have an IGA score of at least 3. The nemolizumab dose in NCT03181503

also differed from the dose used in the OLYMPIA studies: 0.5 mg per kg of body weight compared with different doses for participants above and below 90 kg. Despite these differences, the EAG's clinical adviser considers that the populations were relatively similar to OLYMPIA 1 and OLYMPIA 2 and, therefore, this trial is potentially eligible for inclusion in the company's systematic review of clinical effectiveness evidence.

The company also justified excluding this trial from the CS on the grounds that it is a Phase 2 trial. However, the EAG does not consider this a valid reason for exclusion. The trial appears to be a well-conducted RCT published in a high-impact journal (the *New England Journal of Medicine*) and the EAG has no major concerns about its methodology. While the Phase 2 trial is smaller (n=70) than the Phase 3 trials, the EAG believes the data are equally robust. According to the general principles of systematic reviews, excluding it from the evidence synthesis could introduce bias. Furthermore, the OLYMPIA LTE study was included in the CS, despite including participants from NCT03181503.

Information about the changes to the IGA scale was only provided in the third response to clarification received from the company. This includes a table comparing the IGA categories used in NCT03181503 and in the OLYMPIA studies (Table 12).

Table 12 Evolution of IGA from Phase 2 to Phase 3 nemolizumab clinical trials [Reproduced from Table 1 from the company's third response to clarification]

Score	Category	IGA scale used in trial	
		Stander 2020 (NCT03181503)	OLYMPIA 1 and OLYMPIA 2
0	Clear	No nodules and no activity signs (erythema, excoriations and/or crusts and/or bleeding). Post-inflammatory hypo-/hyperpigmentation may be present.	No nodules
1	Almost clear	Rare single nodules, flattened and activity signs (excoriations/crusts/bleeding) may be present	Rare palpable pruriginous nodules
2	Mild	Few nodules, dome-shaped with activity signs (excoriations/crusts/bleeding) present	Few palpable pruriginous nodules
3	Moderate	Many nodules, flattened with activity signs (excoriations/crusts/bleeding)	Many palpable pruriginous nodules
4	Severe	Generalised nodules, dome-shaped with activity signs (excoriations/crusts/bleeding)	Abundant palpable pruriginous nodules

IGA, Investigator Global Assessment
Source: Galderma, CD14152.CTD2.7.3 Summary of Clinical Efficacy Prurigo Nodularis[36]

Before receiving further information, the EAG was concerned that there was a lack of transparency as to why NCT03181503 was not discussed in the original CS. The EAG agrees that there are some differences between NCT03181503 and the OLYMPIA trials regarding the nemolizumab dosing regime, the IGA assessment scale used for assessment and the time points assessed, but there are potential concerns about selection bias if all identified trials are not included in a meta-analysis. *On balance, because of these differences between the trials, the EAG considers it a reasonable approach to pool data from the OLYMPIA trials only*.

As part of the third clarification response, the EAG eventually received data for NCT03181503 for the composite PP NRS/IGA outcome. These results are provided in Table 11, Section 3.2.5 above. These results showed that [redacted] out of [redacted] participants in the nemolizumab arm and [redacted] out of [redacted] participants in the BSC arm achieved a response. *Based on these results the EAG is now satisfied that including NCT03181503 would not have made a very large difference to the results used in the economic modelling.*

3.3 Critique of trials identified and included in the indirect comparison and/or multiple treatment comparison

According to Appendix D, Table 7, 19 studies were included in the company's systematic literature review, including 12 RCTs.

No indirect comparisons or network meta-analyses (NMA) were undertaken by the company. However, network meta-analyses would have been possible. A possible network diagram of the 12 RCTs indicates that nemolizumab is connected to five other comparators via placebo (aprepitant, nalbuphine, serlopitant, vixarelimab, dupilumab). Therefore, it would have been possible to conduct an NMA to compare nemolizumab against these five comparators. Two further comparators (pimecrolimus and hydrocortisone) are not connected to the rest of the network as they appear in only a single trial.

The EAG requested clarification from the company on why certain RCTs were not included in the NMA. The reasons for exclusion included: different trial populations to the CS; comparator not licensed or not recommended by NICE for use in the UK; and Phase 2 design.

While the EAG acknowledges that conducting an NMA under these circumstances presents limitations, it does not consider the Phase 2 status of a trial sufficient grounds for exclusion

from an indirect treatment comparison or NMA. The EAG notes that the network would be "star-shaped," with each active treatment linked only through placebo, which restricts the robustness of an NMA due to the absence of closed loops for estimating relative effects. Furthermore, there are variations in how outcomes are defined across trials. *Despite these challenges, the EAG believes that an NMA could still have been conducted using the treatments outlined in NICE's final scope.*

The EAG agrees with the company's assertion that certain treatments are unlicensed for use in the UK. However, they believe that including these treatments in the analysis could have offered valuable insights.

3.4 Critique of the indirect comparison and/or multiple treatment comparison

Not applicable

3.5 Additional work on clinical effectiveness undertaken by the EAG

None

3.6 Conclusions of the clinical effectiveness section

- The decision problem deviated from NICE's scope by excluding comparators that are not approved for clinical practice in the UK.
- Nonetheless, comparing nemolizumab against these excluded comparators could have been valuable. An NMA involving approximately five other comparators could have been conducted, though the available evidence would constrain its utility.
- In evaluating nemolizumab against placebo, the company presented data from two well-conducted Phase 3 randomised trials but omitted a relevant Phase 2 trial. This omission raised concerns about potential selection bias, which could affect the completeness of the data used in the economic modelling. However, due to differences in the dosing, time point and IGA scale used, the EAG considers the company's approach reasonable.

4 COST EFFECTIVENESS

4.1 EAG comment on company's review of cost-effectiveness evidence

The company conducted a systematic literature review (SLR) to identify all published studies of treatments for adult patients with PN. The company's SLR approach is summarised in Section B.3.1 of the company submission. Full details of methods and results are provided in Appendix G, H and I for cost-effectiveness, health related quality of life and resource use / cost studies respectively. Briefly, the company searched six databases in September 2023 updated in May 2024 to capture the most recent evidence base. The final search was conducted on May 17th, 2024. The total search period was from database inception until May 2024. Supplemental searches of conference proceedings and HTA websites were also conducted. The combined searches for PN identified N=26 studies, detailed in N=27 publications/reports. N=3 publications from N=3 studies were identified as cost-effectiveness studies (Appendix G of the company submission, tables 9-11), 31 publications from 22 studies were identified as HRQoL studies (summarised in Appendix H, tables 8-13) and 24 publications from 25 studies were identified as resource use/cost studies (Appendix I). For the resource use and cost studies, only UK specific studies were summarised (See Appendix I, tables 9-17 for full details).

The EAG are satisfied that the company have conducted a thorough literature search. A generic search was conducted for PN, with relevant studies classed as HRQoL / HCRU / cost-effectiveness. The EAG note that it was difficult to match the numbers of studies in PRISMA flow charts with the number of studies detailed in results tables. For cost-effectiveness the company summarise three studies (Prada 2023,[38] Whang 2021[39] and NICE TA955).[23] The focus is on the previous NICE appraisal of dupilumab for PN, which is also relevant to the current assessment. The EAG agree that these studies are helpful for informing model development and assumptions for the current appraisal. The validity of assumptions derived and adapted from TA955 will be discussed throughout the EAG report. Similarly, studies identified in the HRQoL, and cost reviews will be referred to, where appropriate in Sections 4.2.7 and 4.2.8 respectively.

4.2 Summary and critique of the company's submitted economic evaluation by the EAG

4.2.1 NICE reference case checklist

Table 13 summarises the EAG's assessment of the company submission against key components of the NICE reference case.

Table 13 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	Aligned with reference case
Perspective on costs	NHS and PSS	Aligned with reference case
Type of economic evaluation	Cost–utility analysis with fully incremental analysis	Aligned with reference case
Time horizon	Long enough to reflect all important differences in costs or outcomes between the technologies being compared	Aligned with reference case, although model structure is quite simplistic with long cycle lengths and extended durations fixed in non-response state. May not capture all benefits and cost savings associated with future lines of treatment.
Synthesis of evidence on health effects	Based on systematic review	Partly. Systematic review conducted, but Stander 2020 omitted. Assumed that no health benefit can be derived from BSC following a loss of response, despite an increase in BSC intensity. Some health effects based on clinical expert opinion.

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 in adults.	Aligned with reference case
Source of data for measurement of health-related quality of life	Reported directly by patients and/or carers	Aligned with reference case
Source of preference data for valuation of changes in health-related quality of life	Representative sample of the UK population	Aligned with reference case
Equity considerations	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	Aligned with reference case
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	Partly. Cheapest generic alternative treatments available to the NHS are not always used.
Discounting	The same annual rate for both costs and health effects (currently 3.5%)	Aligned with reference case, however the EAG identified a minor error in discounting in the first model cycle which is corrected in the EAG base case.

Key: BSC, best supportive care; EAG, external assessment group; EQ-5D, standardised instrument for use as a measure of health outcome; NHS, national health service; PSS, personal social services; QALYs, quality-adjusted life years.

4.2.2 Model structure

The company developed a two-stage decision analysis model in Microsoft excel®. The economic modelling approach was based on that used for the NICE appraisal of dupilumab for PN (TA955). Stage 1 was a decision tree model, with a 16-week time horizon, to capture short term response rates from the pooled OLYMPIA1 and

OLYMPIA2 studies. 16 weeks was chosen as it captured the latest available data collection time point common to both studies. For the economic model, response was defined as a composite measure of itch improvement of ≥ 4 PP NRS compared to baseline, and nodule reduction, measured as an IGA score of 0 or 1, with an improvement of ≥ 2 points from baseline. After week 16, the cohort enter a 3-state Markov cohort model (a maintenance "response" state, a BSC tunnel state for up to three cycles, which is assumed to be a "non-response" state, and death. Those achieving a 16-week response enter the maintenance state where they continue to incur treatment acquisition costs until they discontinue treatment or experience a waning of the treatment effect, at which point they transition to the non-response BSC tunnel states. Those discontinuing from active treatment (Nemolizumab + BSC or BSC alone) then receive more intensive BSC in the non-response BSC states. Those who do not achieve a response by week 16 also enter the semi-absorbing non-response BSC states, where they remain until they die. It is not possible to regain a response in the model once it is lost, regardless of the intensity of BSC treatment provided in the non-response BSC states. The Markov model captures transitions in annual cycles, with a half-cycle correction applied.

The EAG considers the company's decision to develop a model structure around response status to be a reasonable approach to capture costs and QALY implications of treatment. However, there are some limitations. Whilst the company's definition of a composite response outcome is reasonable and aligned with desired treatment goals in UK clinical practice, it may not capture all treatment benefits in either arm. For example, the EAG's clinical expert is of the view that patients could feasibly achieve a symptomatic improvement in itch without resolution of nodules, particularly over a short time-period, which may have quality of life benefits. Clinicians in UK practice may be reluctant to discontinue patients from treatment if they demonstrate a symptomatic benefit, or partial treatment response that may fall slightly short of the composite response. Such a partial treatment response is not captured within the economic model structure, though the company attempt to introduce this through parameterisation and tunnel states. The three BSC non-response tunnel states were not explicitly described in the model structure section of the submission. The main purpose of these tunnel states appears to be to allow the company to apply a utility gain in the non-response state for nemolizumab for the first year following treatment

discontinuation. The company's argument is that these utility gains reflect potential for a partial response. However, the definition of such a partial response is not provided. Should the company wish to include a partial response in their model, the EAG would have preferred for this to be included as a modelled health state, with a clear definition of what a partial response is based on engagement with a range of UK clinical experts. Transition probabilities, costs and utilities could then be derived from the trial data and applied to a partial response state equally across both model arms. Such an approach would allow a proportion of the cohort to remain on treatment for longer, subject to achieving a clinically relevant partial response and may be more aligned with use of nemolizumab in UK clinical practice. The impact of including a partial response state in the model is unclear, though it would increase time on treatment and treatment acquisition costs for nemolizumab. The impact on the ICER would depend on the magnitude of utility benefit for any partial responders.

The EAG note that the company's description of the decision tree and progression to Markov model does not completely reflect the way in which the model is operationalised. For example, within the company submitted model file, cycle 0 is of one year duration, split into two time periods, 16 weeks capturing the short-term outcomes from the trial and 36-weeks capturing the remainder of the first year. The first year of the model (cycle 0) is not half-cycle corrected. The EAG considers this to be generally appropriate as it allows the full consideration of treatment acquisition costs during the maintenance phase of the model. The health state cost and QALY payoffs are then weighted by 16/52 for the decision tree phase and 36/52 for the remainder of the first cycle. The EAG would have found it more transparent to calculate the 16-week payoffs from the decision tree outside of the Markov trace, but after inspection of the model traces, the EAG are satisfied that the cost and QALY payoffs in cycle 0 are broadly implemented in line with the company's described methodology.

The EAG's main concern is that the Markov model does not allow for the possibility for a response to be regained after it is lost in either arm of the model. However, the BSC treatment basket in the non-response state is much more intensive than what was costed in the induction phase or for patients with a maintained response. These additional BSC treatment costs (e.g. all patients receiving emollients, TCI and TCS,

with 77% receiving methotrexate and 15% receiving oral prednisolone) are assumed to be incurred indefinitely for the full model duration in the non-response state, but with no treatment benefit (either in terms of clinical response or utility gain). The EAG does not consider this approach to be appropriate. It is not reflective of UK clinical practice where treatments would not be continued indefinitely unless a treatment benefit or quality of life improvement could be attained. The EAG believe that it is feasible that patients receiving more intensive BSC would experience a clinical benefit / utility gain compared to baseline, especially from treatments like methotrexate and cyclosporine that were discontinued for at least 8 weeks prior to the baseline trial visit.

The EAG queried the modelling approach with the company at clarification stage. The company retain their modelling approach on the grounds that:

1) *Existing treatments target symptoms rather than underlying disease. The EAG appreciate this is the case but note that symptomatic relief can improve quality of life and potentially breaking the itch / scratch cycle could also be anticipated to reduce the number of nodules associated with PN disease.*
2) *28% of patients in a survey across 15 European dermatological centres consider none of the treatment options to be effective. However, this suggests that many patients do gain treatment benefit from TCIs, TCS and immunosuppressants.*
3) *There is a lack of clinical information to support an adaptation to the model structure to allow a response to be regained once it is lost. The EAG disagree and are aware of two studies identified by the EAG during the appraisal of dupilumab which show some benefit from immunosuppressant therapies for people with PN.[40, 41] Whilst the EAG acknowledges that these studies do not measure outcomes aligned directly with the composite response measure included in the economic model, they provide some evidence that a treatment benefit would not be unreasonable.*

In summary, the company's model predicts that more patients treated with BSC initially, end up spending longer in the non-response state of the model compared to the nemolizumab arm. The proportion in the non-response state incur substantially higher BSC treatment costs and substantially lower utility compared to those in the

induction phase. Furthermore, no clinical treatment benefit is modelled for intensive BSC (TCS, TCI, immunosuppressants). Any under-estimation of treatment benefit from a more intensive BSC treatment regimen in the non-response state is likely to generate a potentially substantial bias in favour of nemolizumab. The EAG agrees with the company that there are no data to estimate the impact of these treatments on the composite response included in the economic model. However, the EAG considers it necessary that the base case cost-effectiveness analyses should aim to minimise the magnitude of any bias as much as possible. The EAG explores scenarios equalising induction phase and non-response BSC costs and removing them entirely as a way to minimise the potential bias of modelling costs without any benefit for BSC treatments.

4.2.3 Population

The modelled population are adults with moderate-severe PN. The age (mean 55.19) and sex (proportion male: 40.36%) data from the pooled OLYMPIA studies are used to inform the time horizon (45 years) and general population mortality and utility estimates. The proportion of patients ≥90kg, 30%, is used to inform treatment acquisition costs and is also calculated from the pooled OLYMPIA1 and OLYMPIA2 trial datasets. The economic model does not consider any specific patient subgroups.

The EAG's clinical expert is satisfied that the OLYMPIA studies are broadly representative of the patient population in whom nemolizumab would most likely be used in UK clinical practice (i.e. to treat moderate to severe PN). The EAG have crossed checked the modelled population with the SmPC and note that the licensed indication is broader than the population included in the OLYMPIA studies. The SmPC specifically states that "Nemluvio is indicated for the treatment of Prurigo Nodularis". The EAG would therefore like to draw the committee's attention to the fact that the company's economic model describes the cost-effectiveness of nemolizumab in a subset of the licensed indication. There are insufficient data to draw any conclusions on cost-effectiveness in the full licensed indication, which could feasibly also include mild PN.

The EAG are aware of at least one study which utilises CPRD datasets linked to HES for patients with moderate to severe PN. Their characteristics are compared to the company's baseline characteristics, based on the pooled OLYMPIA 1 and OLYMPIA

2 studies in Table 14 below. The EAG note that the cohort in the CPRD dataset are on average slightly older (approximately 6 years) and are of higher weight (approximately 4kg heavier) than the mean population in the OLYMPIA studies. These characteristics could impact on model results in two ways. First, an older cohort would spend shorter time in the non-response states which could increase the ICER as the benefits of nemolizumab have less time to accrue within the semi-absorbing non-response model state. Secondly, depending on the distribution of weight amongst the general population, if a greater proportion of patients were ≥90kg in clinical practice compared to in the studies, this might mean that the treatment acquisition costs of nemolizumab are underestimated. The EAG explores the potential impact of varying the proportion of adults weighing ≥90kg on the ICER through additional scenario analyses reported in Chapter 6.

Table 14 Generalisability of baseline characteristics for the economic model population

Characteristic	Company modelled population based on OLYMPIA1 & 2 pooled datasets	Bahloul et al, 2023[42] CPRD data for England
Sample	N=560 adult patients with moderate to severe PN.	N=2,462 adult patients with moderate to severe PN.
Age (mean, years)	55	61
Gender (proportion female)	60%	63%
Weight (mean, kg)	82.56	NR, calculated as 86.25kg based on reported BMI = 31kg/m2 and UK age and gender adjusted population height: (175cm x 37%) + (162cm x 63%) = 1.668m obtained from Health survey for England data 2021.

Key: BMI, body mass index; CPRD, clinical practice research database; NR, not reported; PN, prurigo nodularis

4.2.4 Interventions and comparators

The intervention in the company submission is described as nemolizumab plus BSC. Nemolizumab is administered as a loading dose of 60mg for all patients, followed by a Q4W maintenance dose of 30mg or 60mg depending on patient weight. Based on the distribution of weight in the pooled OLYMPIA trials population, it was estimated that 70% of patients with a baseline weight <90kg would receive a 30mg maintenance dose, whilst the remaining 30% weighing ≥90kg would receive a 60mg maintenance dose. Nemolizumab is administered as a subcutaneous injection, using a pre-filled pen-injector.

The EAG are satisfied that the approach to calculating a weighted average 30mg and 60mg dose for use in the model is broadly appropriate, aligned with the draft SmPC provided by the company, and is consistent with the dosing rules applied in the OLYMPIA studies. The EAG however note that the company has not modelled any variation in patient weight over time, so the maintenance dose remains fixed for the duration of response. Whilst somewhat uncertain, over a lifetime horizon, any initial weight increases in the patient population may well be offset by weight decreases in older age. The magnitude of any bias in the ICER is likely to be small.

Both the intervention and comparator arms of the model include BSC. The company submission states that BSC was informed by UK clinical experts in a modified Delphi panel. BSC is stated to include topical emollients, TCSs, TCIs, antihistamines, systemic corticosteroids and immunosuppressants. The comparator arm receives BSC alone until death. It was assumed that the composition of BSC was the same in both arms of the model during the intervention phase and whilst a response was maintained, but that it would increase in intensity if a response was lost.

The EAG were initially concerned that the composition of BSC included in the economic model might not align with the BSC treatments used in the respective arms of the OLYMPIA studies, particularly if rescue treatments were also considered as part of BSC and might be incurred at different rates in both arms. In response to clarification queries, the company provided additional details on the composition of BSC (See clarification response B4, Table 8). The EAG are satisfied that the

distribution of BSC treatments is broadly aligned across treatment arms in the trial with some minor exceptions. The economic model assumes more intensive use of emollients and lower use of antihistamines during the intervention phase compared to what was used in the trial. The EAG's clinical expert does not consider these differences to be sufficient to impact meaningfully on trial outcomes and are unlikely to substantially affect the ICER. However, the EAG have concerns regarding the alignment of BSC costs following non-response with the assumption of no clinical benefit. This is discussed further in Sections 4.2.2 and 4.2.8.

4.2.5 Perspective, time horizon and discounting

The company adopt a UK NHS perspective for costs. The model is run for a lifetime horizon (up to a maximum of 99 years), with costs and utilities discounted at 3.5% per annum.

The EAG is satisfied that the perspective, time horizon and discounting are broadly aligned with the NICE reference case. However, the EAG noted a minor error in the discounting approach taken by the company, where costs and QALYs in cycle 1 (i.e. months 12-24) are discounted by two time periods (years), but costs and QALYs in cycle 0 remain undiscounted. The discounting approach taken therefore lacks consistency. The EAG prefers a more continuous approach to discounting that assumes costs and QALYs are incurred during the cycle rather than at the end of cycle 1 but at the beginning of cycle 0. Given that general convention is not to discount costs or QALYs in year 1, the EAG consider it more appropriate to discount by 1, rather than 2 years. This also applies to all subsequent model cycles. The impact on cost-effectiveness conclusions of applying this correction is minimal, but the EAG have implemented it for completeness.

4.2.6 Treatment effectiveness and extrapolation

Treatment effectiveness and extrapolation in the economic model are based on three key components. These are composite response rates achieved in the OLYMPIA1 and OLYMPIA2 studies, treatment discontinuation assumptions, and treatment waning effects in both arms of the model.

Composite response definition

The key clinical parameter underpinning the economic model is the probability of achieving a composite treatment response (itch improvement of ≥ 4 PP NRS compared to baseline, and nodule reduction, measured as an IGA score of 0 or 1, with an improvement of ≥ 2 points from baseline) at week 16 based on pooled data from the OLYMPIA1 and OLYMPIA2 studies.

The EAG acknowledge that the use of a composite measure of response is aligned with committee's preference from the previous NICE appraisal of dupilumab (TA955). However, the composite response may lead to a potentially conservative estimate of the treatment benefit in both arms of the model. The EAG's clinical expert is of the view that the composite response defined by the company is a high bar to achieve in clinical practice, especially within 16 weeks, where it may be difficult to realise the full benefit of treatment in terms of nodule reduction. The implication is that the composite outcome might not fully capture all potential benefits of treatment that could impact on patient's quality of life. For example, it is feasible to assume that patients achieving itch relief, but not reduction in nodules, might achieve some quality-of-life benefit. Such a partial response is not accounted for in the company's economic model, and it could occur in both arms. The magnitude of any bias is unclear as it would depend on the relative effectiveness in each arm for a partial response but would also depend on the utilities that could be achieved in any "partial response" health state. Given the primary trial outcomes, it is plausible that the company's decision to model success based on the composite outcome might lead to a conservative estimate of the incremental treatment benefit of nemolizumab. However, the direction of any bias in the ICER is less clear because retaining partial responders on treatment would also increase nemolizumab treatment acquisition costs.

The second point of critique with regards to the composite response definition is that there is uncertainty about how this would be implemented in UK clinical practice. The company's economic model assumes that all patients failing to achieve the composite treatment response would be immediately discontinued from treatment, would incur no further treatment acquisition costs, but would incur a utility benefit of the midpoint between response and non-response for six months reflecting an assumption that all

discontinuers were partial responders. The EAG's clinical expert is of the view that clinicians and patients may wish to remain on treatment if it was providing some symptom relief, even if it was not achieving the high bar of the composite response used in the economic model. This would suggest that the ICER in routine clinical practice could feasibly be substantially higher than that reported in the economic model if partial responders were to remain on treatment longer term. The company may wisht to further clarify if they would recommend discontinuing treatment in clinical practice following failure to achieve a composite response as defined in the economic model. If so, committee may wish to consider the appropriateness of a stopping rule for this assessment. Alternatively, if the company wish to allow for continuation of nemolizumab amongst partial responders, further adaptation in the economic model would be required to better understand the implications for cost-effectiveness (See Section 4.2.2).

The composite response used in the company's economic model is calculated as the total number of participants achieving both response definitions across the OLYMPIA1 and OLYMPIA 2 studies, divided by the total number of participants randomised to those studies.

The EAG notes that the company's calculation approach, based on ITT principles essentially assumes that all missing data are non-responders. The EAG notes that this approach may underestimate the absolute response probability in both arms of the study. Assuming that data are missing at random, this should not bias the calculation of the ICER. However, the EAG would have appreciated a more complete description of the proportions of missing data for the composite outcome used in the economic model. This would have allowed for a more complete assessment of whether missing data are a cause for concern.

The company's composite definition of response used in the economic model is based on raw data pooled across the OLYMPIA 1 and OLYMPIA 2 studies. Strata-adjusted effect sizes were provided in the description of clinical effectiveness results (Company submission Table 18*)* for OLYMPIA 1 and OLYMPIA2 separately, but a pooled effect size was not provided for the composite response, nor were the strata adjusted effect sizes included in the economic model.

The EAG would have considered it helpful for the company to include the relative effect sizes for the composite outcome within the economic model, with confidence intervals around a pooled analysis across studies used to derive a standard error for the probabilistic sensitivity analysis. The EAG would have considered this to be the most robust estimation of a composite response effect size for use in the model. To explore this issue further, the EAG have compared the descriptive data and relative effect sizes from the statistical analyses in Table 15. Whilst the raw data underestimate the difference between groups for OLYMPIA2, they overestimate the difference for OLYMPIA 1. On balance, the magnitude of any bias in the ICER associated with applying the raw pooled data as opposed to strata-adjusted effect size from the pooled data is likely to be small,

Table 15 Summary of approaches to calculate the probability of achieving a 16 week composite outcome for use in the economic model.

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

Key: NR, not reported.

For the calculation of response probability in the economic model, the company used data from week 16 pooled across the OLYMPIA1 and OLYMPIA2 studies. OLYMPIA1 data available at week 24 were not considered. The EAG queried why the available 24-week data were not considered in the economic model at clarifications stage and were provided by the company. All available composite

response data for week 16 / 24 across the OLYMPIA 1 and OLYMPIA2 studies are summarised in Table 16.

Table 16 Composite PP NRS + IGA response data from OLYMPIA 1 + OLYMPIA 2 (Re-produced from Table 7 of the company clarification response)

Week	Nemolizumab	BSC	Source
Week 16	[redacted]	[redacted]	OLYMPIA 1[43]
Week 16	[redacted]	[redacted]	OLYMPIA 2[44]
Week 16	[redacted]	[redacted]	OLYMPIA 1 and OLYMPIA 2[43, 44]
Week 24	[redacted]	[redacted]	OLYMPIA 1[43]
Week 16/24	[redacted]	[redacted]	OLYMPIA 1 (Week 24) and OLYMPIA 2 (Week 16)[43, 44]

Key: BSC, best supportive care; IGA, Investigator's Global Assessment; PP NRS, peak pruritus numerical rating score; SE, standard error.

Given the short time frame of follow-up, the EAG consider it important to consider the impact of integrating the available 24-week data into the model. The company have provided two scenario analysis results in response to clarification queries, one which uses the 24-week response data from OLYMPIA1 only, and a second which applies the pooled response rate from OLYMPIA2 at week 16 and OLYMPIA1 at week 24, applied from week 24 onwards in the economic model.

On balance, the EAG is satisfied that the decision to pool the data at week 16 is robust and makes best use of pooled data available at a single time point. However, the EAG also considers the company's scenario that pools the last observed data point across the studies to be a plausible alternative scenario that also considers the available 24-week data from OLYMPIA 1. Whilst the company did provide the results of this scenario in response to clarification queries, they did not integrate the functionality to implement these changes directly within the economic model, instead hard coding the changes. This made it difficult for the EAG to reproduce the analyses

conducted. The EAG generally consider it to be good modelling practice to include functionality to implement all scenario analyses within one model file wherever possible.

Treatment discontinuation:

The company model includes treatment-specific discontinuation rates for nemolizumab and BSC. For nemolizumab, a conditional treatment discontinuation probability is calculated from the LTE study. The sample for the denominator of the percentage calculation was described in the company submission as the total number of 16-week responders from the pooled OLYMPIA 1 and OLYMPIA 2 studies who had received nemolizumab within 12-weeks of the start of the LTE study [redacted], and who also reported 52-week response data. The numerator was the number of participants who entered the LTE study at the end of the lead-in OLYMPIA 1 and 2 studies who were no longer on treatment at week 52. This was [redacted] participant, giving a treatment discontinuation probability at 52 weeks of [redacted]. This discontinuation probability was applied in each model cycle thereafter.

The EAG raise two points of uncertainty with the company's approach to calculating nemolizumab treatment discontinuation. First, the approach may be subject to selection bias. Table 23 of the company submission details a total of [redacted] participants entering the LTE study, of whom Table 24 shows [redacted] had treatment within the 12-week time frame stated by the company. Table 26 then suggests [redacted] had continuous nemolizumab treatment. It is unclear to the EAG whether all these patients came from OLYMPIA1 and OLYMPIA 2 studies, or if some also came from the Phase 2 study (Stander et al).[33] Furthermore, the EAG are concerned that the definition of a "response" used to inform the conditional treatment discontinuation calculation might not be aligned with the composite response definition included in the economic model. Given the company's stated calculation approach that only responders from OLYMPIA 1 and OLYMPIA 2 were included in the denominator and given that the pooled composite response at week 16 was only [redacted] across the nemolizumab arms of the pooled studies and given that [redacted] were randomised in total, the EAG are concerned that the stated methodology for calculating treatment discontinuation may not be aligned with the probability included in the model. The EAG suggest an alternative approach would be that the maximum plausible value for

the denominator of the treatment discontinuation calculation could be [redacted]. It is unclear how many participants discontinued treatment amongst those achieving a composite response, but assuming that it is still [redacted], the calculation would suggest a more plausible treatment discontinuation probability at week 52 of [redacted]. Even if the correct treatment discontinuation probability was [redacted] this still remains highly uncertain, as small changes in numbers of discontinuation events at very low proportions can have substantial relative impact on parameters for the cost-effectiveness model. The EAG are also aware of data from Table 23 showing that the primary reason for treatment discontinuation in the LTE study was adverse events ([redacted], again, substantially higher than the proportion applied in the economic model. For all of these reasons, the EAG are concerned that the company's estimate of treatment discontinuation applied in the economic model may be an underestimate of the true treatment discontinuation rate. If so, the approach would likely lead to over-estimation of treatment acquisition costs. It would also lead to an over-estimation of treatment benefit in the longer-term because the company's base case model analysis assumes all treatment discontinuers are non-responders. In general, higher treatment discontinuation rates lead to increases in the ICER, so it is feasible that any underestimation of the nemolizumab discontinuation rate might create a bias in favour of nemolizumab. Given the information provided in the company submission and cross-checking of the study documentation, the EAG are uncertain about the robustness of the discontinuation probability calculation used by the company.

For BSC, treatment discontinuation was calculated as the proportion of 16-week responders from the OLYMPIA 1 study, who were no longer on treatment at week 24. For both treatment arms in the model, the annual probability of treatment discontinuation at week 52 was extrapolated for the remainder of the model time horizon and treatment discontinuation was modelled independently of treatment effect waning (discussed below).

The EAG consider the true long-term treatment discontinuation probability on both nemolizumab and BSC to be highly uncertain. The EAG does not consider the inclusion of a placebo treatment discontinuation probability to be generalisable to best supportive care treatment adherence in UK clinical practice. First, the definition

of BSC is restricted by treatments allowed in the trial, and likely underestimates both treatment effectiveness and adverse events relative to UK clinical practice. Also, given that treatment discontinuation from the BSC arm leads to a more intensive definition of BSC, without treatment benefit, the EAG does not consider the approach taken by the company to be necessary. The EAG would have considered an approach where everyone receives the BSC as defined in the maintenance phase up until week 16, with the remainder receiving BSC for the remaining duration of the model time horizon to be more plausible. Once single BSC state could be applied within the economic model, perhaps with exploration of different intensities of BSC treatment composition affecting costs. The treatment intervention arm could then simply discontinue treatment to the BSC arm of the model. This approach would negate the need for a "discontinuation" assumption longer term from the placebo arm of the trial. Indeed, varying the BSC treatment discontinuation probability between 0-100% has little impact on the ICER and only complicates the model traces without any benefit in terms of robustness of results.

Treatment effect waning

In addition to treatment discontinuation, the company has also modelled a treatment waning effect, based on the assumptions used in the company submission for dupilumab as part of TA955.[23] The company's preferred treatment waning assumptions are detailed in Table 37 of the company submission and have been validated by UK clinical experts.

The EAG raise several points of uncertainty regarding the appropriateness of the company's approach to modelling treatment waning effects:

1) *Treatment waning effects over the longer-term might risk double counting treatment discontinuation described above because they were derived from different sources of evidence.*
2) *Treatment waning effects for nemolizumab are based on data from TA955 for dupilumab. The EAG's clinical expert has confirmed that both dupilumab and nemolizumab are biologic treatments. However, the mechanism of action is different. The EAGs clinical expert was therefore of the view that treatment effect waning might be lower for nemolizumab compared to dupilumab. The EAG note that higher treatment waning effects increase the ICER by a small*

magnitude. Therefore, the company's approach might be considered conservative for nemolizumab.

3) *Treatment waning effects for BSC are obtained from treatment waning effects for BSC in the appraisal of TA534 for atopic dermatitis, obtained from the ARCADIA 1 study.[45] The EAG does not consider these data to be generalisable to the PN population, but also note that the impact of treatment effect waning assumptions for the BSC arm of the model is minimal because there is no impact on QALYs. The EAG consider the company's modelling approach to BSC treatment effect waning to be overly complicated and a single BSC health state might have been more appropriate.*

In summary, the EAG notes that whilst the treatment discontinuation and treatment effect waning parameters are not key drivers of cost-effectiveness, the parameter values are highly uncertain, and it is unclear how reflective they would be of real-world use of nemolizumab. The net impact of uncertainty around treatment discontinuation and treatment effect waning parameters on the ICER is unclear and will depend on the committee's preferences for other model parameters such as the difference between response and non-response health state utility values (See Section 4.2.7). The EAG applies a range of scenario analyses to both the company and EAG preferred base cases in Chapter 6.

4.2.7 Health related quality of life

General approach to deriving HSUVs

Quality of life was captured in the model by applying age and sex-adjusted health state utility values to the maintenance (response) and BSC (non-response) health states (tunnel states for BSC Y1, BSC Y2 and BSC Y3+) for nemolizumab and BSC respectively. The functionality of the model allows for one-off disutility to be applied for adverse events, but this is not included within the company base case. Health state utility values were based on EQ-5D-3L data pooled across the OLYMPIA 1 & 2 trials at baseline and 16 weeks. Utility weights were derived using the time trade-off (TTO) method.[46] Company base case utilities are presented in table 41, page 154 of the CS.

The EAG were initially concerned that HSUVs included in the economic model appeared substantially higher than the general population utility norms for England.

The EAG queried the face validity of the high utility values, and the company responded to confirm they had checked their calculations and that the estimates were correct. They justified the higher utilities on the grounds that responders to PN may value improvements in health more highly than the general population. The EAG also note that the definition of response included in the economic model is a particularly high bar to achieve, and it is therefore plausible that utility values may be above age and sex adjusted general population norms. Despite some uncertainty, the EAG are satisfied that the company's approach to utility calculation is likely to be accurate and is aligned with the NICE reference case.

HSUV data sources:

The company conducted a systematic literature review for studies reporting quality of life data for PN up to 17th May 2024. However, just two records were found which report EQ-5D utilities in this population. One study, Misery et al. 2023, conducted with a French patient advocacy group in patients with PN reported EQ-5D stratified by mild disease (DLQI<7) and moderate to severe disease (≥7 DLQI).[13] Where the DLQI (Dermatology life quality index) score is a dermatology specific measure which captures the impact upon daily activities, work and school, pain (or itch), and personal relationships. The index consists of 10 items with a maximum score of 30. The mean EQ-5D index score was 0.78 (SD=0.24, n=18) for mild disease and 0.43 (SD=0.32, n=52) for moderate to severe disease. The second record sourced during the review was TA955 (NICE assessment of dupilumab) which reported the EQ-5D-5L crosswalked[47, 48] to the EQ-5D-3L at baseline, 12 and 24 weeks within the PRIME and PRIME 2 trials.

The EAG are satisfied that the Misery et al population is not aligned with the NICE reference case as it does not include UK value sets.[13, 49] Whilst the utilities available from TA955 may be generalisable to the current assessment, the EAG note that none of the existing evidence, other than the OLYMPIA studies provide HSUV data categorised by response status. These data were considered for TA955 but were unfortunately redacted from publicly available documentation and are therefore not available to the EAG for consideration.

For the available OLYMPIA study data, the EAG were concerned that not all available HSUV data had been provided within the company submission. In response to clarification, the company provided the mean EQ-5D index values by treatment arm and response status at each observed timepoint within the OLYMPIA 1 & 2 trials and pooled across studies. The EAG compares the available data from TA955, based on the PRIME trials, and the OLYMPIA study data in Table 17 below.

The EAG would like to highlight that sufficient data to calculate robust estimates of HSUVs are only available from the OLYMPIA1 and 2 studies, not the LTE study. Relying on 16 weeks of data for HSUVs leads to some uncertainty in long-term quality of life. Nevertheless, the EAG are satisfied that the OLYMPIA 1 and 2 studies are the most appropriate source of available utility data to populate the economic model health states.

Table 17 Comparison of EQ-5D index scores from OLYMPIA 1& 2 versus TA955 (adapted from table 14, page 32 of company CQ response and table 27, page 82 of document B in TA955)

Source	OLYMPIA 1 & 2 trials						PRIME & PRIME 2 trials (TA955)[1]	
Time point	Response		Non-response		All (weighted average)			
	Nemolizumab	BSC	Nemolizumab	BSC	Nemolizumab	BSC	Dupilumab	BSC
Baseline (N,SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.643 (153,0.262)	0.662 (156,0.257)
12 weeks (N,SD)	-	-	-	-	-	-	0.766 (152,0.214)	0.735 (153,0.206)
16 weeks (N,SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-	-

24 weeks [2] (N,SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.779 (152,0.218)	0.729 (145,0.218)

Key: BSC, best supportive care; SD, standard deviation.

[1] EQ-5D-5L cross-walked to EQ-5D-3L[47]

[2] OLYMPIA 1 only for nemolizumab and BSC.

Health state utility values used within the model

HSUVs are applied in the model according to response to the composite outcome. Responder utility is based on week 16 mean utility score of all responders, independent of treatment arm, observed in the trials ([redacted](SE=[redacted])) up to year 1. Beyond year 1, all responders are assumed to get a 5% utility increase for the remainder of time in the response state. Non-responders are assumed to return to the mean utility observed at baseline across all participants ([redacted] (SE=[redacted])), with one exception. Nemolizumab non-responders are assumed to have a HSUV equal to the mid-point of baseline and responder values to account for the potential for a partial treatment response. There are three key assumptions that require further critique:

Assumption 1: 5% increase in the utility weight for responders' assumption

The company assumes that all responders realise a 5% increase in utility after the first year. This estimate is based upon data observed between weeks 16 and 104 in the ARCADIA LTE study of nemolizumab in atopic dermatitis (see response to CQ B10).[45] Within the response to CQ (question B10 page 31) the company provided the following arguments to further support their assumption: (1) The ARCADIA LTE study of nemolizumab in atopic dermatitis reported a 10% increase in utility between weeks 16 and 104 and therefore the 5% modelled for PN may be conservative, (2) advice from a UK clinical expert who stated that improvement in QoL in the short term is driven by itch relief, but it will not capture the increased QoL associated with healing of lesions that that will only become apparent in the longer-term, (3) A linear repeated measures mixed effects and an ordinary least squares regression analysis (CQ B13 and CQ2 in the additional clarification questions document) were conducted. The mixed effect regressions included only those who responded at week 16 to the composite outcome for both the OLYMPIA 1&2 trials and the LTE study. The model included a random intercept and the following coefficients: Age, Sex, Week of observation (with and without a squared term to capture non-linear changes over time) and baseline EQ-5D. These models predicted an EQ-5D at 52 weeks of [redacted]/[redacted](Male/Female) for the MMRM with the squared term for analysis week, [redacted]/[redacted](Male/Female) for the MMRM without the squared term for analysis week. The squared term for analysis weeks is negative within the regression which suggests a decreasing rate of increase in utility in the longer term where the model predicted EQ-5D values for males of [redacted] (52 weeks), [redacted] (104 weeks) and

[redacted] (156 weeks). The company finds the prediction of [redacted] at 104 weeks implausible so does not find the inclusion of the squared term appropriate. The model which excludes the squared term for analysis week predicted EQ-5D for males of [redacted] (52 weeks) and full health ([redacted]) for 104 and 156 weeks. This model prediction is used to support the 5% increase in EQ-5D for responders in the long term.

The EAG is not convinced that the company have provided sufficient evidence to support the use of a 5% increase in utility over the observed data for responders for three reasons. First, long-term data from an atopic dermatitis study, with different definitions of response are unlikely to be transferable to patients achieving the composite response outcome in PN. Furthermore, the company have not provided details of the patient numbers, the EQ-5D utility data, or a statistical analysis of the 10% increase in utility observed within the ARCADIA LTE study. So, the EAG cannot comment on the robustness of this evidence. Secondly, whilst the EAG's clinical expert does agree with the company expert that the secondary healing of lesions could feasibly lead to a quality-of-life benefit, the magnitude of any such benefit is unclear. For example, the evidence available from OLYMPIA 1 at 24 weeks is suggestive of a potential reduction, rather than an increase in utility amongst responders over time, though admittedly the available sample is small. Thirdly, the EQ-5D index score of [redacted] at 16 weeks for responders is substantially higher than the age and sex-adjusted general population utility norms for the UK. Whilst the EAG accepts the company's rationale that patients achieving a response might value their health more, applying a somewhat arbitrary 5% increase ([redacted] to [redacted]) to an already overvalued health state lacks face validity. Furthermore, the available data are based on short-term outcomes (16-weeks). There is no robust evidence to suggest that any over-valuation of utility would necessarily remain constant over the patient's lifetime within each state. Fourthly, the EAG are concerned that the MMRM regression models provided by the company are not suitable to inform estimates of long-term HRQoL for the following reasons:

- *The MMRM regression models lack internal validity as it estimates baseline utility value that is higher than the observed baseline values within the trials (OLYMPIA 1& 2 pooled baseline utility: [redacted], MMRM model estimates: [redacted]).*
- *The model outputs lack face validity in terms of longer-term utility projections. The company's MMRM model which excludes the squared term of the analysis visit in weeks predicts a utility value of [redacted] for years 2 and 3. Indeed if the regression output was not capped at full health, then the projections would exceed 1 after year 2. Similarly, including a quadratic term to examine non-linearity with respect to analysis week leads to model predictions outside of the observed data that are implausibly low. However, this model does suggest a trend that EQ-5D utility decreases in the long term which contradicts the 5% long-term utility assumption for non-responders. This is not definitive, as no information of statistical significance or model specification is provided.*
- *The company's clarification response suggests that the company have not included adjustment for observable clinical measures of burden which would impact HRQoL within the model (e.g., disease severity at baseline). These omissions may explain the poor model fit. It is evident that the analyses lack internal and external validity, however without full results of the regression models it is not possible to understand the extent of poor validity.*
- *The company also included EQ-5D values from the LTE study. Whilst the LTE study does provide responder data post-trial follow-up, the number of participants is very small ([redacted] at week 80). The range of values of these [redacted] participants was [redacted]. Long-term projections from the regression model using these data are likely to be highly uncertain.*
- *The total number of random effects groups in the model is [redacted] which is equal to the number of OLYMPIA 1 & 2 participants who responded at week 16 ([redacted]). The EAG are concerned that the total number of observations of the composite response measure is higher than those for the EQ-5D index score at each timepoint for both treatment arms. Therefore, missingness assumptions may bias the results unless evidence for "Missing At Random" can be provided.*

To summarise, the source of data used to inform increasing utility amongst responders over time is obtained from atopic dermatitis and may lack generalisability to PN. The regression model provided by the company has major limitations

regarding data availability, model specification, internal validity and face validity of utility extrapolations. Therefore, the EAG is not satisfied that the company has provided sufficient evidence to support a 5% increase in utility for responders over the observed response utility data in the economic model.

Assumption 2: Nemolizumab non-responders are assumed to incur a utility benefit of partial response in the non-response state but BSC non-responders are not.

The second assumption is that nemolizumab patients who are non-responders in cycle 1 and those who discontinue treatment or lose a response beyond cycle 1 will experience a slower decline in quality of life within the non-response health state compared to BSC non-responders. The company justification is that nemolizumab patients are more likely to be 'partial responders' when they lose their full composite response compared to BSC, or when they discontinue treatment. The company states that their approach is required to account for the utility benefit associated with a partial response to nemolizumab and is in line with the approach within TA955. The "partial response" utility is calculated as the midpoint ([redacted]) of baseline ([redacted]) and responder ([redacted]) utility. The company therefore apply a treatment-specific health state utility benefit to nemolizumab non-responders in the initial model cycle where non-responders are assumed to be "partial responders" and receive the baseline utility ([redacted]) for 8 weeks then ([redacted]) for the subsequent 44 weeks of the initial model cycle. In contrast, BSC non-responders at week 16 are assigned the non-response utility for the full duration of the first model cycle.

Beyond cycle 1, the proportion in any cycle who discontinue nemolizumab treatment or lose a response receive the partial response utility ([redacted]) for the first subsequent cycle (52 weeks) within the non-response state. This approach is applied for the full model time horizon. In contrast, BSC non-responders beyond cycle 1 are assumed to incur the non-response utility value ([redacted]) for the full duration of time in the non-response state.

The EAG does not consider the case for treatment specific health state utility values in the non-response state to be strong. Whilst the EAG accepts that the calculated partial response utility ([redacted] is not dissimilar to the observed utility value for non-responders in the nemolizumab arm at 16 weeks ([redacted]), this effect is observed in

both treatment arms (e.g. an increase to [redacted] for the BSC treatment arm). The EAG does not consider the argument for partial response only applies to the nemolizumab arm. Further, the EAG is concerned that by applying the higher [redacted] to all non-responders in the nemolizumab arm, it implicitly assumes that all non-responders would realise a partial response.

The company provided an ordinary least squares analysis in response to additional clarification question CQ2. This regression includes an interaction term for response and treatment arm which may begin to disentangle any protocol driven effects and true treatment effect. The model found a statistically significant difference of [redacted] ([redacted]) in the EQ-5D utility score between placebo and nemolizumab treatment arms in 16-week utility for non-responders. As stated by the company, this is evidential of either partial response or durability effect of nemolizumab for non-responders. Conversely, it may also be evidence of the treatment regimens within the Olympia 1 & 2 trial designs. In particular, the placebo arm of the trial which, compared to the PN population in the UK, is heavily undertreated (see discussion for assumption 3 below for more detail).

Given a lack of robust evidence in support of a treatment specific benefit amongst nemolizumab non-responders in the longer term, the EAG prefers the use of observed index utility scores where possible with consistent assumptions made between treatment arms regarding partial response. The EAG does acknowledge that there appears to be a difference in observed utility scores for non-responders at week 16 between the nemolizumab and BSC arms, but that the magnitude of difference is substantially smaller than suggested by the company. The EAG therefore conducts a scenario analysis where a smaller magnitude of benefit [redacted] is applied within the first model cycle only. However, there is no strong evidence to support this potential partial response benefit being sustained for the full remaining 44 weeks of the first cycle. The EAG's scenario might therefore be considered as an optimistic scenario for nemolizumab.

Assumption 3: Non-responder health state utility values are assumed to be equal to baseline utility measurement.

The company use observed response utility data for the response model states ([redacted]) but apply the baseline value ([redacted]) to all non-responders, rather than the pooled non-response utility value observed in the OLYMPIA studies ([redacted]). The return to baseline utility is based upon the following from TA955: committee preferred assumption that non-responders would return to baseline utility at 6-months and, clinical experts highlighting protocol driven effects where participants would return to a worse health state post-trial. The company also highlight that this assumption was validated by a UK clinical expert.

The EAG note that the divergence between the utility value for responders ([redacted]) and non-responders ([redacted]) is the most important driver of cost-effectiveness results. That is because, a greater proportion of the BSC cohort enter the non-response early in the model and remain there for longer than the nemolizumab cohort. The utility difference between achieving a response and not, according to the company's base case modelling assumptions, is [redacted] in the first year then [redacted] for each subsequent year. The EAG is concerned that the utility value at baseline might not be generalisable to PN patients receiving BSC in clinical practice. Within the OLYMPIA trials' designs, participants must meet eligibility criteria and undergo an up to 4-week screening period prior to baseline. During this screening period, participants must not receive several medications typically considered BSC at varying treatment specific timepoints before their baseline visit. For example, Table 2, page 27 of the OLYMPIA 1 study CSR states that participants must not have received the following BSC treatments: immunosuppressive or immunomodulatory drugs (i.e., methotrexate or cyclosporine) for [redacted], TCIs or TCSs for [redacted] or systemic corticosteroids for [redacted] prior to study day 1. The baseline index utility score is therefore reflective of a PN population which is not receiving BSC treatment and is likely to be substantially lower than the average utility experienced by BSC non-responders who have not achieved the high bar composite response required to be classed as "responders" in the economic model.

The EAG generally agree with the company that many BSC treatments may have poor effectiveness outcomes, particularly when considering achievement of the composite outcome used in the economic model. However, the EAG clinical expert is of the view that these BSC treatments do provide some symptomatic relief, in particular to the

itch component of PN, even if they might not lead to achievement of the composite outcome used for response definition. This could be achieved for example when interrupting the itch realises improvement in sleep and subsequent healing of lesions. The EAG also acknowledge the potential for protocol driven effects with regard to utility estimates. However, such protocol driven effects might be expected to be achieved in both the nemolizumab and BSC arms of the studies. Applying assumptions about the magnitude of protocol-driven effects to non-responders, but not to responders would likely introduce further bias to the differential utility between responders and non-responders.

An ordinary least squares regression analysis of Olympia 1 & 2 EQ-5D utility estimates undertaken by the company in response to additional clarification question CQ2 estimated 16-week utility values for non-responders as [redacted]. The utility value obtained is not dissimilar to the mean observed EQ-5D utility observed at 16-weeks in the Olympia trials of [redacted].

For these reasons, the EAG prefers the use of non-response health state utility values observed in the trial ([redacted]) rather than assuming the baseline utility value ([redacted]) in the economic model.

In summary, the EAG agrees that the OLYMPIA1 and OLYMPIA2 study provide the best available EQ-5D health state utility value data for use in the economic model. The EAG are satisfied that utilities are aligned with the NICE reference case in terms of methodology. However, the EAG are not satisfied that the company has provided sufficient evidence to support the following three key assumptions:

1) *Applying an additional 5% increase in the responder HSUV after year 1 over the observed value in the trials*
2) *Applying a treatment specific benefit for nemolizumab non-responders in the initial model cycle or in the first cycle following treatment discontinuation or loss of response, but not applying this in the BSC arm*
3) *Returning all non-responders to baseline as opposed to using the non-responder utility available from the trials.*

Company and EAG preferred base case utility values are summarised in Table 18 below. The final column details a scenario analysis assuming that a treatment specific benefit might be achievable for nemolizumab, but that this would only be possible during the period of observed data, between weeks 9 and 24. Any treatment specific benefit for nemolizumab non-responders beyond week 24 lacks robust evidence. The EAG view is that if the company wished to model partial response, this should have been built into the economic model structure as discussed in Section 4.2.2.

Table 18 Comparison of company base case utility weights and EAG preferred (adapted from table 41, page 154 of CS and table 14, page 32 of company response to CQ)

	Company		EAG preferred		EAG extra	
Timepoint	**Nemolizumab**	**BSC**	**Nemolizumab**	**BSC**	**Nemolizumab**	**BSC**
Baseline	0.579	0.579	0.579	0.579	0.579	0.579
Responders						
Y1(week 0-8)	0.579	0.579	0.579	0.579	0.579	0.579
Y1 (week 9-52)	0.922	0.922	0.922	0.922	0.922	0.922
Y2	0.968	0.968	0.922	0.922	0.922	0.922
Y3+	0.968	0.968	0.922	0.922	0.922	0.922
Non-responder						
Y1(week 0-8)	0.579	0.579	0.579	0.579	0.579	0.579
Y1 (week 9-52)	0.751	0.579	0.734	0.734		
Y1 (week 9-24)					0.774	0.673
Week 25-52					0.734	0.734
Y2	0.579	0.579	0.734	0.734	0.734	0.734
Y3+	0.579	0.579	0.734	0.734	0.734	0.734

Adverse event disutilities

Adverse event disutilities are not included in the company preferred base case analysis based on the justification that any HRQoL impact of these events is captured within the EQ-5D HSUVs, and that the approach was accepted in TA955. However, a scenario is applied where adverse event disutility is included. Study drug related adverse events that occurred in at least 2% of participants within the OLYMPIA 1 & 2 trials are included in the scenario analysis. Adverse events include atopic dermatitis, eczema nummular, neurodermatitis, dyspnoea, asthma and headache. These are incorporated by multiplying a rate (adjusted for the 1-year cycle length) by the

disutility for the assumed duration (between 3-14 days) multiplied by all those within the maintenance (responder) health state in each cycle. A disutility of 0.015, based on a US study, is applied for atopic dermatitis, eczema nummular, neurodermatitis. A disutility of 0.030 is applied for headache and a disutility of 0.021 is applied for dyspnoea and asthma. UK clinical expert advice to the company suggested that most adverse events would resolve within 14 days, a duration of 3 days and 7 days was assumed for headache and dyspnoea respectively.

The reasoning given for not including disutilities in the company base case for adverse events is twofold: (1) disutility's from adverse events would be captured within the EQ-5D collected during the trial follow-up, (2) advice from a clinical expert that most would be resolved within 2 weeks. There is little evidence provided which suggests that the EQ-5D index scores captured during the OLYMPIA trials' follow-up are impacted by adverse events. Particularly, given the limited number of events included and assuming that most would be resolved within 14 days. The EAG is not confident in the company's position to not include adverse event disutilities on these grounds and prefers to include adverse event disutilities in the base case.

The EAG is concerned that it has not been able to validate the counts of the included adverse events with tables presented in its submission. In response to clarification, the company provided information of all treatment-related adverse events (TRAE) which occurred in more than 2% of patients within OLYMPIA 1 & 2 trials. The table suggests that several adverse events have not been included in the economic model. For example, musculoskeletal and connective tissue disorders ([redacted]% in the LTE study), infections and infestations (OLYMPIA 1: [redacted] OLYMPIA 2: [redacted], and LTE study:[redacted]) were not included in the economic model. Whilst the EAG appreciates that there may be a difference in the definition of study drug related and treatment related adverse events, it would have been helpful if the company clarified this point. The EAG view is that there remains some uncertainty regarding whether all relevant adverse events have been accounted for in the modelling as well as the likely duration of their impact on patient quality of life.

The study which informs the EQ-5D disutility associated with each event is sourced from a US study of people with chronic conditions.[50] The study did not include the

severity nor duration of each chronic condition in calculating the utility weight. Further, as it is based upon the US scoring algorithm, the EQ-5D index scores are subject to ceiling effects.[51] Consequently, capturing mild disease within the EQ-5D score is highly uncertain. Given that most adverse events reported in table 19, page 40 of company response to clarification are considered "moderate", the EAG is not confident that the Sullivan disutility's would appropriately capture the true disutility of these events.

In summary, the true adverse event rate, particularly in the longer term, is uncertain and the company could have included all available data from the LTE study in the economic model. Additionally, the duration of each adverse event is unclear as is the magnitude of disutility applied to events where the majority of occurrences are of moderate severity.

4.2.8 Resources and costs

The company's modelled healthcare resource use includes treatment acquisition costs for nemolizumab and BSC whilst responding to treatment (maintenance state), treatment acquisition costs for BSC when a response is lost or treatment is discontinued (i.e., the BSC tunnel states), adverse events for those in the maintenance state, and healthcare resource use for PN management (monitoring) for all health states. Costs within the model are calculated by multiplying the half cycle corrected health state occupancy by the respective total health state costs. No cost is applied to those who enter or remain in the absorbing death health state. Within the first year of the model (cycle 0), the annual costs are weighted by the duration applicable to the clinical parameters sourced from OLYMPIA 1 & 2 trials (16 weeks) and the remainder of the year (36 weeks). Therefore, the cost for cycle 0 of the model is a weighted cost calculation based on the proportion of a year for which a patient is considered a responder (maintenance) or non-responder (BSC). For example, a non-responder accrues 16-weeks of nemolizumab plus BSC acquisition cost, plus 36 weeks of BSC non-responder treatment acquisition cost. The following sections discuss nemolizumab treatment acquisition costs, BSC costs, disease management (monitoring), and adverse event costs respectively.

<u>Treatment acquisition costs</u>

Detail of the drug acquisition and administration costs for nemolizumab and BSC are found within sections B.3.5.1.1. and B.3.5.1.2. of document B of the company submission. A summary of the total treatment acquisition costs per cycle is presented in table 19 below.

Table 19 Summary of per cycle treatment acquisition costs included in the model

Cost component	Cost per model cycle (per year)
Annual treatment acquisition cost of Nemolizumab	[redacted]
Acquisition cost of loading doses of Nemolizumab (2 doses of nemolizumab)	[redacted]
Administration of loading doses of Nemolizumab[1]	£29
BSC (with active treatment)	£206
BSC (after active treatment)	£1,386

Key: BSC, best supportive care

[1] *Applied as a one-off cost at the start of the model to capture training requirements for self-administration.*

The stated dosage schedule of nemolizumab within the model aligns with the anticipated marketing authorisation and dosage within the OLYMPIA 1 & 2 trials. The schedule is as follows:

- One loading dose of 2x30 mg
- Patients <90kg: 30mg administered subcutaneously Q4W.
- Patients ≥90kg: 2x30mg administered subcutaneously Q4W.

The list price of Nemolizumab is [redacted] for the 30mg dosage. The SmPC does not indicate that a 60mg size will be available. A PAS discount of [redacted] has been submitted which brings the acquisition cost to [redacted]. Nemolizumab is available as a pen or a pre-filled syringe. There is no price difference between either preparation. Patients are assumed to self-administer nemolizumab after receiving 30 minutes of training from a hospital-based Band 6 nurse.

The loading dose is calculated as 2 x 30mg doses, or [redacted] * 2, equaling [redacted]. The loading dose is not weight specific. The cost of administration, sourced from the

PSSRU is £29,[52] Leading to a drug acquisition and administration cost of [redacted] for the loading doses.

The per cycle (or per year) acquisition cost is a weighted average based on the assumption that 30% of patients weigh ≥90kg which is sourced from the baseline characteristics of the OLYMPIA 1&2 trials. The per cycle cost is [redacted] and [redacted] for patients <90kg and ≥90kg respectively. The weighted average cost per cycle is therefore [redacted] ([redacted]*70% + [redacted]*30%).

The company have not included any stopping rules for nemolizumab nor a relative dose intensity (RDI) within the model and have assumed full compliance with the treatment regimen.

Nemolizumab is available as a pen or pre-filled syringe. Clinical advice to the EAG supports the self-administration of nemolizumab when it is prepared as a pen – stating that it carries less risk and is easier for patients.

The company have not included dispensing, home delivery or collection costs within the model for nemolizumab. Clinical advice to the EAG suggests that self-administered medications are typically delivered to the patient's home and a sharps box is collected from the patient's home approximately every 3 months. The Company have confirmed that these costs would be incurred by the company and not secondary care practice or the patient's GP.

Finally, the EAG note that the proportion of patients weighing greater than 90kg (30%) has a large impact upon the cost effectiveness results (see table 57 document B of the company submission). However, this proportion has not been included in the probabilistic sensitivity analysis (PSA). The EAG prefers all input parameters and their standard errors to be included in the PSA. Additional scenario analyses are provided in Chapter 6 to further illustrate the impact of the proportion weighing over 90KG on cost-effectiveness results.

BSC with active treatment and without active treatment

The definition of BSC, including the treatment basket and treatment strength depends on whether it is administered alongside active treatment (or placebo) in the response health state or in the non-response state. The definition is therefore dependent on whether the patient responds to nemolizumab or not at week 16. The definition of BSC with active treatment, applied in the response (maintenance) state and BSC without active treatment applied in the non-response (BSC) states differs in terms of the proportion of patients receiving antihistamines, emollients, TCS, TCI and immunosuppressant treatments. The definition of the treatment basket for BSC with or without active treatment was informed by the company's modified Delphi panel exercise and TA955.

It is assumed responders on active treatment require fewer BSC treatments than those who are not receiving active treatment (i.e. non-responders). BSC with active treatment consists of: Antihistamines (5%), Emollients (100%), TCS (20%) and TCI (30%). This BSC cost is applied to all responders regardless of model arm. BSC without active treatment is applied to non-responders (i.e. in the BSC model state). No drug administration cost is applied to BSC as it is assumed that all treatments are self-administered. Table 20 below summarises the BSC treatment basket by response status for the company base case (modified Delphi panel), by treatment arm in OLYMPIA 1&2 (response to clarification Q B4) and the EAG clinical expert in TA955 for those with moderate to severe PN.

Table 20 BSC treatment basket for company base case, OLYMPIA 1+2 and TA955 EAG clinical expert (adapted from table 44, page 157 document B of CS and table 8, page 20 of company response to CQs)

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

Key: Cyclo, Cyclosporin; MTX, Methotrexate; Nem, Nemolizumab; TCI, topical calcineurin inhibitor; TCS, topical corticosteroid

[1] Adapted from Table 4, page 35 of EAG report for TA955 to fulfill medicine categories within this appraisal (low-medium potency TCS (>50%), High or super potent TCS (>80%), Cyclosporine (~20%), Methotrexate (~50%) and antidepressants (~10%)).

The company states that the dosage and medication under each class (i.e., antihistamines, emollients, TCSs, TCIs) were determined based on TA955 and validated with UK clinical experts.[28] For BSC with active treatment, per week this includes: 7.5g of clobetasol 0.05% cream (TCS), 7.8g of protopic 0.1% ointment (TCI), 10mg QD of cetirizine (antihistamine) and 250g (or ml) of an emollient. For BSC without active treatment, per week this includes: 45g of clobetasol 0.05% cream (TCS), 30g of protopic 0.1% ointment (TCI), 10mg QD of cetirizine (antihistamine), 500g (or ml) of an emollient, 12.5mg of oral methylprednisolone and 20mg of oral methotrexate. No wastage was accounted for in the company base case. BSC dosage assumptions for each treatment class in the response and non-response states are compared alongside TA955 assumptions in Table 21.

Table 21 Dosage assumptions per week for BSC treatment basket for company base case versus TA955

Treatment	Responders	Non-responders	TA955[1]
Antihistamines	70mg	70mg	Not included
Emollients	250g/ml per week	500ml per week	NR[2]
TCS	7.5g	45g	50g
TCI	7.8g	30g	16.67g
Systemic corticosteroids	0mg	12.5mg	Not included
Immunosuppressants (MTX)	0mg	20mg (oral)	Not included

Key: MTX, methotrexate; TCI, Topical calcineurin inhibitor; TCS, topical corticosteroids
[1] Adapted from table 41, page 98 of Document B TA955 to account for treatment classes within this appraisal. Assumes 100g mild/moderate TCS every two weeks and 100g TCI every 6 weeks.
[2] Emollients are included as "Background medication" assumed to increase by a factor of 2.38 for non-responders.

Tables 20 and 21 above illustrate substantial uncertainty regarding the most appropriate treatment shares and dosages for BSC in UK clinical practice. For example, it is unclear why the company's approach to BSC has diverged from the assumptions of dosage and treatment shares in TA955. There are also substantial differences between TCS and TCI use between TA955 and the company's base case analysis informed by the modified Delphi panel. The EAG were unable to source discussions regarding dosage within the modified Delphi panel conducted by the company. The EAG has explored a scenario which uses the dosage assumptions from TA955. The company preparation assumed for TCS was also unclear within their submission, but again it would appear that there were some differences compared to TA955. TCS and TCI dosing assumptions from the current appraisal are compared to TA955 in Table 22.

Table 22 Comparison of TCS and TCI assumptions with TA955

Medication	TA955	ID6451
TCS	Assumes 50g per week of low to medium potency TCS ointments and creams. Dosage based upon BNF guidance[53] guided by the inclusion criteria for PRIME2 and PRIME trials. An average cost was calculated based upon a selection of 11 TCSs, assuming they are used in equal proportion.	7.5g for responders and 45g for non-responders per week of Clobetasol 0.05% cream. Stated sourced from TA955 and validated with clinical experts.
TCI	Assumes 100g every 6 weeks (or 16.67g per week) of Tacrolimus ointment. It is assumed that 0.03% and 0.1% are used in equal proportion and an average is taken. Based upon the following assumptions: long term use of topical medications, tacrolimus doses for atopic eczema are valid for PN, a 100g pack of topical tacrolimus delivers same number of applications as a 100g pack of TCI. Dosage information for tacrolimus on the BNF for severe atopic eczema suggests that application is 1/3 less frequent than TCS so 100g every 6 weeks was used.	Assumes 7.8g per week for responders and 30g per week for non-responders of Protopic Tacrolimus 0.1% ointment. Stated sourced from TA955 and validated with clinical experts.

Key: BNF, British national formulary; PN, prurigo nodularis; TCI, Topical calcineurin inhibitor; TCS, Topical corticosteroid

The EAG was able to match many of the company's BSC medicines with the treatment basket from TA534, an appraisal of dupilumab for atopic dermatitis.[54] The basket of emollient products was based upon the most frequently prescribed emollient products

in the prescription cost analysis data 2016 (page 199 document B of TA534). The EAG has inspected the PCA 2023/24 and identified no major differences in the use of the emollients within the basket to PCA 2016. Similarly, protopic 0.1% ointment was also assumed within TA534. Finally, the EAG was able to replicate most of the costs sourced by the company from the BNF. Where minor discrepancies were identified these have been updated in table 23. The EAG preferred per cycle (per year) treatment cost of BSC is presented in table 24. The EAG approach includes wastage, updates to unit costs where these could not be verified, and treatment baskets as described in the tables above. Given that the EAG base case analysis prefers to remove BSC costs from the model to align costs with benefits modelled, the data below are included in scenario analyses applied to both the company and EAG base case in Chapter 6.

Table 23 Summary of all BSC costs within model with EAG corrections (adapted from table 44, 45, 46 of document B and Table 2 appendix K1.2 of the company submission)

Medication	Pack size	Price	Dose per unit	Dose per week	Cost per week	Cost per cycle, no wastage	Cost per cycle, with wastage
Antihistamines							
Cetirizine	30	£0.74	10mg	70mg	£0.17	£9.00	£9.62
Emollients (average)					£3.20	£167.06	**£173.02**
Aveeno cream	500ml	£6.47	N/A	250ml/250ml	£3.24	£168.80	£174.69
Cetraben ointment	450g	£5.67	N/A	250ml/250ml	£3.15	£164.36	£164.43
Dermol cream	500g	£7.19	N/A	250ml/250ml	£3.60	£187.58	£194.13
Epaderm ointment	1kg	£13.01	N/A	250ml/250ml	£3.25	£169.71	£182.14
Hydromol ointment	500g	£5.50	N/A	250ml/250ml	£2.75	£143.49	£148.50
White soft paraffin 50%/ liquid paraffin 50% ointment	500g	£4.57-	N/A	250ml/250ml	£2.29	£119.23	£123.39
Oilatum cream	500ml	£8.29	N/A	250ml/250ml	£4.15	£216.28	£223.83
Emollients (average)					£6.40	£334.13	**£339.60**
Aveeno cream	500ml	£6.47	N/A	500ml/500ml	£6.47	£337.60	£342.91
Cetraben ointment	450g	£5.67	N/A	500ml/500ml	£6.30	£328.73	£328.86
Dermol cream	500g	£7.19	N/A	500ml/500ml	£7.19	£375.16	£381.07
Epaderm ointment	1kg	£13.01	N/A	500ml/500ml	£6.51	£339.42	£351.27

Medication	Pack size	Price	Dose per unit	Dose per week	Cost per week	Cost per cycle, no wastage	Cost per cycle, with wastage
Hydromol ointment	500g	£5.50	N/A	500ml/500ml	£5.50	£286.98	£291.50
White soft paraffin 50%/ liquid paraffin 50% ointment	500g	£4.57	N/A	500ml/500ml	£4.57	£238.46	£242.21
Oilatum cream	500ml	£8.29	N/A	500ml/500ml	£8.29	£432.56	£439.37
TCS							
Clobetasol propionate (ClobaDerm 0.05% cream)	30	£2.69	0.05%	7.5	£0.67	£35.09	£37.66
Clobetasol propionate (ClobaDerm 0.05% cream)	100	£7.90	0.05%	45	£3.56	£185.49	£189.60
Clobetasol propionate (ClobaDerm 0.05% cream)	100	£7.90	0.05%	50	£3.95	£206.11	£213.30
TCI							
Tacrolimus (Protopic) 0.1% ointment	60g	£28.10	0.10%	7.8g	£3.65	£190.61	£196.70
Tacrolimus (Protopic) 0.1% ointment	60g	£28.10	0.10%	30g	£14.05	£733.11	£758.70
Tacrolimus (Protopic) 0.1% ointment	60g	£28.10	0.10%	16.67g	£7.81	£407.36	£421.50

Medication	Pack size	Price	Dose per unit	Dose per week	Cost per week	Cost per cycle, no wastage	Cost per cycle, with wastage
Immunosuppressants							
Methotrexate	28	£1.64	2.5g	20mg	£0.47	£24.45	£24.60
Systemic corticosteroids							
Prednisolone (Company states methylprednisolone but 2.5mg size not available on BNF)	28	£3.94	2.5mg	12.5g	£0.70	£36.71	£39.40

Key: BNF, British national formulary; TCI, Topical calcineurin inhibitor; TCS, Topical corticosteroid

Table 24 Company and EAG preferred BSC per cycle cost

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

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

Disease management and monitoring costs

The health state cost for disease management and monitoring is applied to all health states and is not time variant. Similar to BSC treatment cost, it is assumed that responders (maintenance health state) would receive less Health Care Resource Use (HCRU) than non-responders (BSC health states). This is reflective of the nature of the HCRU required for PN – where HCRU is predominantly required for symptomatic management of the disease and to alleviate the "itch-scratch" cycle. The argument follows that in meeting the clinical composite outcome measure, which informs the occupancy of the maintenance health state, these patients require less HCRU.

The type and frequency of utilisation per year is informed by TA955, validated by a UK clinical expert. Unit costs were sourced from a combination of the NHS reference costs and the PSSRU to reflect the reference case. The cost includes contacts with primary care, dermatology outpatient visits, dermatology nurse visit, dermatology inpatient hospitalisation, day case, full blood counts, phototherapy and psychologist visit. Unit costs were multiplied by the frequency to generate a cost per year of £1,240 for responders (maintenance state) and £2,535 for non-responders (BSC states). The unit cost and corresponding rates is presented in table 47 of the company submission.

The EAG recognise that there is limited evidence to inform PN monitoring requirements in UK clinical practice. There is some uncertainty about whether the estimates from TA955 are generalisable to PN. For example, the frequency of day case attendances, full blood count and phototherapy are all sourced from TA534 (dupilumab for atopic dermatitis).[54]

The EAG are aware of two retrospective cohort studies which report HCRU for PN of patients diagnosed in England, however these studies may overestimate, or underestimate resource use due to diagnostic coding inconsistencies within the CPRD and HES. Further, these studies report all HCRU contacts, therefore including contacts that may not necessarily all be associated with the patient's PN. Details of the studies are provided in table 25 below. Table 26 presents the estimates of HCRU sourced from these studies. Both the company's approach and the existing literature have some limitations. The EAG therefore considers it appropriate to conduct scenario analyses to investigate the impact of these uncertainties on the ICER.

Table 25 Summary of studies reporting HCRU of patients with PN

Author	Data source	Baseline demographics	Subgroup analyses	Limitations
Bahoul et al. 2024[42]	N=8,933 patients with codes indicative of PN diagnosed between 2007-2019 within CPRD or HES (read code M1830, SNOMED 63501000, ICD-10 L28.1)	Age=61 (SD=17) % Female=57%	Mild and moderate/severe PN. Where mild defines a patient with no record of a prescription for systemic immunosuppressants or gabapentinoids.	May underestimate total HCRU due to diagnostic coding issues within the CPRD and HES. Not included patients with a record of other psychotropic medications and psychological interventions.
Morgan et al. 2023[11]	N=2,416 PN patients with first and second confirmatory diagnosis between 2008-2018 with CPRD HES linkage	Age = 61 (SD=18.4) % Female = 59.4%	None	Primary care contacts may be underestimated as diagnostic codes may not be reported for all contacts. Secondary care contacts may be overestimated as HES data does not routinely record diagnosis for outpatient visits –therefore used any visits with dermatology as a proxy.

Key: CPRD, clinical practice research database; HCRU, healthcare resource use; HES, hospital episode statistics; PN, prurigo nodularis; SD, standard deviation.

Table 26 Annual HCRU estimates from 2 retrospective cohort studies in England.

Item	Morgan et al. 2023	Bahloul et al. 2024		
		All	Mild PN	Moderate/Severe PN
Primary care contacts	14.77	14.27	11.35	21.27
Outpatient	7.64	6.68	4.87	10.72
Inpatient hospitalisation	1.30	1.07	0.66	1.75
Accident & Emergency	0.63	-	-	-

Key: PN, prurigo nodularis.

To summarise, the EAG's clinical expert agrees with the company approach and agrees that the monitoring requirements for responders would be less than those of non-responders. The EAG considers the company's approach to calculating healthcare resource use for monitoring PN patients to be uncertain, but broadly acceptable given the available data.

Adverse events

The model includes all study drug related adverse events that occurred in more than 2% of the population in the OLYMPIA 1 and OLYMPIA 2 trials. This includes atopic dermatitis, eczema nummular, neurodermatitis, dyspnea, asthma and headache (see response to clarification question B16. Table 20). The company applied a per cycle cost by adjusting the 16-week rate to an annual rate, multiplying it by the occupancy of the maintenance health state and the unit cost. The model assumes that each adverse event (apart from asthma) is resolved through one GP consultation – the cost of which is sourced from the PSSRU for a 10-minute consultation.[52] The cost of resolving asthma is £99.50. Within the model, the company assumes two 10-minute GP consultations and 1 inhaler. The type of inhaler is not described. The company states that the resource use required to resolve these adverse events is informed by

published literature with no details provided, however it has been validated by a UK clinical expert (see page 162 section B.3.5.3. of document B).

The EAG note that there remains some uncertainty about the most appropriate HCRU to manage adverse events. Costs of resolving some events may have been underestimated. Clinical advice to the EAG suggests that whilst most of the adverse events listed can be resolved with a GP, some many be recurrent and, on rare occasions, may require hospitalisation. Other events such as asthma are a chronic condition which would typically require more than one inhaler per year.

Whilst the inclusion or exclusion of adverse events has minimal impact upon the ICER, this is driven by the low rate of occurrence, restricted number of included events, low unit costs and minimal disutility applied. It would have been helpful if the company details about what healthcare resource use was required within the OLYMPIA 1 & 2 trials. This would help validate the modelling assumptions.

5 COST EFFECTIVENESS RESULTS

Section 5.1 provides the company preferred deterministic and probabilistic base case model results, including Markov cohort traces demonstrating modelled health state occupancy over time. Section 5.2 summarises sensitivity and scenario analyses completed by the company in their original submission and in their clarification queries response. Section 5.3 describes quality assurance, model validation and face validity checks conducted by both the company and EAG.

5.1 Company's base case cost effectiveness results

Markov cohort traces were not provided within the company submission but can be calculated from the economic model file. Given the EAG's concerns about the simplifying model structure assumption that a nemolizumab or BSC response cannot be regained once it is lost detailed in Section 4.2.2, it is important to consider the plausibility of the longer-term model projections. Figures 3 and 4 reproduce the Markov cohort traces from the company's preferred base case analysis (post clarification queries model) for the nemolizumab and BSC treatment arms of the model respectively. The traces show health state occupancy in the response and non-response health states, and the death state over time. The EAG note that for the BSC arm of the model, almost 100% of the cohort who are alive at any given time are in the non-response health state and remain there until death. Nemolizumab + BSC initially gain a substantial response benefit based on the OLYMPIA 1 and 2 trial results, but this wanes over time, with the treatment arm specific non-response curves converging for both modelled arms by approximately 25 years.

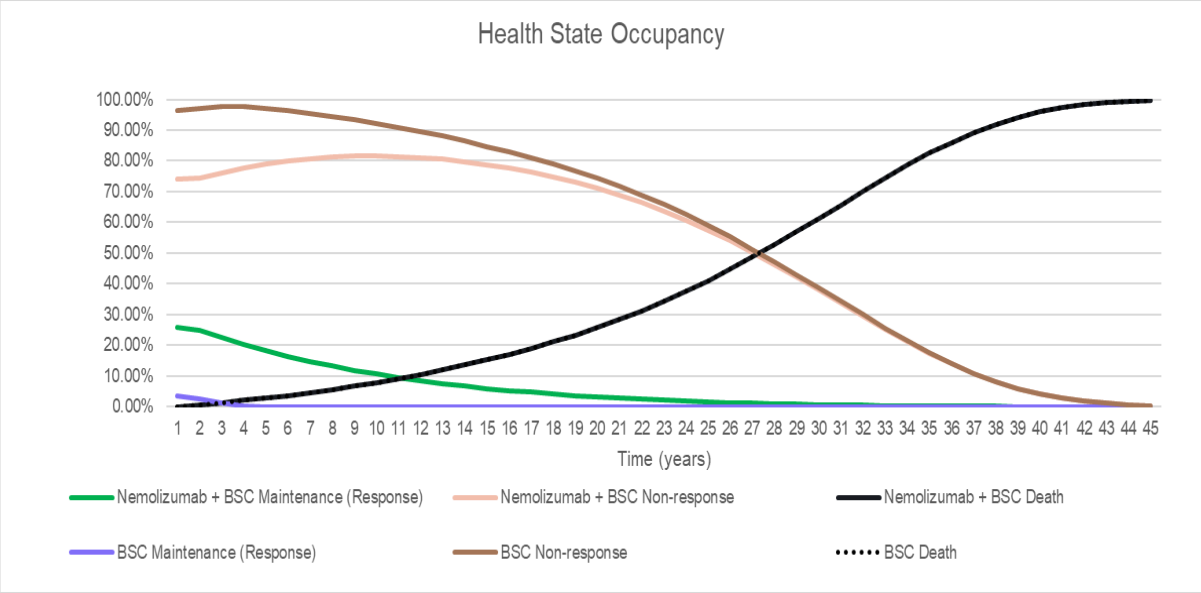

Figure 3 Company preferred Markov cohort traces

The company preferred base case analysis remained largely unchanged post clarification queries as demonstrated in Table 27 below. There were only minor amendments made by the company to their preferred base case at clarification query stage. Clinical input parameters were included as n/N as opposed to rounded, hard coded entries into the model; and updated adverse events from OLYMPIA 1 and OLYMPIA 2 were applied as opposed to from OLYMPIA 1 alone in the original company submission.

The EAG considers both changes to the company base case analysis in response to clarification queries to be appropriate. Therefore, further deterministic scenario analyses are applied to the company's preferred base case post-clarification queries.

Table 27 Comparison of company preferred base case analyses before and after clarification queries.

	Total Costs	Total QALYs	Incremental Costs	Incremental QALYs	ICER
Company original base case analysis					
Nemolizumab + BSC	[redacted]	[redacted]	[redacted]	[redacted]	£34,477
BSC	[redacted]	[redacted]	[redacted]	[redacted]	
Company base case deterministic analysis following clarification queries					
Nemolizumab + BSC	[redacted]	[redacted]	[redacted]	[redacted]	£34,523
BSC	[redacted]	[redacted]	[redacted]	[redacted]	
Company base case probabilistic analysis following clarification queries					
Nemolizumab + BSC	[redacted]	[redacted]	[redacted]	[redacted]	£34,655
BSC	[redacted]	[redacted]	[redacted]	[redacted]	

Key: BSC, best supportive care; ICER, incremental cost-effectiveness ratio; QALY, quality adjusted life years.

The results of the company conducted probabilistic analyses, applied to the updated base case post clarification queries are illustrated using scatter plots of the cost-effectiveness plane and cost-effectiveness acceptability curves (CEACs) in Figures 4 and 5 respectively.

Figure 4 Company base case probabilistic analysis post clarification queries, scatter plot of incremental costs and QALYs on the cost-effectiveness plane.

Figure 5 Company base case probabilistic analysis post clarification queries, CEACs

The EAG has reviewed the company's base case probabilistic analysis and is mostly satisfied that it has been implemented correctly and that selection of distributions for each parameter is appropriate (e.g., beta distributions for probabilities and utilities, gamma distributions for costs). However, the EAG are not satisfied that the full range of uncertainty has been captured within the PSA. The original company submission assumed that the standard error was equal to 10% of the mean for all model parameters with the exception of health state

utility values. Following clarification queries, the company updated standard errors to use data available from the OLYMPIA 1 and OLYMPIA 2 studies for clinical response parameters. The EAG welcome this update, but notes that some key areas of uncertainty, particularly around treatment acquisition costs, calculated using uncertain weight-based dosing remain set at 10% of the mean parameter estimate. Furthermore, key parameters such as treatment waning effect, and treatment discontinuation parameters over the longer term are not included in the company's probabilistic analyses. The EAG notes that there is no discussion of variation of experience in UK clinical practice within the company submission and variation in the opinion of clinical experts has not been incorporated. The EAG are therefore of the view that the probabilistic analysis does not capture the full impact of parameter uncertainty in the model.

It should be noted that the PSA does not capture uncertainty surrounding differences in EAG and company preferred structural assumptions or the inconsistency between how the model captures costs vs. benefits of BSC in non-responders, uncertainty around the most appropriate utility sources and assumptions, or issues around the composition of BSC used in the model non-response states. These issues are all addressed by the EAG in Chapter 6 through additional scenario analyses.

5.2 Company's deterministic sensitivity and scenario analyses

Tornado diagrams illustrating the impact on the ICER of increasing / decreasing key model parameters are reported in the company's response to clarification response.

As with the EAG's critique of the probabilistic sensitivity analysis, the company's deterministic analyses are useful for understanding the key parameters that drive uncertainty, but the magnitude of that uncertainty is likely better captured through scenario analyses.

The company conducted seven scenario analyses in the original submission. The scenarios explored the impact of varying the clinical response definition, including indirect costs, including AE disutilities, removing treatment waning effects, varying the nemolizumab dose between 30 and 60mg Q4W, removing excess PN mortality.

The EAG are satisfied that the company's scenario analyses are implemented within the economic model as described in the documentation and have cross checked the model

outputs. The EAG raise the following critique points regarding the appropriateness and completeness of the scenario analyses undertaken:

- *The clinical response definition is varied to include only the PN NRS ≥ 4 improvement. The related HSUVs are not updated, despite the functionality within the model to apply these. The EAG would have preferred to see the scenario with the relaxed response definition to also include the linked HSUVs.*
- *The EAG acknowledge that indirect societal costs are substantial, and that successful treatment could have a substantial impact on lost workdays and productivity. However, the EAG note that such costs are not part of the NICE reference case and should not be considered directly when calculating the most plausible preferred ICER.*
- *The EAG prefer to apply the company's scenario where adverse event disutilities are included in the base case analysis.*

A further five scenario analyses were conducted by the company in response to clarification queries, varying the response measurement time point to include week 24 data from the OLYMPIA 1 study, capping all health state utility values at general population norms, and removing/adapting BSC treatment discontinuation assumptions.

The EAG raises the following critique points about scenario analyses conducted in response to clarification queries:

- *The EAG were unable to fully replicate the results of all conducted scenario analyses as these were not provided as switches within the company's submitted economic model file. It was not possible to understand how the company implemented these scenarios. Whilst it was not possible to fully replicate results, the scenario results provided in the clarification response appear to have a good degree of face validity with directional effects on the ICER as would be expected. However, the EAG would have preferred the economic model to include the functionality to turn on / off switches to allow for full verification of the formula adaptations required to implement the scenarios and would have been useful should committee wish to see some scenarios combined with EAG adaptions to the model.*

- *The EAG does not consider the application of the general population utility cap to be a sufficient scenario to address the concern about over-estimation of health state utility values in the response state. However, the EAG does accept the company's rationale and explanation of why those values are likely to be plausible. The EAG therefore does not consider this specific scenario further.*
- *The EAG asked the company to consider several additional scenario analyses during the clarification stage which were not provided, including considering approaches to remove biases associated with including BSC costs in the non-response state, but no associated benefits. This is an important consideration and the EAG provides several scenarios in Chapter 6.*
- *The EAG notes that the company's results are sensitive to health state utility values, particularly those applied in the semi-absorbing non-response health state and the magnitude of difference between response / non-response states. The EAG notes that whilst the company provided relevant data in response to clarification queries, these were not included in scenario analyses. The EAG applies these in Chapter 6.*

The results of the scenario analyses conducted by the company are summarised in Table 28. These analyses are all applied deterministically to the company adapted base case following response to clarification queries.

Table 28 Summary of company conducted scenario analyses (applied to company preferred base case post clarification queries)

Company base case assumption	Scenario analysis assumption	Comparator	Total Costs	Total QALYs	Incremental Costs	Incremental QALYs	ICER
Company base case post clarification queries		Nemolizumab + BSC	[redacted]	[redacted]	[redacted]	[redacted]	£34,523
		BSC	[redacted]	[redacted]	[redacted]	[redacted]	
Composite response definition	Response defined as PN NRS ≥4	Nemolizumab + BSC	[redacted]	[redacted]	[redacted]	[redacted]	£35,120
		BSC	[redacted]	[redacted]	[redacted]	[redacted]	
Exclude indirect costs	Include indirect costs	Nemolizumab + BSC	[redacted]	[redacted]	[redacted]	[redacted]	£24,699
		BSC	[redacted]	[redacted]	[redacted]	[redacted]	
Exclude AE disutilities	Include AE disutilities	Nemolizumab + BSC	[redacted]	[redacted]	[redacted]	[redacted]	£34,538
		BSC	[redacted]	[redacted]	[redacted]	[redacted]	
Include Tx waning effect	Exclude Tx waning effect	Nemolizumab + BSC	[redacted]	[redacted]	[redacted]	[redacted]	£37,054
		BSC	[redacted]	[redacted]	[redacted]	[redacted]	
Weight based dosing	All receive 60mg Q4W maintenance	Nemolizumab + BSC	[redacted]	[redacted]	[redacted]	[redacted]	£54,867
		BSC	[redacted]	[redacted]	[redacted]	[redacted]	
Weight based dosing	All receive 30mg Q4W maintenance	Nemolizumab + BSC	[redacted]	[redacted]	[redacted]	[redacted]	£25,804
		BSC	[redacted]	[redacted]	[redacted]	[redacted]	
Include excess mortality for PN	Remove excess mortality for PN	Nemolizumab + BSC	[redacted]	[redacted]	[redacted]	[redacted]	£34,475
		BSC	[redacted]	[redacted]	[redacted]	[redacted]	
		Nemolizumab + BSC	[redacted]	[redacted]	[redacted]	[redacted]	£37,231

Company base case assumption	Scenario analysis assumption	Comparator	Total Costs	Total QALYs	Incremental Costs	Incremental QALYs	ICER
Response defined at week 16 (OLYMPIA 1 and 2 pooled)	Response defined at week 24 (OLYMPIA 1)	BSC	[redacted]	[redacted]	[redacted]	[redacted]	
Response defined at week 16 (OLYMPIA 1 and 2 pooled)	Response defined at week 24 (OLYMPIA 1)/ week 16 (OLYMPIA 2)	Nemolizumab + BSC	[redacted]	[redacted]	[redacted]	[redacted]	£36,731
		BSC	[redacted]	[redacted]	[redacted]	[redacted]	
Health state utility values from company data	HSUV capped at general population norms with decrements applied to all health states	Nemolizumab + BSC	[redacted]	[redacted]	[redacted]	[redacted]	£34,523
		BSC	[redacted]	[redacted]	[redacted]	[redacted]	
Include BSC treatment discontinuation	Remove BSC treatment discontinuation	Nemolizumab + BSC	[redacted]	[redacted]	[redacted]	[redacted]	£34,647
		BSC	[redacted]	[redacted]	[redacted]	[redacted]	
Include BSC treatment discontinuation	BSC tx discontinuation from OLYMPIA 1, placebo arm, week 24.	Nemolizumab + BSC	[redacted]	[redacted]	[redacted]	[redacted]	£34,400
		BSC	[redacted]	[redacted]	[redacted]	[redacted]	

Abbreviations: AE, adverse events; Tx, Treatment; BSC, best supportive care; ICER, incremental cost-effectiveness ratio; LYG, life years gained; NR, not reported; PN, prurigo nodularis; QALYs, quality-adjusted life years.

5.3 Model validation and face validity check

The EAG have quality assessed the company's submitted economic model against relevant items from the TechVer checklist.[55] By relevant items, this means that checks specific to survival analysis models have been excluded as they are not applicable to the Markov model structure applied for this appraisal. The EAG's findings are summarised in Table 29 below. Minor issues identified during the checks are described in the relevant sections of Chapter 4, and EAG suggested corrections are applied in Chapter 6 where possible.

Table 29 Model validation checklist

Test description (Please document how the test is conducted, as well)	Expected result of the test	Result
Pre-analysis calculations		
Does the technology (drug/device, etc.) acquisition costs increase with higher prices?	Yes	Yes
Does the drug acquisition cost increase for higher weight or body surface area?	Yes	Yes
Does the probability of an event, derived from an odds ratio (OR)/ relative risk (RR) / hazard ratio (HR) and baseline probability, increases with higher OR/RR/HR?	Yes	Yes. Increased SMR leads to increased occupancy of Dead health state.
Event-state calculations		
Calculate the sum of the number of patients at each health state	Should add up to the cohort size	Yes
Check if all probabilities and number of patients in a state are greater than or equal to zero	Yes	Yes
Check if all probabilities are smaller than or equal to one	Yes	Yes
Compare the number of dead (or any absorbing state) patients in a period with the number of dead (or any absorbing state) patients in the previous periods?	Should be larger	Yes
In case of lifetime horizon, check if all patients are dead at the end of the time horizon	Yes	Yes, but mortality rate hard coded to 1 at age 100
Set all utilities to one / zero	QALYs = Life years / Zero QALYs	Yes

Test description (Please document how the test is conducted, as well)	**Expected result of the test**	**Result**
Decrease all state utilities simultaneously (but keep event based utility decrements constant)	Lower utilities will be accumulated each time	N/A *No events within the model*
Set all costs to zero	No costs will be accumulated in the model at any time	Yes *Data validation in the model prohibits replacing costs to 0 removed for test*
Put mortality rates to 0	Patients never die	Yes
Put mortality rate extremely high	Patients die in the first few cycles	Yes, although mortality not considered in the decision tree.
Set the effectiveness, utility and safety related model inputs for all treatment options equal	Same life years and QALYs should be accumulated for all treatment at any time	Yes
In addition to the inputs above, set cost related model inputs for all treatment options equal	Same costs, life years and QALYs should be accumulated for all treatment at any time	Yes
Change around the effectiveness, utility and safety related model inputs between two treatment options	Accumulated life years and QALYs in the model at any time should be also reversed	Yes
Check if the number of alive patients estimated at any cycle is in line with general population life table statistics	At any given age, the % alive should be lower or equal in comparison to the general population estimate	Yes
Check if the QALY estimate at any cycle is in line with general population utility estimates	At any given age, the utility assigned in the model should be lower or equal in comparison to the general population estimate	Yes, all utility values are age and sex adjusted against UK general population norms.

Test description (Please document how the test is conducted, as well)	**Expected result of the test**	**Result**
Set the inflation rate of the previous year higher	The costs (which are based on a reference from previous years) assigned at each time will be higher	N/A
Calculate the sum of all ingoing and outgoing transition probabilities	Both should be one	Yes.
Calculate the number of patients entering and leaving a tunnel state throughout the time horizon	Numbers entering = Numbers leaving	Yes (BSC tunnel states for 3 tunnels). Note tunnel states not described in company submission.
Check if the time conversions for probabilities were conducted correctly.	Yes	Partly, some minor discrepancies in application of mortality HRs. Equal across arms, no impact on ICERs. Note treatment discontinuation rates and waning not applied prior to week 16 (decision tree phase).
Decision tree specific: calculate the sum of the expected probabilities of the terminal nodes	Should sum up to one	Yes
Increase the treatment acquisition cost	Costs accumulated at a given time will increase during the period when the treatment is administered	Yes

Test description (Please document how the test is conducted, as well)	**Expected result of the test**	**Result**
Result calculations		
Check the incremental life years and QALYs gained results. Are they in line with the comparative clinical effectiveness evidence of the treatments involved?	If a treatment is more effective, it generally results in positive incremental LYs and QALYs in comparison with the less effective treatments	Yes
Check the incremental cost results. Are they in line with the treatment costs?	If a treatment is more expensive, and if it does not have much effect on other costs, it generally results in positive incremental costs.	Yes
Total life years > total quality adjusted life years	Yes	Yes
Undiscounted results > discounted results	Yes	Partly, minor discrepancy in application of discount factor in year 1.
Divide undiscounted total QALYs by undiscounted life years.	This value should be within the outer ranges (maximum and minimum) of the all utility value inputs.	Partly. Very minor differences in life year gains up to 3 decimal places between treatment arms. Highlights potential for competing risk issues in a 1-year cycle length, particularly when transition probabilities are high in year 1. Very minor impact on ICER.

Test description (Please document how the test is conducted, as well)	**Expected result of the test**	**Result**
Subgroup analysis results: How do the outcomes change if the characteristics of the baseline change?	Better outcomes for better baseline health conditions and worse outcomes for worse health conditions are expected.	N/A, baseline health not varied in subgroup analyses.
Could you generate all the results in the report from the model (including the uncertainty analysis results)?	Yes	Yes for the company submission, though it is noted that the PSA average is not calculated as the average of all the runs in the MC simulation (N=1,000) presented. No for the company clarification response because functionality was not provided within the model to implement scenario analyses. Results appear to have face validity but could not be replicated by the EAG.
Does the total life years, QALYs and costs decrease if a shorter time horizon is selected?	Yes	Yes
Is the reporting and contextualisation of the incremental results correct?	The use of the terms such as: “dominant”/ “dominated”/ “extendedly dominated”/ “cost-effective” etc. should be in line with the results. In the incremental analysis table involving multiple treatments, ICERs should be	Yes

Test description (Please document how the test is conducted, as well)	**Expected result of the test**	**Result**
	calculated against the next non-dominated treatment.	
Are the reported ICERs in the fully incremental analysis non-decreasing?	Yes	N/A
If disentangled results are presented, do they sum up to the total results? (e.g. different cost types sum up to the total costs estimate)	Yes	Yes
Check if half cycle correction is implemented correctly (total life years with half cycle correction should be lower than without)	The half cycle correction implementation should be error free. Also check if it should be applied for all costs, for instance if a treatment is administered at the start of a cycle, half cycle correction might be unnecessary.	No. Whilst total life years without the half cycle correction is higher, the half cycle correction is applied as the current versus the future cycle for all cycles of the model from cycle 1 onwards. This leads to an underestimation in cycle 1 of the model.
Check the discounted value of costs/QALYs after 2 years	Discounted value=undiscounted/$(1+r)^2$	No, discounting factor in year 1 requires updating.
Set discount rates to zero	The discounted and undiscounted results should be the same	Yes
Set mortality rate to zero	The undiscounted total life years per patient should be equal to the length of the time horizon	Yes

Test description (Please document how the test is conducted, as well)	**Expected result of the test**	**Result**
Put the consequence of adverse event/discontinuation to zero. (zero costs and zero mortality/utility decrements)	The results would be the same as the results when AE rate is set to zero.	Yes.
Divide total undiscounted treatment acquisition costs by the average duration on treatment.	This should be similar to treatment related unit acquisition costs	Yes
Set discount rates to a higher value	Total discounted results should decrease	Yes
Set discount rates of costs/effects to an extremely high value	Total discounted results should be more or less the same as the discounted results accrued in the first cycles	Yes
Put adverse event/discontinuation rates to zero and then to extremely high level.	Less costs higher QALYS/LYs when adverse event rates are 0, higher costs and lower QALYS/LYs when AE rates are extreme	Yes
Uncertainty analysis calculations		
Are all parameters subject to uncertainty included in the one-way sensitivity analysis (OWSA)? Check if the OWSA includes any parameters associated with joint uncertainty (e.g. parts of a utility regression equation, survival curves with multiple parameters).	Yes No	No No
Check that all parameters used in the sensitivity analysis have an appropriate associated distributions.	Yes	Yes, though assumed SE sizes may not capture the full magnitude of uncertainty.

Test description (Please document how the test is conducted, as well)	**Expected result of the test**	**Result**
Check PSA output mean costs, QALYs and ICER compared to the deterministic results. Is there a large discrepancy?	No (in general)	Comparable. But it should be acknowledged that the greatest cost impacts are not run through the PSA, i.e., proportion of the population over 90kg.
If you take new PSA runs from the excel model do you get similar results?	Yes	Yes
Is(are) the CEAC line(s) in line with the CE scatter plots and the efficient frontier?	Yes	Yes
Does the PSA cloud demonstrate an unexpected behavior or has an unusual shape?	No	No
Is the sum of all CEAC lines equal to 1 for all WTP values?	Yes	Yes
Do the explored scenario analyses provide a balanced view on the structural uncertainty? (i.e. not always looking at more optimistic scenarios)	Yes	No. Structural uncertainty not considered (e.g. inability to regain response once lost, partial response not considered, generalisability of response definition, and hence treatment discontinuation, to UK clinical practice not explored).
Are the scenario analysis results plausible and in line with a priori expectations?	Yes	Yes

Test description (Please document how the test is conducted, as well)	Expected result of the test	Result
Check the correlation between 2 PSA results (i.e. costs/QALYs under the SoC and costs/QALYs under the comparator)	Should be very low (very high) if different (same) random streams are used for different arms	Correlation of 0.6. The same random number is used for all parameters and arms. The seed is then changed for the next run.
If a certain seed is used for random number generation (or previously generated random numbers are used), check if they are they scattered evenly between 0-1 when they are plotted?	Yes	Yes. Starts with seed 7 then increments towards the total number of run. Checked for a random amount of seed values.
Check if sensitivity analyses include any parameters associated with methodological/ structural uncertainty (e.g. annual discount rates, time horizon).	No	No.
Value of information analysis if applicable: Was this implemented correctly?	Yes	N/A
Did the electronic model pass the black-box tests of the previous verification stages in all PSA iterations and in all scenario analysis settings? (additional macro can be embedded to PSA code, which stops the PSA when an error such as negative transition probability, is detected)	Yes	Yes

Key: CE, cost-effectiveness; CEAC, cost-effectiveness acceptability curve; HR, hazard ratio; ICER, incremental cost-effectiveness ratio; LY, life years; OR, odds ratio; OWSA, one-way sensitivity analysis; PSA, probabilistic sensitivity analysis; QALYs, Quality adjusted life years; RR, relative risk; WTP, willingness to pay.

6 EVIDENCE REVIEW GROUP'S ADDITIONAL ANALYSES

Chapter 4 has identified several issues of remaining uncertainty and differences between EAG, and company preferred assumptions. The additional scenario analyses contributing to the EAG preferred base case are described in Table 30. This includes the impact of several minor corrections to the company's preferred model following clarification queries. A description and justification for further scenario analyses, applied to both the company and EAG preferred base case analyses is provided in Table 31.

6.1 Exploratory and sensitivity analyses undertaken by the EAG

Table 30 Summary description and justification for EAG preferred model base case assumptions

Analysis number	Parameter/ Analysis	Company base case assumptions	EAG preferred / exploratory analysis	Justification for EAG's assumption	EAG report section
Corrections to the company base case analysis					
1.	Discounting in cycle 1 (year 2 of the model)	No discounting applied to costs or QALYs	**EAG preferred scenario:** Costs and QALYs discounted by 3.5% in year 2.	Discounting should be applied at all time points beyond the first year of costs and QALYs in the model	4.2.5
2.	BSC unit costs	Unclear	**EAG preferred scenario:** EAG sourced unit costs	The EAG were unable to reproduce all of the company sourced unit costs for BSC and have therefore updated these to the most recently available drug tariff prices, as reported in the BNF	4.2.8
3.	BSC cost wastage	No wastage applied to BSC costs	**EAG preferred scenario:** Apply wastage to BSC costs	The EAG are of the view that applying wastage to BSC costs would present a more accurate account of the company's intended BSC costs in the model.	4.2.8
4.	Company base case	As per company submission	**EAG preferred scenario:** Scenarios 1-4 combined.	This is the EAG's interpretation of the company corrected base case analysis. All	5.2 & 5.3

Analysis number	Parameter/ Analysis	Company base case assumptions	EAG preferred / exploratory analysis	Justification for EAG's assumption	EAG report section
				further scenario analyses are applied to this ICER.	
SCENARIO ANALYSES APPLIED TO THE EAG CORRECTED COMPANY BASE CASE					
Health state utility values					
5.	Utility values for the response health state	Applies a 5% increase in responder HSUV from [redacted] to [redacted] beyond year 1 for the full duration of response.	**EAG preferred scenario**: Remove the 5% increase in response HSUV, relying instead on observed utility data from the OLYMPIA studies.	The EAG does not consider the 5% increase in responder utility to be evidence based because i) AD data are not generalisable to PN; ii) a 5% increase in responder utility would lead to implausibly high utilties; iii) the regression model provided by the company to support an increase in utility lacks internal and face validity	4.2.7
6.	Utility value for the non-response state	The company prefer to assume that the non-responder HSUV is equal to	**EAG preferred scenario:** Use a non-responder HSUV obtained directly from the OLYMPIA trial data for non-responders.	The company's approach may underestimate the utility amongst non-responders because patients at baseline in the trial were not in receipt of any BSC treatment. Whilst reasonable for estimating trial relative	4.2.7

Analysis number	Parameter/ Analysis	Company base case assumptions	EAG preferred / exploratory analysis	Justification for EAG's assumption	EAG report section
		the baseline utility value.		clinical effect sizes, patients may have been in a poorer health state than if they were receiving BSC treatments such as immunosuppressive therapy, TCS and TCI.	
7.	Utility value for nemolizumab non-responders	Nemolizumab non-responders are assigned a utility value equal to the average of baseline and responder for one year following a loss of response. BSC non-responders are assigned the non-response utility value.	**EAG preferred scenario:** Assume all non-responders are treated equally in the model and assigned the non-responder HSUV.	The company's approach assumes that a partial response can be achieved for nemolizumab but not for BSC. Whilst there may be some gradual reduction in HSUV for all non-responders, it is unclear whether this would be treatment specific, and if so, what the magnitude of difference between arms might be. The EAG's approach is therefore less biased given the lack of evidence in support of treatment specific HSUVs.	4.2.7

Analysis number	Parameter/ Analysis	Company base case assumptions	EAG preferred / exploratory analysis	Justification for EAG's assumption	EAG report section
8.	AE disutility	Excluded	**EAG preferred scenario:** Included	AE disutilities should be included in the economic model. Given the assumed short duration of AEs in the company's model, unless all EQ-5D utilities were collected at the exact time an adverse event was occurring, the risk of double counting is very low. Given that AE costs are included, it is also reasonable to include the corresponding utility decrements.	4.2.7
Resource use and costs					
9.	BSC costs in the non-response state.	The model includes additional costs of BSC in the non-response state in both model arms but assumes no treatment benefit	**EAG preferred scenario:** Remove all BSC costs from the non-response state of the model.	The EAG would have preferred the use of a model structure that allowed some benefit to be accrued in the non-response state. Whilst some clinical and QoL benefit is plausible, the magnitude of such benefit is unclear. Removal of treatment costs minimises bias	4.2.2 & 4.2.8

Analysis number	Parameter/ Analysis	Company base case assumptions	EAG preferred / exploratory analysis	Justification for EAG's assumption	EAG report section
		(either utility of clinical).		associated with assuming no benefits in the model.	
Probabilistic analyses parameters					
10.	Weight parameter	Excluded from the PSA	**EAG preferred scenario:** Include within the PSA	No impact on deterministic analysis but important to incorporate uncertainty around weight in the PSA.	5.2
11.	Combined scenarios 1-10 EAG preferred base case analysis				

Key: AD: atopic dermatitis; AE: adverse events; BSC: Best supportive care; EAG: external assessment group, HSUV: health state utility values; PN: prurigo nodularis; QALY: quality adjusted life years; QoL: quality of life; TCI: topical calcineurin inhibitor; TCS: topical corticosteroid

Table 31 Summary of additional scenario analyses conducted by the EAG

Analysis number	Parameter/ Analysis	Company base case assumptions	EAG preferred / exploratory analysis	Justification for EAG's assumption	EAG report section
Response parameters					
12-14.	Complete response probability	Based on week 16 data pooled across OLYMPIA1 and OLYMPIA2 studies	Apply strata adjusted effect size from: A) OLYMPIA 1 alone; B) OLYMPIA 2 alone; C) data from all 3 nemolizumab studies	The EAG scenarios demonstrate the impact of alternative data sources to populate the composite response probability in the economic model.	3.2.6 & 4.2.6
15 & 16	BSC treatment basket	Differential BSC treatment for responders and non-responders	Equalise the treatment basket for responders and non-responders based on OLYMPIA or TA955 data	The EAG's scenario analysis essentially assumes that the composition of BSC is independent of whether a response has been achieved or not, scenario may also be appropriate to align assumptions about costs and benefits in the model.	4.2.8
17	TCS and TCI dosage	Based on assumption and expert opinion	Explore use of alternative data from TA955	Exploratory analysis to determine importance of TCS and TCI dosages on the ICER	4.2.8

Analysis number	Parameter/ Analysis	Company base case assumptions	EAG preferred / exploratory analysis	Justification for EAG's assumption	EAG report section
18-20	Nemolizumab treatment discontinuation	Conditional discontinuation amongst OLYMPIA1 and OLYMPIA2 responders in the LTE study	Apply alternative definitions that increase the discontinuation rate	The discontinuation calculation is unclear, and these scenarios are intended to explore the potential range of discontinuation and its impact on the ICER. Further information from the company may help resolve these uncertainties.	4.2.6
21-30	Baseline, YR1, responder and non-responder HSUVs	As per company submission	Varying parameters amongst a range of plausible values to explore the impact of baseline utility, 1 year of partial response on results	Exploratory analyses to demonstrate the impact of increasing baseline utility and differing approaches to reduce the duration of partial response utility on results.	4.2.7

6.2 Impact on the ICER of additional clinical and economic analyses undertaken by the EAG

Table 32 reports the cumulative impact of the EAG corrections applied to the company's economic model base case analysis. The net impact of all the EAG's corrections is a small reduction in the ICER from that company submitted base case analysis. Table 33 presents the independent impact of each of the EAG's preferred scenario analyses on the ICER. These analyses are all applied to the EAG corrected base case from Table 32. The main driver of differences between the EAG and company preferred base case analyses is the magnitude of difference between response and non-response health state utility values. It should be noted that the EAG preferred base case analysis refers to analyses which the EAG were able to implement within the company's economic model. It does not, for example, consider the implication of potentially considering extending nemolizumab treatment amongst patients who may receive a partial response, as the EAG do not have access to the underlying individual participant data from the OLYMPIA studies. Table 34 presents a summary of the key analyses preferred by the company and the EAG and includes the mean results of simulations from the EAG preferred PSA. Figures 6 and 7 then illustrate the uncertainty surrounding the EAG's preferred base case scenario analysis showing a very low probability of cost-effectiveness at a willingness to pay threshold of £20,000 to £30,000 per QALY gained.

Table 32 EAG corrections, applied to the company preferred base case post clarification queries, applied cumulatively.

		Total Costs	Total QALYs	Incremental Costs	Incremental QALYs	ICER
Company preferred base case	**Nemolizumab + BSC**	[redacted]	[redacted]	[redacted]	[redacted]	**£34,523**
	BSC	[redacted]	[redacted]	[redacted]	[redacted]	
EAG correction of discount rate in cycle 1	Nemolizumab + BSC	[redacted]	[redacted]	[redacted]	[redacted]	£34,424
	BSC	[redacted]	[redacted]	[redacted]	[redacted]	
EAG updated unit costs of BSC	Nemolizumab + BSC	[redacted]	[redacted]	[redacted]	[redacted]	£34,718
	BSC	[redacted]	[redacted]	[redacted]	[redacted]	
EAG updated unit costs of BSC with wastage applied	Nemolizumab + BSC	[redacted]	[redacted]	[redacted]	[redacted]	£34,657
	BSC	[redacted]	[redacted]	[redacted]	[redacted]	
EAG corrected company base case	**Nemolizumab + BSC**	[redacted]	[redacted]	[redacted]	[redacted]	**£34,657**
	BSC	[redacted]	[redacted]	[redacted]	[redacted]	

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

Table 33 EAG's preferred model assumptions (applied independently to the EAG corrected company base case)

		Total Costs	Total QALYs	Incremental Costs	Incremental QALYs	ICER
EAG corrected company base case	**Nemolizumab + BSC**	[redacted]	[redacted]	[redacted]	[redacted]	**£34,657**
	BSC	[redacted]	[redacted]	[redacted]	[redacted]	
Remove the 5% increase in response HSUV beyond OLYMPIA trial data EQ-5D.	Nemolizumab + BSC	[redacted]	[redacted]	[redacted]	[redacted]	£38,064
	BSC	[redacted]	[redacted]	[redacted]	[redacted]	
Use a non-responder HSUV ([redacted] obtained directly from the OLYMPIA trial data.	Nemolizumab + BSC	[redacted]	[redacted]	[redacted]	[redacted]	£42,068
	BSC	[redacted]	[redacted]	[redacted]	[redacted]	
Remove nemolizumab partial response utility from the non-response state.	Nemolizumab + BSC	[redacted]	[redacted]	[redacted]	[redacted]	£41,495
	BSC	[redacted]	[redacted]	[redacted]	[redacted]	
Include AE disutility	Nemolizumab + BSC	[redacted]	[redacted]	[redacted]	[redacted]	£34,672
	BSC	[redacted]	[redacted]	[redacted]	[redacted]	
Remove all BSC costs from the non-response state of the model.	Nemolizumab + BSC	[redacted]	[redacted]	[redacted]	[redacted]	£37,038
	BSC	[redacted]	[redacted]	[redacted]	[redacted]	
EAG preferred base case	**Nemolizumab + BSC**	[redacted]	[redacted]	[redacted]	[redacted]	**£90,712**
	BSC	[redacted]	[redacted]	[redacted]	[redacted]	

Key: AE, adverse event; BSC, best supportive care; HSUV, health state utility value; ICER, incremental cost-effectiveness ratio; QALY, quality adjusted life year.

Table 34 Summary of company and EAG preferred analyses

		Total Costs	Total QALYs	Incremental Costs	Incremental QALYs	ICER
Company base case	Nemolizumab + BSC	[redacted]	[redacted]	[redacted]	[redacted]	£34,523
	BSC	[redacted]	[redacted]	[redacted]	[redacted]	
Company corrected base case	Nemolizumab + BSC	[redacted]	[redacted]	[redacted]	[redacted]	£34,657
	BSC	[redacted]	[redacted]	[redacted]	[redacted]	
EAG preferred deterministic base case	Nemolizumab + BSC	[redacted]	[redacted]	[redacted]	[redacted]	£90,712
	BSC	[redacted]	[redacted]	[redacted]	[redacted]	
EAG preferred probabilistic base case	Nemolizumab + BSC	[redacted]	[redacted]	[redacted]	[redacted]	£89,990
	BSC	[redacted]	[redacted]	[redacted]	[redacted]	

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

Figure 6 Incremental cost-effectiveness plane of the EAG preferred base case

Figure 7 Cost-effectiveness acceptability curves for the EAG preferred base case

Table 35 Additional scenario analyses conducted by the EAG, applied independently to the EAG corrected company base case analysis

		Total Costs	Total QALYs	Incremental Costs	Incremental QALYs	ICER
Company corrected base case	**Nemolizumab + BSC**	[redacted]	[redacted]	[redacted]	[redacted]	**£34,657**
	BSC	[redacted]	[redacted]	[redacted]	[redacted]	
Strata adjusted effect size from: A) OLYMPIA 1 alone	Nemolizumab + BSC	[redacted]	[redacted]	[redacted]	[redacted]	£35,006
	BSC	[redacted]	[redacted]	[redacted]	[redacted]	
Strata adjusted effect size from: B) OLYMPIA 2 alone	Nemolizumab + BSC	[redacted]	[redacted]	[redacted]	[redacted]	£34,632
	BSC	[redacted]	[redacted]	[redacted]	[redacted]	
Strata adjusted effect size from: all 3 nemolizumab studies	Nemolizumab + BSC	[redacted]	[redacted]	[redacted]	[redacted]	£34,591
	BSC	[redacted]	[redacted]	[redacted]	[redacted]	
Equalise the treatment basket for responders and non-responders: Olympia 1 & 2 treatment basket	Nemolizumab + BSC	[redacted]	[redacted]	[redacted]	[redacted]	£35,361
	BSC	[redacted]	[redacted]	[redacted]	[redacted]	
Equalise the treatment basket for responders and non-responders: TA955 EAG clinical expert treatment basket	Nemolizumab + BSC	[redacted]	[redacted]	[redacted]	[redacted]	£36,314
	BSC	[redacted]	[redacted]	[redacted]	[redacted]	
TCI dose 16.67g for all + TCS dose of 50g for all	Nemolizumab + BSC	[redacted]	[redacted]	[redacted]	[redacted]	£35,578
	BSC	[redacted]	[redacted]	[redacted]	[redacted]	

		Total Costs	Total QALYs	Incremental Costs	Incremental QALYs	ICER
Nemolizumab discontinuation = [redacted] Total who discontinued from the LTE study)	Nemolizumab + BSC	[redacted]	[redacted]	[redacted]	[redacted]	£35,443
	BSC	[redacted]	[redacted]	[redacted]	[redacted]	
Nemolizumab discontinuation = [redacted] Total randomised for Olympia with a response that discontinued from LTE)	Nemolizumab + BSC	[redacted]	[redacted]	[redacted]	[redacted]	£34,721
	BSC	[redacted]	[redacted]	[redacted]	[redacted]	
Remove BSC discontinuation	Nemolizumab + BSC	[redacted]	[redacted]	[redacted]	[redacted]	£34,781
	BSC	[redacted]	[redacted]	[redacted]	[redacted]	
Baseline utility = [redacted] (NR utility at week 16)	Nemolizumab + BSC	[redacted]	[redacted]	[redacted]	[redacted]	£58,885
	BSC	[redacted]	[redacted]	[redacted]	[redacted]	
Baseline utility = [redacted] (BSC NR utility at week 16)	Nemolizumab + BSC	[redacted]	[redacted]	[redacted]	[redacted]	£44,755
	BSC	[redacted]	[redacted]	[redacted]	[redacted]	
Nemolizumab NR Y1 utility (Baseline+[redacted]) not applied to BSC Y1	Nemolizumab + BSC	[redacted]	[redacted]	[redacted]	[redacted]	£37,175
	BSC	[redacted]	[redacted]	[redacted]	[redacted]	
Remove NR utility benefit in Y1	Nemolizumab + BSC	[redacted]	[redacted]	[redacted]	[redacted]	£41,495
	BSC	[redacted]	[redacted]	[redacted]	[redacted]	
	Nemolizumab + BSC	[redacted]	[redacted]	[redacted]	[redacted]	£69,446

		Total Costs	Total QALYs	Incremental Costs	Incremental QALYs	ICER
Remove 5% increase to long term responder + Baseline utility [redacted] (NR utility at week 16)	BSC	[redacted]	[redacted]	[redacted]	[redacted]	
Remove 5% increase to long term responder + Baseline utility = [redacted] (BSC NR utility at week 16)	Nemolizumab + BSC	[redacted]	[redacted]	[redacted]	[redacted]	£50,604
	BSC	[redacted]	[redacted]	[redacted]	[redacted]	
NR Y1: Nemolizumab: [redacted] for intervention from week 9-24. BSC(placebo) [redacted] from week 9-24. Weighted average of both [redacted] for the rest of the year.	Nemolizumab + BSC	[redacted]	[redacted]	[redacted]	[redacted]	£40,040
	BSC	[redacted]	[redacted]	[redacted]	[redacted]	
Remove 5% increase to long term responder + NR Y1: Nemolizumab: [redacted] for intervention from week 9-24. BSC(placebo) [redacted] from week 9-24. Weighted average of both [redacted] for the rest of the year.	Nemolizumab + BSC	[redacted]	[redacted]	[redacted]	[redacted]	£44,658
	BSC	[redacted]	[redacted]	[redacted]	[redacted]	
Remove 5% increase to long term responder + Baseline utility = [redacted] (BSC NR utility at week 16) + NR Y1: Nemolizumab: [redacted] for	Nemolizumab + BSC	[redacted]	[redacted]	[redacted]	[redacted]	£57,489
	BSC	[redacted]	[redacted]	[redacted]	[redacted]	

		Total Costs	Total QALYs	Incremental Costs	Incremental QALYs	ICER
intervention from week 9-24. BSC(placebo) [redacted] from week 9-24. Weighted average of both [redacted] for the rest of the year.						

Key: BSC, best supportive care; ICER, incremental cost-effectiveness ratio; LTE, long-term effectiveness; NR, non-response; QALY, quality adjusted life years.

Table 36 Additional scenario analyses conducted by the EAG, applied independently to the EAG preferred base case analysis

		Total Costs	Total QALYs	Incremental Costs	Incremental QALYs	ICER
EAG preferred base case	**Nemolizumab + BSC**	[redacted]	[redacted]	[redacted]	[redacted]	**£90,712**
	BSC	[redacted]	[redacted]	[redacted]	[redacted]	
Strata adjusted effect size from: A) OLYMPIA 1 alone	Nemolizumab + BSC	[redacted]	[redacted]	[redacted]	[redacted]	£98,078
	BSC	[redacted]	[redacted]	[redacted]	[redacted]	
Strata adjusted effect size from: B) OLYMPIA 2 alone	Nemolizumab + BSC	[redacted]	[redacted]	[redacted]	[redacted]	£88,080
	BSC	[redacted]	[redacted]	[redacted]	[redacted]	
Strata adjusted effect size from: all 3 nemolizumab studies	Nemolizumab + BSC	[redacted]	[redacted]	[redacted]	[redacted]	£90,978
	BSC	[redacted]	[redacted]	[redacted]	[redacted]	
Nemolizumab discontinuation = [redacted], Total who discontinued from the LTE study)	Nemolizumab + BSC	[redacted]	[redacted]	[redacted]	[redacted]	£101,206
	BSC	[redacted]	[redacted]	[redacted]	[redacted]	
Nemolizumab discontinuation = [redacted], Total randomised for Olympia with a response that discontinued from LTE)	Nemolizumab + BSC	[redacted]	[redacted]	[redacted]	[redacted]	£91,648
	BSC	[redacted]	[redacted]	[redacted]	[redacted]	
Remove BSC discontinuation	Nemolizumab + BSC	[redacted]	[redacted]	[redacted]	[redacted]	£91,074
	BSC	[redacted]	[redacted]	[redacted]	[redacted]	

		Total Costs	Total QALYs	Incremental Costs	Incremental QALYs	ICER
Turn off Half cycle correction	Nemolizumab + BSC	[redacted]	[redacted]	[redacted]	[redacted]	£90,421
	BSC	[redacted]	[redacted]	[redacted]	[redacted]	
Baseline utility [redacted] (NR utility at week 16)	Nemolizumab + BSC	[redacted]	[redacted]	[redacted]	[redacted]	£90,712
	BSC	[redacted]	[redacted]	[redacted]	[redacted]	
Baseline utility = [redacted] (BSC NR utility at week 16)	Nemolizumab + BSC	[redacted]	[redacted]	[redacted]	[redacted]	£90,712
	BSC	[redacted]	[redacted]	[redacted]	[redacted]	
NR Y1: Nemolizumab: [redacted] for intervention from week 9-24. BSC (placebo) [redacted] from week 9-24. Weighted average of both [redacted] thereafter	Nemolizumab + BSC	[redacted]	[redacted]	[redacted]	[redacted]	£83,856
	BSC	[redacted]	[redacted]	[redacted]	[redacted]	

Key: BSC, best supportive care; ICER, incremental cost-effectiveness ratio; LTE, long-term effectiveness; NR, non-response; QALY, quality adjusted life years;

6.3 Conclusions of the cost effectiveness section

The economic modelling results are most sensitive to assumptions about the treatment acquisition cost for nemolizumab (i.e. the proportion of the treated population <90kg achieving the lower 30mg Q4W dose), the magnitude of utility gain for responders compared to non-responders, and the most appropriate costing approach for BSC given the model structural limitations that prevent a QALY gain in the BSC non-response state.

The EAG consider several areas of uncertainty remain, including whether the modelling approach taken is generalisable to UK clinical practice. The EAG would appreciate further engagement with clinical experts about whether treatment would be discontinued in patients failing to achieve a composite response, even if the treatment was providing some symptomatic relief and improvement in quality of life. This could be included by considering a partial response health state in the model, defined appropriately based on clinical and patient opinion. Such a partial response health state could also be used to allow some modelled benefits for BSC treatments also addressing the EAG's main concern around bias of including BSC costs with no assumed benefit.

The EAG and company base case preferences also diverge in terms of the magnitude of difference in QALY gains between response and non-response health states. The EAG prefers to rely on the observed EQ-5D data from the OLYMPIA studies where possible as opposed to applying assumptions, and the EAG prefers that treatment specific utilities in the non-response state for one year post nemolizumab discontinuation are removed.

7 Severity weighting

Severity weighting does not apply to this appraisal.

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Single Technology Appraisal

Nemolizumab for treating prurigo nodularis [ID6451]

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 the end of **17 December 2024** 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 information that is submitted as [redacted] should be highlighted in turquoise and all information submitted as '[redacted]' in pink.

Issue 1 Errors

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Section 1.5, page xvii 'The company preferred analysis includes three key assumptions that may over-estimate the magnitude of QALY gains for responders compared to non-responders'	'The company' should be updated to 'The company's'	Typographical error	Accepted.
Section 2.2, page 1 'The primary symptom of PN is frequent severe and persistent itching that is often painful, causes a constant urge to scratch.'	The word 'and' is missing; therefore, the text should be amended to 'The primary symptom of PN is frequent, severe and persistent itching that is often painful and causes a constant urge to scratch.'	Typographical error	Accepted.
Section 2.2, page 2 'An IGA scale of 3 denotes moderate disease'	This should be updated to 'An IGA score of 3'	Typographical error	Accepted.
Section 2.2, page 4	'Any' should not have a capitalised 'A'	Typographical error	Accepted.

‘The company states that Any use of TCSs or TCIs should aim to be tapered and subsequently discontinued when the disease has sufficiently improved’			
Section 2.3, page 8, table 3 The outcome measures to be considered include: • Measures of disease severity • Measures of symptom control including improvement in itch • Adverse effects of treatment HRQoL	In the outcomes row, ‘HRQoL’ should be bullet-pointed	Typographical error	Accepted.
Section 3.2.1, page 12 ‘neomlizumab’ Section 4.2.2, page 44 ‘Nnmolizumab’	Text should be amended to ‘nemolizumab’	Typographical error	Accepted.

Section 3.2.1, page 18, table 6 ‘moisturizers’	Should be written as ‘moisturisers’ as per UK English spelling	Typographical error	Accepted.

Section 3.2, page 20, table 7 – Row ‘Height (cm) at baseline’; ‘N=507’ Section 4.2.6, ‘Treatment discontinuation’ Section 4.2.7, pages 57 & 62 ‘N’ numbers in these sections are incorrectly capitalised	Instances of ‘N=x’ should be changed to ‘n=x’, as subsections of the study populations are being referred to rather than the full study population	Typographical error	Accepted.

Section 3.2, page 20, table 7 Section 3.2.4, page 29, table 9 Section 3.2.4, page 31, table 10 Inconsistency in reporting of SD; either missing, or not reported to 1 decimal place consistently	Where data equals zero, corresponding SD data is either missing, or not presented to one decimal place consistently Table 7, rows: 'Not reported', 'Hawaiian or Other Pacific Islander', 'Smoking status – missing', 'IGA category – missing', 'Pain frequency – missing', 'Prurigo Activity Score item 5a – 0%', 'Prurigo Activity Score item 5a – missing', 'Prurigo Activity Score item 5b – missing' Table 9, rows – 'Elevated ALT or AST (>3 x ULN) in combination with elevated bilirubin', 'TEAE related to study drug leading to death' Table 10, rows – 'Psychiatric disorders', 'Dyspnoea', 'Dermatitis atopic', 'Pruritus', 'Vascular disorders'	Omission of data	Accepted.

Section 3.2.1, page 25, table 8	Row 'Time since PN diagnosis (months)' is not sufficiently large to display all data in each cell in this row	Formatting error in table	Accepted.
Section 3.3, page 37 '…the rest of the network as they appear in only a single trial.'	Text should be amended to 'single arm trial'	Typographical omission	Not a mistake or omission. NCT0050783 is not a single-arm trial as it compares two interventions (Appendix D, Table 7). It is the only trial that is disconnected from the rest of the network.
Section 4.2.2, page 41, 'Microsoft excel ®'	Text should be amended to 'Microsoft Excel®'	Typographical error	Accepted.
Section 4.2.2, page 41 'The key clinical parameter underpinning the economic model is the probability of achieving a composite treatment response (nodule reduction of ≥ 4 PP NRS compared to baseline, and itch improvement, measured as an IGA score of 0 or 1 , with an improvement of ≥ 2 points from baseline)' Section 4.2.6, page 49	The text should be amended to reflect that nodule reduction is measured using IGA and itch improvement is measured using PP NRS	Nodule reduction is measured using the IGA scale, and itch reduction is measured using the PP NRS scale. The scales reflecting each clinical endpoint are incorrect on these two occasions	Accepted.

'The key clinical parameter underpinning the economic model is the probability of achieving a composite treatment response (nodule reduction of ≥ 4 PP NRS compared to baseline, and itch improvement, measured as an IGA score of 0 or 1 , with an improvement of ≥ 2 points from baseline)'			
Section 4.2.2, page 42 'The three BSC non-response tunnel states were not described in the company submission. The main purpose of these tunnel states appears to be to allow the company to apply a utility gain in the non-response state for nemolizumab for the first year following treatment discontinuation.'	Text should be amended to 'The main purpose of these tunnel states appears to be to allow the company to apply a utility gain in the non-response state for nemolizumab for the first year following treatment discontinuation.'	Tunnel health states were introduced only to account for differences in non-responder utility values for nemolizumab versus BSC in year 1. The difference in utility values for non-responders in year 1 was clearly described in the Company submission (Section B.3.4.3); therefore, the text should be amended accordingly.	The text has been amended to further clarify that the EAG is specifically referring to the model structure section of the submission.
Section 4.2.3, page 46, table 14	'47%' should be amended to '37%'	Typographical error	Accepted.

'(175cm x 47%) + (162cm x 63%)'			
Section 4.2.4, page 47 'The company's model assumes that there will not be any increases in nemolizumab dosage for non-responders. The EAG's clinical expert advises that some clinicians may wish to retain the option for dose escalation in some patients, especially if some quality-of-life benefit was observed at the lower dose. Any further dose increases in clinical practice would increase the treatment acquisition costs for nemolizumab'	This text should be deleted based on factual accuracy	Firstly, in the economic model non-responders to nemolizumab discontinue treatment. Therefore, it would not be feasible for non-responders to increase their nemolizumab dose as they will not be receiving nemolizumab treatment at all. Secondly, the dose for nemolizumab is dependent on patients' weight and not their response to treatment. This is supported by the expected regulatory label and draft SmPC shared in the Company Submission. Overall, this statement should be deleted as it does not align with how nemolizumab would be used in UK clinical	Accepted.

		practice and contradicts the draft SmPC.	
Section 4.2.5, page 48 'However, the EAG noted a minor error in the discounting approach taken by the company, where costs and QALYs in cycle 1 (i.e. months 12-24) are discounted by two time periods (years).'	Text should be amended to 'However, the EAG noted the discounting approach taken by the company, where costs and QALYs in cycle 1 (i.e. months 12-24) are discounted by two time periods (years).'	The approach used for discounting in the model is based on Severens et al., 2004, where in the formula, the power should be t instead of the suggested 't - 1'. Therefore, Galderma does not consider the approach to be an error, and the text should be updated to reflect this.	Not a factual inaccuracy. The discounting approach taken in the economic model lacks consistency. For example, cycle 0 is not discounted, but cycle 1 is discounted by 2 time periods. The EAG prefers a more continuous approach to discounting that assumes costs and QALYs are incurred during the cycle rather than at the end of cycle 1 but at the beginning of cycle 0.
Section 4.2.6 page 54. (373*.2601)"	Text should be amended to '(373*0.2601)'	Typographical error	Accepted.
Section 4.2.6, page 52, table 16 'IGA, Investigator' Global Assessment'	Should read 'Investigator's Global Assessment'	Typographical error	Accepted.
Section 4.2.6, page 55 'The company preferred treatment waning assumptions are detailed in	First line should be replaced with 'The company's preferred treatment…'	Typographical error	Accepted.

Table 37 of the company submission and have been validated by UK clinical experts'			
Section 4.2.6, page 56 'The net impact of uncertainty around treatment discontinuation and treatment effect waning parameters on the ICER is unclear and will depend on committee's preferences for other model parameters such as the difference between response and non-response health state utility values	The text should be amended to '…the ICER is unclear and will depend on the committee's preferences…'	Typographical error	Accepted.
Section 4.2.7, page 59, table 17 Section 4.2.7, page 62 Section 4.2.7, page 64 Section 4.2.7, page 67 (four instances) Section 4.2.8, page 71 & 72 (table 20)	Key pivotal trial written as 'Olympia' rather than 'OLYMPIA'	Typographical error	Accepted throughout the report.

Section 4.2.8, page 83 (three instances) Section 5.2, page 91 & 92, table 28 (five instances) Section 6.2, page 117, table 35 Section 6.2, page 121, table 36 (two instances)			
Section 4.2.7, page 63, 64 'realize'; 'realizes'	Should be written as 'realise' and 'realises', respectively, as per UK English spelling	Typographical error	Accepted.
Section 4.2.7, page 64 'Within the Olympia trials designs, participants must meet eligibility criteria and undergo an up to 4-week screening period prior to baseline'	An apostrophe should be added, i.e. trials' designs	Typographical error	Accepted.
Section 4.2.7, page 64 'The baseline index utility score is therefore reflective of a PN population which is not receiving BSC treatment and is likely to be	This text should be deleted as there is no evidence to support that baseline utility is 'substantially lower' than	In the absence of long-term utility values for non-responders with PN, it cannot be assumed that non-responders would have	Not a factual inaccuracy. The EAG's statement is supported by the available evidence from the trial data, which clearly shows higher utility amongst non-responders compared to baseline values.

substantially lower than the average utility experienced by BSC non-responders who have not achieved the high bar composite response required to be classed as “responders” in the economic model’	long-term utility for non-responders.	a long-term utility value substantially higher than baseline. The utility value for non-responders returning to baseline was validated by a UK clinical expert and is in line with the Committee’s preferred approach in TA955. Therefore, this text should be deleted as there is no clinical evidence to support the assumption, and it contradicts both UK clinical expert opinion and the Committee conclusions from TA955.	
Section 4.2.8, page 71 ‘proportion of patients receiving antihistamines, emollients, TSC, TCI and immunosuppressant treatments’	‘TSC’ should read ‘TCS’	Typographical error	Accepted.

Section 4.2.8, page 80 'utilization'; 'hospitalization' Section 4.2.8, page 82, table 26 'hospitalization'	US English spelling used rather than UK; should be 'utilisation' and 'hospitalisation'	Typographical error	Accepted.
Section 4.2.8, page 81, table 25 'Mild and moderate/severe PN. Where Mild defines a patient with no record of a prescription for systemic immunosuppressants or gabapentinoids.'	Second usage of 'Mild' is unnecessarily capitalised; should read 'mild'	Typographical error	Accepted.
Section 5.2, page 89 'The company conducted seven scenario analyses in the original company.'	Sentence should end 'in the original company submission.'	Typographical error	Accepted.
Section 5.2, page 89 'The EAG acknowledge that indirect societal costs are substantial, and that successful treatment could have a substantial impact on	End of the sentence should read '…substantial impact on lost workdays and productivity'	Typographical error	Accepted.

lost days and work and lost productivity’			
Section 5.3, page 98, table 29 ‘contextualization’	Should be written as ‘contextualisation’ as per UK English spelling	Typographical error	Accepted. Please note that this table was lifted directly from the published TECH-VER checklist. Accessible here: https://github.com/nasuhcagdas/TECHVER
Section 5.2, page 91, table 28 ‘Include tx waning effect’ ‘Exclude tx waning effect’	‘T’ should be capitalised in ‘Tx’, and this should be added to the abbreviations list	Typographical error and omission from abbreviations footnote	Accepted.
Section 5.3, page 101, table 29 ‘Are the explored scenario analyses provide a balanced view on the structural uncertainty?’	Text should be amended to ‘Do the explored scenario analyses provide a balanced view on the structural uncertainty?’	Grammatical error	Accepted.
Section 6.1, page 108, table 30 ‘minimizes’	Should be written as ‘minimises’ as per UK English spelling	Typographical error	Accepted.

Section 6.2, page 111 '…the EAG do not have access to the underlying IPD data from the OLYMPIA studies'	'IPD' should be written out in full as 'individual participant data', as this abbreviation is not used elsewhere in the report, also by doing so it removes the implied repetition of the word 'data', (i.e., individual participant data data)	Typographical error	Accepted.

Issue 2 Clarifications

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Section 1.1, page xii 'The company prefer to assume that the non-responder HSUV is equal to the baseline utility value' Section 4.2.7, page 64 'The company use observed response utility data for the response model states [redacted] but apply the baseline value [redacted] to all non-responders, rather than the pooled non-response utility value observed in the OLYMPIA studies [redacted]'	Relevant sections discussing the utility value for non-responders should make clear that Company approach is in line with approach used in TA955 that was considered appropriate for decision making by the Committee and has been further validated by a UK clinical expert and a UK health economic expert.	The assumption for utility for non-responders to return to baseline is in line with the approach used in TA955, where the committee concluded that the utility value for non-responders returning to baseline was appropriate for decision making. Furthermore, the assumption for the utility value for non-responders to return to baseline was validated by a UK clinical expert and a UK health economic expert as representative of UK clinical practice. Therefore, it should be made clear in the text that the approach for non-responder utility returning to baseline has been validated by a UK clinical expert and is in line with the Committee's conclusions from TA955.	This is not a factual inaccuracy; therefore, no amendment is needed. This particular issue does not appear to have been addressed in detail in the FAD for TA955. The EAG retains the points of critique raised in the EAG report. Please note the EAG has identified a typographical error in the quoted text and consequently have replaced [redacted] with [redacted] on page 64 of the report which has now been corrected.

Section 1.1, page xiii 'The EAG would have preferred to model the benefits of BSC treatment alongside costs, but in the absence of any data to inform that analysis, the EAG prefers to exclude BSC costs from the model to minimise bias' Section 4.2.7, page 64 and 65 'the EAG clinical expert is of the view that these BSC treatments do provide some symptomatic relief, in particular to the itch component of PN, even if they might not lead to achievement of the composite outcome used for response definition' 'the EAG prefers the use of non-response health state utility values observed in the trial [redacted] rather than assuming the baseline utility value [redacted] in the economic model.'	In the EAG's preferred analysis, the approach to both increase the health state utility for non-responders and exclude costs of BSC is contradictory. Therefore, the EAG's preferred analysis should be updated to focus on only one of these points.	In the EAG's preferred analysis, the utility values for non-responders have been significantly increased from [redacted] to [redacted], with the EAG stating that BSC would provide symptomatic relief even if patients do not achieve composite response. However, in addition to the increase in utility in the EAG's preferred analysis, the cost of BSC treatment for non-responders has been removed due to the EAG not considering there to be clinical or quality of life benefit modelled for non-responders on BSC. Therefore, the EAG's preferred analysis has included a quality of life benefit for non-responders based on BSC treatment but also removed the cost of BSC treatment for non-responders stating no quality of life benefit has been modelled. This approach is inappropriately biased against nemolizumab and should therefore be amended.	This is not a factual inaccuracy; therefore, no amendment is needed. The non-response utility used by the EAG reflects the BSC treatments allowed within the trial, which were heavily restricted whilst on treatment. As a result, the non-response HSUV likely represents the utility associated with minimal BSC. Further increasing the intensity of BSC following a loss of response could reasonably be assumed to provide a treatment benefit that is not captured in the economic model (beyond the utility value of [redacted]).

			The EAG's preferred scenario of removing BSC costs and increasing the non-response utility value is a plausible combination of assumptions for the Committee's consideration. Consequently, the EAG has not revised our base case assumptions.
Section 1.1, page xiii 'the company's economic model structure assumes that treatment non-responders incur additional BSC costs, but that there is no potential for clinical or quality of life benefit of these treatments' Section 1.5, page XV 'The company's economic model assumes that patients will discontinue treatment once a composite response has been lost. This may not reflect real world use of	Relevant sections discussing the model structure should make it clear that the model structure is in line with model structure from TA955, which was considered appropriate for decision making by the Committee and has been further validated by both a UK clinical expert and a UK health economic expert.	The model structure in the Company submission is aligned with the model structure used in TA955. Both model structures assume that patients discontinue treatment once a composite response has been lost, and do not include a partial response health state. In TA955, the NICE Committee concluded that the model structure was acceptable for decision making. Furthermore, the model structure was validated by both a UK clinical expert and a UK health economic expert during the submission development.	Not a factual inaccuracy; therefore, no amendments have been made to Section 1. However, Section 4.2.2 is updated to acknowledge that the model structure was informed by TA955.

nemolizumab in UK clinical practice where clinicians and patients may wish to continue treatment if an improvement in symptoms can be achieved' Section 4.2.2, page 42 'Those who do not achieve a response by week 16 also enter the semi-absorbing non-response BSC states, where they remain until they die. It is not possible to regain a response in the model once it is lost, regardless of the intensity of BSC treatment provided in the non-response BSC states'		Therefore, when discussing the model structure, context should be provided that it is in line with UK clinical expert opinion and the Committee's conclusions from TA955.	
Section 1.1, page xiii 'The company's economic model structure assumes that treatment non-responders incur additional BSC costs, but that there is no potential for clinical or quality of life benefit of these treatments' Section 1.5, page xvi	Relevant sections discussing the potential treatment benefits of more intensive BSC should be updated to also consider the treatment limitations of more intensive BSC	The more intensive BSC treatments, such as immunosuppressants, carry notable risks and issues with their usage. Even at low doses, methotrexate can be associated with significant side effects such as gastrointestinal manifestations and severe adverse events such as hepatotoxicity, pulmonary toxicity, myelosuppression, and	The EAG thanks the company for the clarification and accepts that the exclusion of BSC adverse events may have led to a slight underestimation of the cost and QALY impact of AEs. However, the EAG notes that AEs are not a major driver of the ICER

‘The proportion of the cohort in the “non-response” state, who fail to achieve a composite response, who discontinue treatment or who lose a composite response incur an increase in costs of intensive BSC management, but no clinical or quality of life benefit is modelled. This is an important issue as it creates a bias because non-responders remain on treatment for their remaining lifetime without benefit.’ ‘The company’s assumption likely creates a bias in favour of nemolizumab by under-estimating the benefits or over-estimating the costs in the non-response BSC arm of the model.’ Section 4.2.2, page 44-45 ‘Furthermore, no clinical treatment benefit is modelled for intensive BSC (TCS, TCI, immunosuppressants). Any under-estimation of treatment		nephrotoxicity, which require regular blood monitoring. When discussing the potential bias of not including potential clinical and quality of life benefit of these more intensive BSC treatments, the clinical and quality of life limitations of these treatments should also be discussed. Based on both the potential clinical benefits and limitations of more intensive BSC that are excluded from the model, it cannot be concluded that the approach introduces bias in favour of nemolizumab. The cost of BSC to the NHS is a certainty, whereas there is significant uncertainty regarding the clinical benefits and limitations of these treatments for patients who have not responded to treatment. Therefore, the assumption to remove modelling costs of BSC should be considered to be increasing bias against	in the economic model. The magnitude of impact on costs and utilities is unknown as the company have not provided detailed adverse event information for a more intensive definition of BSC. Any bias is likely to be small in magnitude and would not materially impact on the EAG base case conclusions. The EAG’s primary concern relates to the lack of consistency between treatment costs and modelled health benefits.

benefit from a more intensive BSC treatment regimen in the non-response state is likely to generate a potentially substantial bias in favour of nemolizumab'		nemolizumab rather than decreasing bias.	
Section 1.5, page xvii 'B) Assuming that nemolizumab non-responders are partial responders and therefore receive a utility benefit in the nemolizumab non-response state, calculated as the average of baseline and response utility'	This statement should be amended to read 'B) Assuming that nemolizumab non-responders are partial responders and therefore receive a utility benefit in the nemolizumab non-response state the first year following loss of response, calculated as the average of baseline and response utility'	The increased utility in the nemolizumab arm versus the BSC arm is only applied in the first year following loss of response. This must be made clear in the text and throughout the document to avoid implying that the utility benefit is applied throughout the entire time horizon.	Accepted.
Section 2.2, page 2 'Overexpression of cytokine interleukin-31 (IL-31) is associated with neuroimmune responses that promote the sensation of intense itching. This promotes a scratching response (either voluntary or involuntary), known as the itch-scratch cycle'	It should be added that the process of scratching itself also increases the release of IL-31 in the skin, which in turn induces further itching and subsequent scratching, which completes the 'itch-scratch' cycle	While the process of IL-31 inducing itch has been interpreted correctly, the elucidation of the itch-scratch cycle has been slightly misinterpreted.	Accepted.

Section 3.3, page 37 'A possible network diagram of the 12 RCTs indicates that nemolizumab is connected to five other comparators via placebo (aprepitant, nalbuphine, serlopitant, vixarelimab, dupilumab). Therefore, it would have been possible to conduct an NMA to compare nemolizumab against these five comparators'	This statement should be amended to 'A possible network diagram of the 12 RCTs indicates that nemolizumab is connected to five other comparators via placebo (aprepitant, nalbuphine, serlopitant, vixarelimab, dupilumab). However, these comparators are not included as comparators in the Company decision problem'	The statement is misleading and implies that an NMA is feasible versus relevant comparators in the decision problem. The text should be amended to make clear that an NMA versus the comparators included in the decision problem is not feasible.	
Section 4.2.1, page 40 'Assumed that no health benefit can be derived from BSC'	This statement should be amended to 'Assumed that no health benefit can be derived from BSC following loss of response.'	This statement is misleading, as patients in the BSC arm can respond to treatment at week 16 and enter the maintained response health state.	The text has been amended for clarity to read "Assumed that no health benefit can be derived from BSC following a loss of response, despite an increase in BSC intensity"
Section 4.2.7, page 60 'A linear repeated measures mixed effects regression	The text only references the regression model presented in the first round of clarification	The text discusses lack of validity of the models presented in the first round of the clarification	The EAG confirms that most of the critique regarding the usefulness

analysis (CQ B13) was conducted. The regression included only those who responded at week 16 to the composite outcome for both the OLYMPIA 1&2 trials and the LTE study. The model included a random intercept and time of analysis visit as a fixed effect. Based on EQ-5D data available the model predicted an EQ-5D of [redacted] at 1 year and [redacted] at years 2 and 3' Section 4.2.7, page 61 'The regression model lacks internal validity as it estimates baseline utility value (model intercept) that is substantially higher than the observed baseline values within the trials (Olympia 1& 2 pooled baseline utility: [redacted], Model intercept: [redacted]).'	questions and not the updated models presented in the second round of clarification questions. Additional context should be provided for the updated regression models presented by Galderma.	question response but does not provide sufficient detail or results regarding the updated models presented in the second round of clarification question responses. Therefore, this section of the report does not provide full context of the analyses conducted by Galderma and focuses on outdated models that have subsequently been updated based on feedback provided by the EAG.	of the models provided in the first clarification response also applies to the second response. However, the EAG appreciates the company's engagement on this issue and the additional responses provided. We have now provided greater detail about the additional evidence provided by the company, and the EAG's specific critique of that evidence in Section 4.2.7. Further, the EAG has added greater detail of the company reasoning behind the return to baseline utility value for non-responders discussed within CQ2

			under assumption 3, section 4.2.7.
Section 4.2.7, page 65 'The EAG also acknowledge the potential for protocol driven effects with regard to utility estimates'	This statement should be amended to state 'The EAG also acknowledge the potential for protocol driven effects with regard to utility estimates. In TA955, clinical experts stated that in clinical trials patients are typically more energised and adherent to the treatment regimens and that a decrease in health-related quality of life (HRQoL) is expected post-trial on return to real-world clinical practice, with patients returning to their previous worse health state post-trial.'	This statement does not provide sufficient detail of the 'protocol driven effects' on utility or acknowledge that clinical experts have supported that the utility value for non-responders in clinical trials would not reflect long-term utility for non-responders in UK clinical practice.	Not a factual inaccuracy. The EAG would note that any protocol-driven effects are likely to apply to both arms of the study.
Section 4.2.8, page 69 'The company does not state within document B whether there is a price difference between either preparation	This statement should be amended to 'There is no price difference between either preparation'.	Galderma can confirm that the price of the nemolizumab pen and pre-filled syringe are equal.	Accepted. Also, amended text within the EAG comments on page 70 as follows: "*Nemolizumab is available as a pen or*

			pre-filled syringe. Clinical…"
Section 4.2.8, page 70 'Clinical advice to the EAG suggests that self-administered medications are typically delivered to the patient's home and a sharps box is collected from the patient's home approximately every 3 months. It is unclear from the submission documentation whether these costs would be incurred by the company, secondary care practice or the patient's GP. Should the cost fall to the NHS, this should also be included within the economic model. The EAG would welcome further clarification from the company regarding this point'	This statement should be amended to 'Clinical advice to the EAG suggests that self-administered medications are typically delivered to the patient's home and a sharps box is collected from the patient's home approximately every 3 months. The Company have confirmed that these costs would be incurred by the company and not secondary care practice or the patient's GP'	Galderma can confirm that they will cover this cost as part of patient support programme. Therefore, the cost does not need to be included in the economic analysis.	Accepted.
Section 4.2.8, page 70 - 71 'Based on the Q4W dosing schedule all patients should receive 13.04 administrations	The text should be deleted and the update to the model amended in line with the Company submission so the first	Treatment starts with loading dose at week 0 (2 doses) followed by 1 dose every 4 weeks until week 52. This means patient ≥	The EAG thanks the company for identifying our misinterpretation. The relevant text has

per year. In the first administration, all patients should receive 2 doses then receive their weight-based dosing schedule for all administrations Q4W thereafter. Therefore, the EAG believes that those ≥90kg should receive 26.09 doses and those <90kg should receive 14.04 doses in the 13.04 administrations in the first year. The EAG finds that the company may have over costed nemolizumab in year 1'	year assumes that those ≥90kg would receive 28.09 doses and <90kg would receive 15.04 doses.	90kg would receive 28 doses and < 90kg would receive 15 doses over 14 administrations in 52 weeks (weeks 0 to 52). Patients will then receive their next dose at week 56 in year 2.	been deleted. Relevant results tables have been updated throughout the report accordingly.
Section 6.2, Table 33, page 113 Scenario: 'Remove nemolizumab partial response utility from the non-response state.'	This scenario analysis should be re-assessed as the results lack face validity based on the description of the analysis.	The QALY results from this scenario analysis do not align with the description and lack face validity. Removing the nemolizumab partial response utility benefit from the non-response state significantly increases the total QALYs in both treatment arms. However, this scenario is only removing the utility benefit for nemolizumab non-responders; therefore, the total QALYs for the nemolizumab arm should decrease and the total	The EAG thanks the company for identifying this error. We have corrected this scenario, and the relevant tables accordingly.

		QALYs for the BSC arm should remain unchanged. Furthermore, the removal of the nemolizumab partial response utility from the non-response state (which is only applied for the first year following loss of response) has a significantly greater impact on total QALYs compared to the scenario that updates the non-responder utility for both treatment arms from [redacted] to [redacted] (which is applied for the entire model time horizon). This therefore further supports that the results are not plausible and lack face validity.	

Location of incorrect marking	Description of incorrect marking	Amended marking	EAG response
All yellow AIC marking in the EAG report Title page '**Contains [redacted]'** Section 1.1, page xi '[redacted])' Section 3.2.1, page 12 '[redacted]'; [redacted] Section 3.2.1, page 123 '([redacted]% versus [redacted]%)' Section 3.2.1, page 20 & 21, Table 7 (columns 2 through 5) Section 3.2.1, page 22-25, Table 8(columns 2 through 5) Section 3.2.2, page 26 Section 3.2.4, page 27	NICE have updated the approach for confidential marking to include all 'confidential information' highlighted in turquoise and all 'depersonalised data' highlighted in pink.	Update yellow AIC marking to turquoise marking	Accepted.

Section 3.2.4, page 28-30, Table 9 (columns 2 through 5) Section 3.2.4, page 31-32, Table 10 (columns 2 through 5) Section 4.2.7, page 57 '0.78 (SD=0.24, [redacted])'			
Section 3.2.1, page 20-25, Table 7 (columns 2 through 4), Table 8 (columns 2 through 4)	No CIC marking needed for OLYMPIA 1 or 2 baseline characteristics and baseline disease characteristics	De-highlight and de-underline all baseline characteristics from the OLYMPIA 1 and OLYMPIA 2 trials data	Accepted.
Section 3.2.4 page 26-32, text and Table 9 (column 2 through 4) and Table 10 *column 2 through 4)	No CIC marking needed for OLYMPIA 1 or 2 adverse event data	De-highlight and de-underline all data from the OLYMPIA 1 and OLYMPIA 2 trials data	Accepted.