Medicinrådet

Bilag til Medicinrådets anbefaling vedr. nemolizumab til behandling af voksne med moderat til svær prurigo nodularis

Vers. 1.0

Bilagsoversigt

1. Forhandlingsnotat fra Amgros vedr. nemolizumab til PN
2. Ansøgers endelige ansøgning vedr. nemolizumab til PN

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08.08.2025

DBS/KLE/LSC

Forhandlingsnotat

Dato for behandling i Medicinrådet	03.09.2025
Leverandør	Galderma
Lægemiddel	Nemluvio (nemolizumab)
Ansøgt indikation	Moderat til svær prurigo nodularis (PN) hos voksne, som er kandidater til systemisk behandling
Nyt lægemiddel / indikationsudvidelse	Nyt lægemiddel

Prisinformation

Amgros har forhandlet følgende pris på Nemluvio (nemolizumab):

Tabel 1: Forhandlingsresultat

Lægemiddel	Styrke (pakningsstørrelse)	AIP (DKK)	Forhandlet SAIP (DKK)	Forhandlet rabat ift. AIP
Nemluvio	30 mg pulver og solvens, 1 stk. forfyldt sprøjte	14.995	[redacted]	[redacted]

Prisen er betinget af Medicinrådets anbefaling. Det betyder, at hvis Medicinrådet ikke anbefaler Nemluvio, indkøbes det til AIP.

Aftaleforhold

Amgros vil indgå en aftale på Nemluvio, der vil køre sideløbende med de øvrige lægemidler som bruges til behandling af atopisk eksem, svær astma og svær kronisk rhinosinuitis med næsepolypper.

[redacted]

Konkurrencesituationen

Nemluvio bliver vurderet overfor Dupixent (dupilumab) som tidligere er blevet godkendt til behandling af prurigo nodularis.

Der forventes ikke nye lægemidler eller indikationsudvidelser til prurigo nodularis inden for den nærmeste fremtid, men da lægemidler til behandling af prurigo nodularis indgår i et større udbud på biologiske lægemidler forventes det, at priskonkurrence inden for disse områder vil kunne påvirke lægemidler til behandling af prurigo nodularis.

Tabel 2 viser lægemiddeludgifter i relation til Dupixent. Lægemiddeludgiften per patient er beregnet for en periode på 24 måneder.

Tabel 2: Sammenligning af lægemiddeludgifter pr. patient

Lægemiddel	Styrke (pakningsstørrelse)	Dosering	Pris pr. pakning (SAIP, DKK)	Lægemiddeludgift pr. 24 mdr. (SAIP, DKK)
Nemluvio < 90kg (s.c.)	30 mg (1 stk.)	Opstart: 60 mg (2x30 mg) Vedligeholdelse: 30 mg hver 4. uge	[redacted]	[redacted]
Nemluvio > 90kg* (s.c.)	30 mg (1 stk.)	Opstart: 60 mg (2x30 mg) Vedligeholdelse: 60 mg hver 4. uge	[redacted]	[redacted]
Dupixent (s.c.)	300 mg (2 stk.)	Opstart: 600 mg (2x300 mg) Vedligeholdelse: 300 mg hver 2. uge	[redacted]	[redacted]

*Medicinrådet har vurderet at 25% af patienterne vil veje ≥90 kg.

Status fra andre lande

Tabel 3: Status fra andre lande

Land	Status	Link
England	Under vurdering	Link til status

Opsummering

[redacted]

[redacted]

Application for the assessment of Nemluvio® (nemolizumab) for the treatment of adults with moderate-to-severe prurigo nodularis who are candidates for systemic therapy

Color scheme for text highlighting	
Color of highlighted text	Definition of highlighted text
	Confidential information
[Other]	[Definition of color-code]

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Tables and Figures

Abbreviations

Abbreviation	Explanation	Abbreviation	Explanation
ACT	Asthma control test	NICE	Health and Care Excellence
AE	Adverse event	NMA	Network meta-analysis
ALT	Alanine aminotransferase	NRI	Non-responder imputation
ANCOVA	Analysis of covariance	NRS	Numerical rating scale
AST	Aspartate aminotransferase	OC	Observed cases
CFB	Change from baseline	PEF	Peak expiratory flow
CI	Confidence interval	PICOS	Study design
CMH	Cochran-Mantel Haenszel	PN	Prurigo nodularis

CrI	Credible interval	PGAD	Patient Global Assessment of Disease
DETs	Data extraction templates	PP	Peak pruritus
DKK	Danish krone	Q2W	Every 2 weeks
DLQI	Dermatology Life Quality Index	Q4W	Every 4 weeks
DMC	Danish Medicines Council	QoL	Quality of life
DPS	Dynamic pruritus score	RE	Random-effects
EMA	European Medicines Agency	SC	Subcutaneously
EPAR	European Public Assessment Report	SD	Standard deviation
EQ-5D	European Quality of Life-5 Dimensions	SE	Standard error
FE	Fixed-effects	SLR	Systematic literature review
HADS	Hospital Anxiety and Depression Scale	SNRIs	Norepinephrine reuptake inhibitors
HRQoL	Health-related quality of life	SSRIs	Selective serotonin reuptake inhibitors
IGA	Investigator's Global Assessment	TB	Tuberculosis
IL	Interleukin	TCI	Topical calcineurin inhibitor
ITC	Indirect treatment comparison	TCS	Topical corticosteroids
ITT	Intent-to-treat	TEAE	Treatment-emergent adverse event
MAR	Missing at random	VAS	Visual analogue scale
MI	Multiple imputation	WI	Worst itch
MD	Mean difference	refID	Reference identification number
MMRM	Mixed effects model for repeated measures		

1. Regulatory information on the medicine

Overview of the medicine	
Proprietary name	Nemluvio®
Generic name	Nemolizumab
Therapeutic indication as defined by EMA	Nemluvio® is indicated for the treatment of adults with moderate-to-severe prurigo nodularis who are candidates for systemic therapy.
Marketing authorization holder in Denmark	Galderma Nordic AB
ATC code	D11AH12
Combination therapy and/or co-medication	Not applicable
(Expected) Date of EC approval	12th of February 2025
Has the medicine received a conditional marketing authorization?	No
Accelerated assessment in the European Medicines Agency (EMA)	No
Orphan drug designation (include date)	No
Other therapeutic indications approved by EMA	Nemluvio® is indicated for the treatment of moderate-to-severe atopic dermatitis in patients aged 12 years and older who are candidates for systemic therapy.
Other indications that have been evaluated by the DMC (yes/no)	Nemluvio® is indicated for the treatment of moderate-to-severe atopic dermatitis in patients aged 12 years and older who are candidates for systemic therapy.
Joint Nordic assessment (JNHB)	Are the current treatment practices similar across the Nordic countries (DK, FI, IS, NO, SE)? No, dupilumab is not reimbursed in Finland for the treatment of prurigo nodularis. Is the product suitable for a joint Nordic assessment? No If no, why not? The comparator is not the same in all countries.
Dispensing group	BEGR

Overview of the medicine	
Packaging – types, sizes/number of units and concentrations	Each single-use pre-filled pen contains 30 mg of nemolizumab per 0.49 ml dose following reconstitution. Pack size: 1 pre-filled pen.

2. Summary table

Summary	
Indication relevant for the assessment	Nemluvio® is indicated for the treatment of adults with moderate-to-severe prurigo nodularis (PN) who are candidates for systemic therapy.
Dosage regiment and administration	The recommended dose for patients weighing < 90 kg is an initial dose of 60 mg (two 30 mg injections), followed by 30 mg given every 4 weeks (Q4W). The recommended dose for patients weighing ≥ 90 kg is an initial dose of 60 mg dose (two 30 mg injections), followed by 60 mg given every 4 weeks (Q4W). Method of administration: subcutaneous use.
Choice of comparator	Dupilumab. It is the only recommended medicine for the treatment of moderate-to-severe PN by the DMC [1].
Prognosis with current treatment (comparator)	PN is associated with a significant reduction in quality of life compared with the general population, and those with other skin conditions. Itch is seen as a key driver of the impact on quality of life, especially nocturnal itch, which is strongly associated with sleep disturbance [2, 3]. Also, there is evidence that poor sleep could be related to depression, suicide and anxiety, which are significantly increased in patients with PN, and are observed at the highest rates among skin diseases [4, 5]. In addition, PN patients are often affected by several comorbidities [6-9], and experience a 28% increase in mortality compared with the general population [9]. Therefore, there is substantial need for additional targeted therapies in PN.
Type of evidence for the clinical evaluation	Indirect comparison: network meta-analysis (NMA) for the clinical evaluation of nemolizumab vs dupilumab.
Most important efficacy endpoints (Difference/gain compared to comparator)	PP-NRS improvement ≥4 points: nemolizumab was numerically better, but non-statistically significantly favourable to dupilumab at week 16 (OR: 1.65; 95% CrI: 0.67, 4.00) and at week 24 (OR: 1.23; 95% CrI: 0.54, 2.91). PP-NRS absolute change from baseline: nemolizumab was numerically better, but non-statistically significantly favourable to dupilumab at week 16 (MD: -1.23; 95% CrI: -2.83, 0.55). At week 24, nemolizumab was statistically significantly superior to dupilumab (MD: -1.30; 95% CrI: -2.49, -0.18). IGA success: at week 24, there was no difference between nemolizumab and dupilumab (OR: 0.99; 95% CrI: 0.42, 2.58).

Summary	
	DLQI absolute change from baseline: comparing 12-week data for dupilumab with 16-week data for nemolizumab, nemolizumab was numerically better, but non-statistically significantly favourable to dupilumab (MD: -0.94; 95% CrI: -6.56, 4.85), also at week 24 (MD: -1.50; 95% CrI: -4.39, 1.25).
Most important serious adverse events for the intervention and comparator	In the studies included in this application – NCT03181503, OLYMPIA 1, and OLYMPIA 2 (nemolizumab) and LIBERTY-PN PRIME and PRIME2 (dupilumab) – a low proportion of patients developed serious adverse events (SAEs) and there were no SAEs with frequency of ≥ 5% recorded in the nemolizumab or dupilumab arms. Results from the comparative analysis showed no significant differences when comparing rates of TEAEs between nemolizumab and dupilumab (OR: 0.96; 95% CrI: 0.53, 1.730) at the end of the study.
Impact on health-related quality of life	Clinical documentation: • DLQI absolute change from baseline at week 12/16: nemolizumab (week 16) was numerically better than dupilumab (week 12), but differences were not statistically significant (mean difference: -0.94; 95% CrI: -6.56, 4.85). • DLQI absolute change from baseline at week 24: nemolizumab was numerically better than dupilumab, but differences were not statistically significant (mean difference: -1.50; 95% CrI: -4.39, 1.25). Health economic model: Since a cost comparison is submitted, the impact on health-related quality of life is not included in the analysis, but described for the included studies.
Type of economic analysis that is submitted	A cost comparison, comparing the total treatment costs of nemolizumab vs dupilumab.
Data sources used to model the clinical effects	No clinical effect was modelled since the efficacy is considered equivalent between nemolizumab) and dupilumab.
Data sources used to model the health-related quality of life	N/A
Life years gained	N/A
QALYs gained	N/A
Incremental costs	28,350 DKK
ICER (DKK/QALY)	N/A
Uncertainty associated with the ICER estimate	N/A

Summary	
Number of eligible patients in Denmark	Incidence: 1.1/100,000 people Prevalence: 14.1/100,000 people Number of patients eligible for treatment with nemolizumab or the comparator in Denmark: 10 patients (year 1), 3 patients (from year 2 onwards).
Budget impact (in year 5)	42,840.71 DKK

3. The patient population, intervention, choice of comparator(s) and relevant outcomes

3.1 The medical condition

Prurigo nodularis (PN) is a rare and chronic neuroimmune skin disease. It is a distinct disease, characterized by the presence of chronic itch (≥ 6 weeks), history and signs of repeated scratching, such as excoriation and scars, and multiple, localized or generalized, hyperkeratotic, dome-shaped inflammatory nodules (lesions) that typically affect the trunk and extremities [6, 10-12].Its aetiology and pathophysiology are still unclear, although it is thought to be associated with IL-31 driven immune and neuronal dysregulation and skin tissue remodelling [13]. Moreover, no clear biomarker has been identified that would explain PN pathophysiology [14].

The primary signs of PN are pruriginous lesions, symmetrically distributed, on areas of the skin generally accessible to scratching, with normal or lichenified skin between lesions and some excoriations and scars (scratch-induced lesions). However, the face and palms are rarely affected [14]. PN symptoms are characterized by itch which precedes development of skin lesions and may be accompanied by burning, stinging, pain and other sensations [14]. Pruriginous lesions in PN are defined as elevated lesions (papules, nodules, or plaques) that can range in number from 1 to over 100. Papule size is up to 0.5 cm, while nodules are firm and dome-shaped lesions with a diameter of up to 1 cm that often show a whitish or pink centre with a hyperpigmented border [6, 15, 16]. Furthermore, these lesions 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, sparing the palms, soles, scalp and genitals [6, 17]. The surrounding skin can also be affected and can become lichenified, dry and crusted, with pigmentation changes [6, 17]. Lesions are generally found on areas of the body accessible to scratching [6, 14, 15]. In fact, most PN patients present the

“butterfly” pattern, which is the absence of PN lesions at the centre of their back caused by the inability to scratch in that area [6, 14, 15]. However, the clinical presentation of PN can be very heterogeneous, resulting in lesions that vary in quantity, quality, size (from a few millimetres to a few centimetres), and colour (from the natural skin colour to pink, red, brown, and black) [18].

The disease burden associated with PN can severely impact several aspects of a patient’s life. PN is associated with a significant reduction in quality of life (QoL) compared with the normal population, and those with other skin conditions. In fact, PN is recognized as one of the worst skin conditions in terms of QoL disruption. Itch is seen as a key driver of the impact on QoL, especially nocturnal itch, which is strongly associated with sleep disturbance [2, 19]. Furthermore, there is evidence that poor sleep could be related to depression, suicide and anxiety, which are significantly increased in patients with PN, and are observed at the highest rates among skin diseases [4, 5].

3.2 Patient population

3.2.1 Worldwide

Epidemiological data regarding incidence and prevalence of PN are scarce [20, 21] and prospective studies are still lacking or unclear [20, 21]. Until recently, PN was grouped with other pruritic conditions in disease classification systems [21], generating poor clarity in the epidemiology data. An ICD-10 code for PN was introduced in 2015 (ICD-10: L28.1) and PN was recognized as a distinct disease in 2018 [21]. Currently, the prevalence data available for PN span from approximately seven per 100,000 in Poland to 111 per 100,000 in Germany, with 32.7 per 100,000 in the UK, 36.7 to 52.2 per 100,000 in the US and 8.4 to 46.7 per 100,000 in France [22-26].

3.2.2 Denmark

3.2.2.1 National register-based study in Denmark (Elberling et. al. 2024)

The annual prevalence and annual incidence of PN in Denmark in 2021 reported in the register-based study by Elberling et al. [27] were 14.1 and 1.1 per 100,000 inhabitants, respectively (Table 1).

Table 1 Incidence and prevalence of PN in the past 5 years

Year	2020	2021	2022	2023	2024
Incidence in Denmark	1.0	1.1	NA	NA	NA
Prevalence in Denmark	13.5	14.1	NA	NA	NA

Note: Incidence and prevalence values are expressed per 100,000 people. Source: [27]

3.2.2.2 Previous DMC assessment

A previous assessment by the DMC for dupilumab for the treatment of adults with moderate to severe prurigo nodularis [1] estimated that there are approximately 1,100 patients with PN in Denmark. Of these, around 120 have moderate to severe PN and will be candidates for systemic treatment. These patients may have an atopic disposition and therefore some will also have another atopic disease, such as atopic eczema, and they may already be on treatment with monoclonal antibodies, such as dupilumab, tralokinumab or lebrikizumab. Accounting for this, the DMC estimated around 60 new patients each year with PN, of which 8 are moderate to severe (all candidates for systemic treatment) [1]. Of these, half are assumed to already receive dupilumab due to another atopic disease. Therefore, the DMC expects 10-30 new patients with PN each year for the first 2-3 years, after that, approximately three new patients per year [1]. These values were used to estimate the number of patients in Denmark who would be eligible for treatment with nemolizumab in the coming years (Table 2).

Table 2 Estimated number of new patients eligible for treatment

Year	Year 1	Year 2	Year 3	Year 4	Year 5
Number of new patients in Denmark who are eligible for treatment in the coming years	10	3	3	3	3

Source: [1].

3.3 Current treatment options

The treatment options for PN are limited. The only two currently EMA-approved medicines for the treatment of PN are dupilumab and nemolizumab. Dupilumab is the only treatment currently recommended by the DMC for the treatment of moderate-to-severe PN requiring systemic therapy [1]. According to “The Danish Medicines Council's criteria for starting, monitoring and discontinuing dupilumab for moderate to severe prurigo nodularis” dupilumab should be used in patients with insufficient effect of optimal local treatment and who have tried at least one systemic treatment for three months [28]. Other systemic treatments currently used in clinical practice in Denmark are prescribed off-label and consist mostly of methotrexate , thalidomide, calcineurin inhibitors, ciclosporin, mycophenolate, azathioprine, gabapentinoids and antidepressants [1, 29].

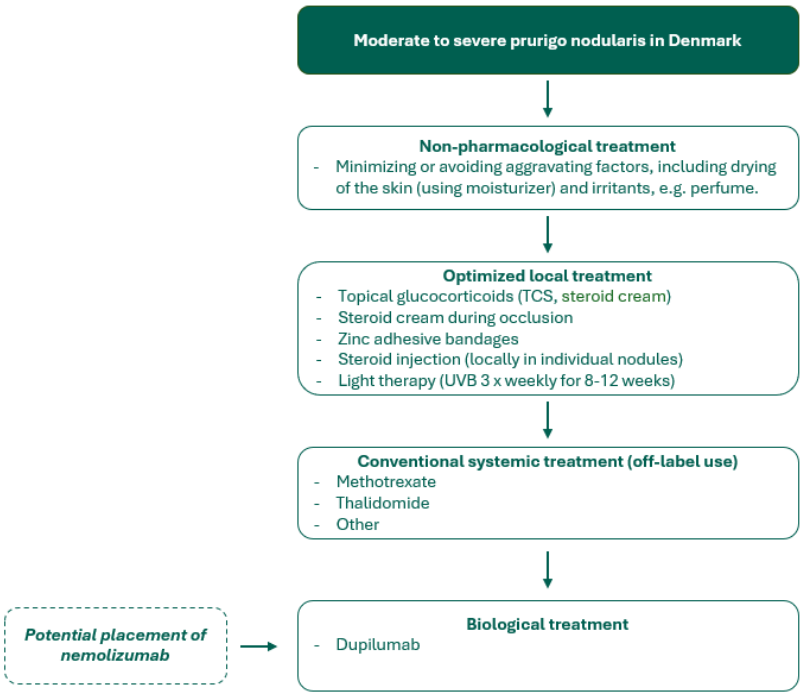
3.4 The intervention

Table 3 Overview of the intervention

Overview of intervention	
Indication relevant for the assessment	Nemolizumab is indicated for the treatment of adults with moderate-to-severe prurigo nodularis who are candidates for systemic therapy.
ATMP	N/A
Method of administration	Subcutaneous injection.
Dosing	The recommended dose for patients weighing < 90 kg is an initial dose of 60 mg (two 30 mg injections), followed by 30 mg given every 4 weeks (Q4W). The recommended dose for patients weighing ≥ 90 kg is an initial dose of 60 mg dose (two 30 mg injections), followed by 60 mg given every 4 weeks (Q4W).
Dosing in the health economic model (including relative dose intensity)	As per SmPC; see above
Should the medicine be administered with other medicines?	No
Treatment duration / criteria for end of treatment	As PN is a chronic disease, nemolizumab is intended for long-term treatment with the aim of achieving disease control. Consideration should be given to discontinuing treatment in patients who have shown no response on pruritus after 16 weeks of treatment for prurigo nodularis.
Necessary monitoring, both during administration and during the treatment period	N/A
Need for diagnostics or other tests (e.g. companion diagnostics). How are these included in the model?	No test is required.
Package size(s)	Pack of 1 pre-filled pen

3.4.1 The intervention in relation to Danish clinical practice

Figure 1 Potential placement of the intervention (nemolizumab) in Denmark



Source: [1, 16]

3.5 Choice of comparator(s)

The only two currently EMA-approved medicines for the treatment of PN are dupilumab and nemolizumab. Dupilumab is the only medicine that has been assessed and recommended by the DMC for the treatment of PN [1]. Nemolizumab and dupilumab are both biologics but they are inhibiting different interleukins (IL). Dupilumab inhibits the IL-4 and IL-13 signalling, and nemolizumab inhibits IL-31 signalling by binding selectively to interleukin-31 receptor alpha (IL-31 RA). Therefore, dupilumab is the most appropriate comparator for nemolizumab for the treatment of PN.

Table 4 Overview of the comparator

Overview of comparator	
Generic name	Dupilumab
ATC code	D11AH05

Overview of comparator	
Mechanism of action	Dupilumab is a recombinant human IgG4 monoclonal antibody that inhibits interleukin-4 and interleukin-13 signalling. IL-4 and IL-13 are major drivers of human type 2 inflammatory disease, such as atopic dermatitis, asthma, chronic rhinosinusitis with nasal polyposis, PN, eosinophilic esophagitis, and chronic obstructive pulmonary disease. Blocking the IL-4/IL-13 pathway with dupilumab in patients decreases many of the mediators of type 2 inflammation.
Method of administration	Subcutaneous injection
Dosing	The recommended dose of dupilumab for adult patients is an initial dose of 600 mg (two 300 mg injections), followed by 300 mg given every other week (Q2W) administered as subcutaneous injection.
Dosing in the health economic model (including relative dose intensity)	As per SmPC; see above.
Should the medicine be administered with other medicines?	Dupilumab can be used with or without topical corticosteroids and/or topical calcineurin inhibitors.
Treatment duration/ criteria for end of treatment	As PN is a chronic disease, dupilumab is intended for long-term treatment with the aim of achieving disease control. According to “The Danish Medicines Council's criteria for starting, monitoring and discontinuing dupilumab for moderate to severe prurigo nodularis” patients who achieve a sustained response should attempt to discontinue treatment after 2 years of treatment [28].
Need for diagnostics or other tests (i.e. companion diagnostics)	No
Package size(s)	Pack of 2 pre-filled syringes. Pack of 2 pre-filled pens.

Source: [28, 30]

3.6 Cost-effectiveness of the comparator(s)

Dupilumab, the comparator, has been evaluated and recommended by the DMC for the treatment of moderate-to-severe prurigo nodularis (PN) in adults who are candidates for systemic treatment [1].

3.7 Relevant efficacy outcomes

3.7.1 Definition of efficacy outcomes included in the application

The relevant comparator to nemolizumab is dupilumab. In the absence of direct comparative studies, an indirect treatment comparison (ITC) was conducted. The efficacy outcomes assessed in the ITC are deemed to be relevant for this application and are presented in Table 5. The Dermatology Life Quality Index (DLQI)-related outcome (DLQI absolute change from baseline) is also relevant for this application and it was assessed in the ITC, DLQI outcome and results are presented in section 10.

Table 5 Efficacy outcome measures relevant for the application

Outcome measure	Time point*	Definition	How was the measure investigated/method of data collection
PP-NRS improvement ≥4 points [OLYMPIA 1, OLYMPIA 2]	Week 16 Week 24	Number of participants with an improvement of ≥4 from Baseline in weekly Peak Pruritus Numeric Rating Scale	The Peak Pruritus NRS is a scale that was used by the participants to report the intensity of their pruritus (itch) during the last 24 hours. For maximum itch intensity: the scores were provided on a scale of 0 to 10, with 0 being 'no itch' and 10 being 'worst itch imaginable'. Higher scores indicate worse outcome.
PP-NRS absolute change from baseline [NCT03181503, OLYMPIA 1, OLYMPIA 2, LIBERTY-PN PRIME, PRIME 2]	Week 16 Week 24	Absolute change from baseline in weekly Peak Pruritus Numeric Rating Scale	The Peak Pruritus NRS is a scale that was used by the participants to report the intensity of their pruritus (itch) during the last 24 hours. For maximum itch intensity: the scores were provided on a scale of 0 to 10, with 0 being 'no itch' and 10 being 'worst itch imaginable'. Higher scores indicate worse outcome.
WI-NRS improvement ≥4 points [LIBERTY-PN PRIME, PRIME 2]	Week 12 Week 24	Number of participants with an improvement of ≥4 From Baseline in weekly Worst Itch Numeric Rating Scale	The Worst Itch NRS is a scale that was used by the participants to report the worst itch over the past 24 hours. For maximum itch intensity: the scores were provided on a scale of 0 to 10, with 0 being 'no itch' and 10 being 'worst itch imaginable'. Higher scores indicate worse outcome.
WI-NRS absolute change from baseline [LIBERTY-PN PRIME, PRIME 2]	Week 24	Absolute change from baseline in weekly Worst Itch Numeric Rating Scale	The Worst Itch NRS is a scale that was used by the participants to report the worst itch over the past 24 hours. For maximum itch intensity: the scores were provided on a scale of 0 to 10, with 0 being 'no itch' and 10 being 'worst itch imaginable'. Higher scores indicate worse outcome.

Outcome measure	Time point*	Definition	How was the measure investigated/method of data collection
IGA success [OLYMPIA 1, OLYMPIA 2, LIBERTY-PN PRIME, PRIME 2]	Week 16 Week 24	IGA success was defined as clear (0) or almost clear (1), and a reduction from baseline of ≥2 points.	The IGA is a 5-point scale used by the Investigator to evaluate the severity of PN. Full scale is scored from 0-4, higher score indicates more severe symptoms. The investigator reviewed the participant's skin and assigned a score of 0 (clear), 1 (almost clear), 2 (mild), 3 (moderate), or 4 (severe) and a ≥2-point improvement from baseline.
Composite PP-NRS improvement ≥4 points and IGA success [OLYMPIA 1, OLYMPIA 2]	Week 16 Week 24	Achieving both endpoints: ”PP-NRS improvement ≥4 points” and “IGA success”	See” PP-NRS improvement ≥4 points” and “IGA success”
Composite WI-NRS improvement ≥4 points and IGA success [LIBERTY-PN PRIME, PRIME 2]	Week 16 Week 24	Achieving both endpoints: ”WI-NRS improvement ≥4 points” and “IGA success”	See” WI-NRS improvement ≥4 points” and “IGA success”

* Time point for data collection used in analysis (follow up time for time-to-event measures). Abbreviations: DLQI, Dermatology Life Quality Index; HADS, Hospital Anxiety and Depression Scale; IGA, Investigator’s Global Assessment; PP-NRS, Peak Pruritus Numerical Rating Scale; WI-NRS, Worst Itch Numeric Rating Scale.

Validity of outcomes

The efficacy outcome measures listed in Table 5 were used in the assessment of dupilumab. The DMC has found them adequate to assess the efficacy of dupilumab for the treatment of adults with moderate-to-severe prurigo nodularis who are candidates for systemic therapy in Denmark [1].

4. Health economic analysis

Both nemolizumab and dupilumab are monoclonal antibodies with different mechanism of action, but comparable efficacy and safety profile. Therefore, a cost analysis was conducted, with a simple cost comparison model comparing the total treatment cost of nemolizumab vs dupilumab.

4.1 Model structure

The health economic model is based on a simple cost comparison of the treatment costs of nemolizumab and dupilumab accumulated over a two-year time horizon, to capture both the treatment initiation phase and the maintenance phase.

The yearly doses are calculated based on the summary of product characteristics. Both nemolizumab and dupilumab are administered subcutaneously by the patient at home, hence no administration costs were included in the analysis.

To consider for the posology of nemolizumab, the model allows to calculate cost weighted by the share of patients above 90 kg in relationship to the average weight of the patients. In the base case, this share is set to 0%, as the mean weight of the Danish population is reported at 72.6 kg [31]. The impact of different average patient weights is tested in the sensitivity analysis. Moreover, the model takes into account the discontinuation based on assessment of response rate at two different time points, 16 weeks for nemolizumab and at 24 weeks for dupilumab. The same discontinuation rate, 42.6%, is used for both arms and it is based on the average response rate as reported in non-responder imputation (NRI) in both the OLYPMIA 1 and 2 trials [32, 33] and it is accounted for through the two years. When the yearly doses are calculated, these are weighted based on the share of patients that discontinue at different timepoints during the year. For the treatment with dupilumab, the use of topical corticosteroids (TCS) and calcineurin inhibitors (TCI) as concomitant treatments are included in the cost comparison [1]. Since the analysis period continues over 2 years, a discount rate of 3.5% is applied as prescribed by the Danish Ministry of finance guidelines [34].

4.2 Model features

Table 6 presents the model features as included in the main cost comparison.

Table 6 Features of the economic model

Model features	Description	Justification
Patient population	Adult patients with moderate-to-severe prurigo nodularis who are candidates for systemic therapy.	Based on the clinical trial
Perspective	N/A	N/A
Time horizon	2 years	To cover initiation and maintenance phases
Discontinuation for nemolizumab	42.6% at 16 weeks	Based on the share of non-responders, measured with PP-NRS improvement ≥4 points at week 16 endpoint from the clinical trials OLYMPIA 1 and OLYMPIA 2.
Discontinuation for dupilumab	42.6% at 24 weeks	Assumed to be equal to nemolizumab.
Cycle length	N/A	N/A

Model features	Description	Justification
Half-cycle correction	N/A	N/A
Discount rate	3.5% yearly	Based on the guidelines prescribed by the Ministry of finance-
Intervention	Nemolizumab	N/A
Comparator(s)	Dupilumab	N/A
Outcomes	Average yearly cost comparison	Total treatment cost comparison calculated through the treatment period of 2 years.

5. Overview of literature

5.1 Literature used for the clinical assessment

In order to identify the relevant trials and literature for comparing the efficacy and safety of nemolizumab and dupilumab, a systematic literature review (SLR) was performed. The SLR is described in detail in Appendix H. No head-to-head trials comparing nemolizumab and dupilumab, the intervention and the comparator, respectively, exist. Therefore, a network meta-analysis (NMA), based on the SLR results, was performed. The NMA is explained in detail in Section 7.

The relevant literature included in the assessment of efficacy and safety is presented in Table 7.

Table 7 Relevant literature included in the assessment of efficacy and safety

Reference (Full citation incl. reference number)*	Trial name*	NCT identifier	Dates of study (Start and expected completion date, data cut-off and expected data cut-offs)	Used in comparison of*
Full paper – Ständer S, Yosipovitch G, Legat FJ, Lacour JP, Paul C, Narbutt J, Bieber T, Misery L, Wollenberg A, Reich A, Ahmad F, Piketty C. Trial of Nemolizumab in Moderate-to-Severe Prurigo Nodularis. N Engl J Med. 2020 Feb 20;382(8):706-716. [35] Full paper – Ständer S, Yosipovitch G, Lacour JP, Legat FJ, Paul C, Reich A, Chaouche K, Ahmad F, Piketty C. Nemolizumab efficacy in prurigo nodularis: onset of action on itch and sleep disturbances. J Eur Acad Dermatol Venereol. 2022 Oct;36(10):1820-1825. doi: 10.1111/jdv.18377. Epub 2022 Jul 4. PMID: 35766128; PMCID: PMC9796585. [36] Clinicaltrials.gov – Safety and Efficacy of Nemolizumab in PN, NCT03181503. 2020. [37]	NCT03181503	NCT03181503	Start: 02/10/17 Completion: 26/09/18 Data cut-off: 12-week treatment period. Future data cut-offs: N/A	Nemolizumab vs. placebo in patients with prurigo nodularis.
Conference abstract – Ständer S, Yosipovitch G, Legat FJ, Reich A, Paul C, Simon D, Naldi L, Chen X, Jabbar Lopez ZK, Piketty C, Kwatra SG. Nemolizumab monotherapy improves itch and skin lesions in patients with moderate-to-severe prurigo nodularis: Results from a global Phase 3 trial (OLYMPIA 1). Presented at European Academy of Dermatology and Venereology (2023). [3] Full paper – Ständer S, Yosipovitch G, Legat FJ, Reich A, Paul C, Simon D, Naldi L, Metz M, Tsianakas A, Pink A, Fage S, Micali G, Weisshaar E, Sundaram H, Metelitsa A, Augustin M, Wollenberg A, Homey B, Fargnoli MC, Sofen H, Korman NJ, Skov L, Chen X, Jabbar-Lopez ZK, Piketty C, Kwatra SG; OLYMPIA 1 Investigators. Efficacy and Safety of Nemolizumab in Patients	OLYMPIA 1	NCT04501666	Start: 02/10/17 Completion: 26/09/18 Data cut-off: 16 and 24 week treatment period. Future data cut-offs: N/A	Nemolizumab vs. placebo in patients with prurigo nodularis.

Reference (Full citation incl. reference number)*	Trial name*	NCT identifier	Dates of study (Start and expected completion date, data cut-off and expected data cut-offs)	Used in comparison of*
With Moderate to Severe Prurigo Nodularis: The OLYMPIA 1 Randomized Clinical Phase 3 Trial. JAMA Dermatol. 2024 Nov 27. [38] Clinicaltrials.gov – Study to Assess the Efficacy and Safety of Nemolizumab (CD14152) in Participants With Prurigo Nodularis (PN), NCT04501666. 2024. [39] Galderma data on file, OLYMPIA 1, 2023 [32]				
Conference abstract – Ständer S YG, Lacour JP, et al. Patients with prurigo nodularis treated with nemolizumab achieved itch-free state: results from a phase 3 trial (OLYMPIA 2). Abstract presented at: 25th World Congress of Dermatology; July 3-8, 2023; Singapore. [40] Conference abstract – Reich A, Legat F, Paul C, et al. Nemolizumab modulates prurigo nodularis-associated skin pain and markedly improves patient reported outcomes in patients with moderate-to-severe prurigo nodularis in a phase 3 study (OLYMPIA 2). 32nd European Academy of Dermatology and Venereology Congress; October 11-14; Berlin, Germany 2023. [41] Full paper – Kwatra SG, Yosipovitch G, Legat FJ, Reich A, Paul C, Simon D, Naldi L, Lynde C, De Bruin-Weller MS, Nahm WK, Sauder M, Gharib R, Barbarot S, Szepietowski JC, Conrad C, Fleischer A, Laquer VT, Misery L, Serra-Baldrich E, Lapeere H, Ahmad F, Jabbar Lopez ZK, Piketty C, Ständer S; OLYMPIA 2 Investigators. Phase 3 Trial of Nemolizumab in Patients with Prurigo Nodularis. N Engl J Med. 2023 Oct 26;389(17):1579-1589. [42]	OLYMPIA 2	NCT04501679	Start: 02/10/17 Completion: 26/09/18 Data cut-off: 16 and 24 week treatment period. Future data cut-offs: N/A	Nemolizumab vs. placebo in patients with prurigo nodularis.

Reference (Full citation incl. reference number)*	Trial name*	NCT identifier	Dates of study (Start and expected completion date, data cut-off and expected data cut-offs)	Used in comparison of*
Clinicaltrials.gov – A Study to Assess the Efficacy and Safety of Nemolizumab (CD14152) in Participants With Prurigo Nodularis (PN), NCT04501679. 2024. [43] Galderma data on file, OLYMPIA 2, 2023 [33]				
Full paper – Yosipovitch G, Mollanazar N, Ständer S, Kwatra SG, Kim BS, Laws E, Mannent LP, Amin N, Akinlade B, Staudinger HW, Patel N, Yancopoulos GD, Weinreich DM, Wang S, Shi G, Bansal A, O'Malley JT. Dupilumab in patients with prurigo nodularis: two randomized, double-blind, placebo-controlled phase 3 trials. Nat Med. 2023 May;29(5):1180-1190. [44] Full paper – Yosipovitch G, Kim BS, Kwatra SG, Mollanazar NK, Ständer S, Satoh T, Mendes-Bastos P, Tsai TF, Laws E, Nivens MC, Maloney J, Shi G, Bansal A, Dubost-Brama A. Dupilumab improves pruritus and skin lesions in patients with prurigo nodularis: Pooled results from 2 phase 3 trials (LIBERTY-PN PRIME and PRIME2). JAAD Int. 2024 Apr 10;16:163-174. [45] Clinicaltrials.gov – Study of Dupilumab for the Treatment of Patients With Prurigo Nodularis, Inadequately Controlled on Topical Prescription Therapies or When Those Therapies Are Not Advisable (LIBERTY-PN PRIME), NCT04183335. 2022. [46]	LIBERTY-PN PRIME	NCT04183335	Start: 02/10/17 Completion: 26/09/18 Data cut-off: 24 weeks of treatment period and 12 weeks of post treatment period. Future data cut-offs: N/A	Dupilumab vs. placebo in patients with prurigo nodularis inadequately controlled on topical prescription therapies or when those therapies are not advisable.
Full paper – Yosipovitch G, Mollanazar N, Ständer S, Kwatra SG, Kim BS, Laws E, Mannent LP, Amin N, Akinlade B, Staudinger HW, Patel N, Yancopoulos GD, Weinreich DM, Wang S, Shi G, Bansal A, O'Malley JT. Dupilumab in patients with prurigo nodularis: two randomized, double-blind, placebo-controlled phase 3 trials. Nat Med. 2023 May;29(5):1180-1190. [44]	PRIME2	NCT04202679	Start: 02/10/17 Completion: 26/09/18 Data cut-off: 24 weeks of treatment period and 12 weeks of post treatment period.	Dupilumab vs. placebo in patients with prurigo nodularis inadequately controlled on topical prescription therapies or when those therapies are not advisable.

Reference (Full citation incl. reference number)*	Trial name*	NCT identifier	Dates of study (Start and expected completion date, data cut-off and expected data cut-offs)	Used in comparison of*
Clinicaltrials.gov – Study of Dupilumab for the Treatment of Patients With Prurigo Nodularis, Inadequately Controlled on Topical Prescription Therapies or When Those Therapies Are Not Advisable (PRIME2), NCT04202679. 2022. [47]			Future data cut-offs: N/A	
Conference abstract- Gil Yosipovitch, Shawn G Kwatra, Nicholas Mollanazar, Sonja Ständer, Takahiro Satoh, Elizabeth Laws, Leda P Mannent, Eric Mortensen, Jennifer Maloney, Genming Shi, Ashish Bansal, Renata Martinčová, 344 Dupilumab significantly improves itch and skin lesions in patients with prurigo nodularis: pooled results from two phase 3 trials (LIBERTY-PN PRIME and PRIME2), *British Journal of Dermatology*, Volume 188, Issue Supplement_2, February 2023, ljac140.038 [48] Conference abstract- Brian S Kim, Gil Yosipovitch, Shawn G Kwatra, Sonja Ständer, Nicholas Mollanazar, Genming Shi, Ashish Bansal, Melanie Makhija, 510 - Dupilumab is efficacious in patients with prurigo nodularis regardless of stable use of topical corticosteroids and topical calcineurin inhibitors: pooled results from two phase 3 trials (LIBERTY-PN PRIME and PRIME2), *British Journal of Dermatology*, Volume 190, Issue Supplement_2, February 2024, Pages ii14–ii15 [49] Full paper – Yosipovitch G, Kim BS, Kwatra SG, Mollanazar NK, Ständer S, Satoh T, Mendes-Bastos P, Tsai TF, Laws E, Nivens MC, Maloney J, Shi G, Bansal A, Dubost-Brama A. Dupilumab improves pruritus and skin lesions in patients with prurigo nodularis: Pooled results from 2 phase 3 trials (LIBERTY-PN PRIME and PRIME2). JAAD Int. 2024 Apr 10;16:163-174. [45]	LIBERTY-PN PRIME and PRIME2 pooled	NCT04183335 and NCT04202679	See above for LIBERTY-PN PRIME and PRIME2, respectively.	Dupilumab vs. placebo in patients with prurigo nodularis inadequately controlled on topical prescription therapies or when those therapies are not advisable.

5.2 Literature used for the assessment of health-related quality of life

In the NCT03181503 trial, health-related quality of life (HRQoL) data was collected through the DLQI questionnaire. In the OLYMPIA 1 and 2 trials, the HRQoL data was collected with three QoL questionnaires, the DLQI and Hospital Anxiety and Depression Score (HADS) questionnaires, and with the European Quality of Life-5 Dimensions (EQ-5D) instrument, which included two parts – the first part consisted of 5 multiple choice QoL questions and the second was a 100-point visual analogue scale (VAS). In the LIBERTY-PN PRIME and, PRIME2 studies, the HRQoL data was collected through the DLQI, and HADS. In these two trials, EQ-5D was also included as a tertiary/exploratory endpoint, but since not data is publicly available, results are not presented in this application.

An overview of the relevant literature included in the documentation of HRQoL is shown in Table 8.

Table 8 Relevant literature included for (documentation of) health-related quality of life (See section 10)

Reference (Full citation incl. reference number)	Health state/Disutility	Reference to where in the application the data is described/applied
Full paper – Ständer S, Yosipovitch G, Legat FJ, Lacour JP, Paul C, Narbutt J, Bieber T, Misery L, Wollenberg A, Reich A, Ahmad F, Piketty C. Trial of Nemolizumab in Moderate-to-Severe Prurigo Nodularis. N Engl J Med. 2020 Feb 20;382(8):706-716. [35] Full paper – Ständer S, Yosipovitch G, Lacour JP, Legat FJ, Paul C, Reich A, Chaouche K, Ahmad F, Piketty C. Nemolizumab efficacy in prurigo nodularis: onset of action on itch and sleep disturbances. J Eur Acad Dermatol Venereol. 2022 Oct;36(10):1820-1825. doi: 10.1111/jdv.18377. Epub 2022 Jul 4. PMID: 35766128; PMCID: PMC9796585. [36]	N/A	NCT03181503 trial in section 10.
Full paper – Ständer S, Yosipovitch G, Legat FJ, Reich A, Paul C, Simon D, Naldi L, Metz M, Tsianakas A, Pink A, Fage S, Micali G, Weisshaar E, Sundaram H, Metelitsa A, Augustin M, Wollenberg A, Homey B, Fargnoli MC, Sofen H, Korman NJ, Skov L, Chen X, Jabbar-Lopez ZK, Piketty C, Kwatra SG; OLYMPIA 1 Investigators. Efficacy and Safety of Nemolizumab in Patients With Moderate to Severe Prurigo Nodularis: The OLYMPIA 1 Randomized Clinical Phase 3 Trial. JAMA Dermatol. 2024 Nov 27. [38] Galderma data on file, OLYMPIA 1, 2023 [32]	N/A	OLYMPIA 1 trial in section 10.

Reference (Full citation incl. reference number)	Health state/Disutility	Reference to where in the application the data is described/applied
Full paper – Kwatra SG, Yosipovitch G, Legat FJ, Reich A, Paul C, Simon D, Naldi L, Lynde C, De Bruin-Weller MS, Nahm WK, Sauder M, Gharib R, Barbarot S, Szepietowski JC, Conrad C, Fleischer A, Laquer VT, Misery L, Serra-Baldrich E, Lapeere H, Ahmad F, Jabbar Lopez ZK, Piketty C, Ständer S; OLYMPIA 2 Investigators. Phase 3 Trial of Nemolizumab in Patients with Prurigo Nodularis. N Engl J Med. 2023 Oct 26;389(17):1579-1589. [42] Galderma data on file, OLYMPIA 2, 2023 [33]	N/A	OLYMPIA 2 trial in section 10.
Full paper – Yosipovitch G, Mollanazar N, Ständer S, Kwatra SG, Kim BS, Laws E, Mannent LP, Amin N, Akinlade B, Staudinger HW, Patel N, Yancopoulos GD, Weinreich DM, Wang S, Shi G, Bansal A, O'Malley JT. Dupilumab in patients with prurigo nodularis: two randomized, double-blind, placebo-controlled phase 3 trials. Nat Med. 2023 May;29(5):1180-1190. [44]	N/A	LIBERTY-PN PRIME and PRIME2 2 trials in section 10.

5.3 Literature used for inputs for the health economic model

A cost comparison was conducted for drug acquisition costs (medicine costs) between intervention (nemolizumab) and comparator (dupilumab). The costs of dupilumab, TCS and TCIs were sourced from medicinpriser.dk [50] (Table 9).

Table 9 Relevant literature used for input to the health economic model

Reference (Full citation incl. reference number)	Input/estimate	Method of identification	Reference to where in the application the data is described/applied
Publicly available sources/literature	Medicine costs	According to DMC guidelines, medicine costs were sourced from medicinpriser.dk [50].	Section 11. Table 57 and Table 58.

6. Efficacy

6.1 Efficacy of nemolizumab compared to dupilumab for adults with moderate-to-severe prurigo nodularis

6.1.1 Relevant studies

As previously described in section 5.1, in the absence of head-to-head studies comparing nemolizumab and dupilumab in adults (aged ≥ 18 years) with moderate-to-severe PN, an ITC (network meta-analysis [NMA]) was conducted. In order to find the relevant studies for nemolizumab and dupilumab for patients with prurigo nodularis, an SLR was performed. Details of the SLR are presented in Appendix H. The studies included in the ITC were NCT03181503, OLYMPIA 1, and OLYMPIA 2, which compared nemolizumab to placebo, and LIBERTY-PN PRIME and PRIME 2, which compared dupilumab to placebo.

The endpoints were evaluated at different time points. In this dossier, only endpoints at week 16 and week 24 will be presented, as they are relevant for the application.

For the endpoints “DLQI absolute change from baseline at week 12/16”, and “Peak Pruritus Numerical Rating Scale (PP-NRS) improvement ≥4 points and IGA success at week 12/16” 12-week data for dupilumab was compared with 16-week data for nemolizumab in the ITC. Therefore, data for those endpoints at week 12 are presented. In this section, efficacy data is presented and DLQI-related data is presented in section 10.

All studies used in the comparison are presented in Table 10. All the studies are presented in detail in Appendix A.

Table 10 Overview of study design for studies included in the comparison

Trial name, NCT-number (reference)	Study design	Study duration	Patient population	Intervention	Comparator	Outcomes and follow-up time
NCT03181503 [35, 37]	Randomized, placebo-controlled, double-blinded, parallel group, multicenter study, phase II, to evaluate the safety and efficacy of nemolizumab compared to its placebo.	12-week treatment period.	Patients with prurigo nodularis.	Nemolizumab (subcutaneous administration), 3 subcutaneous injections of nemolizumab 0.5 milligram per kilogram (mg/kg) Q4W up to Week 8.	Placebo (subcutaneous administration), 3 subcutaneous injections of placebo (matched to nemolizumab) every 4 weeks (Q4W) up to Week 8.	The primary outcome was the percent change from baseline in the peak pruritus score on the numerical rating scale at week 4. Secondary outcomes were the changes from baseline in the peak and mean pruritus scores on the numerical rating scale at week 12, in the verbal rating scale score for itch (on a scale from 0 [no pruritus] to 4 [very severe pruritus]) at week 12, in the dynamic pruritus score for the change in itch (on a scale from 0 [strongly worsened pruritus] to 8 [almost no pruritus or no pruritus], with a score of 4 indicating no change) at week 4, in the investigator's global assessment of disease severity on the basis of the appearance of lesions (on a scale from 0 [clear] to 4 [severe]), and in a multi-dimensional, 7-item prurigo activity score to monitor the stage of disease (number, distribution, and activity of prurigo lesions) at week 12. Exploratory outcomes included changes in the Dermatology Life Quality Index (scores range from 0 to 30, with 30 representing the worst possible quality of life due to pruritus; a change in the score of ≥4 points is considered to be clinically important) and in the numerical rating scale score for sleep disturbance to determine sleep quality (on a scale from 0 to 10, with higher scores indicating worse sleep quality). Patients' assessments of the numerical rating scale score for pruritus, the verbal rating scale score for pruritus, and the numerical rating scale score for sleep disturbance were performed daily by the patients at home in the evening using a handheld device. The dynamic pruritus score was assessed 24 hours, 48 hours, and 72 hours after the first injection and at week 4 before the second injection. The Dermatology Life Quality Index was assessed at baseline and at weeks 4 and 12 or at early discontinuation of

Trial name, NCT-number (reference)	Study design	Study duration	Patient population	Intervention	Comparator	Outcomes and follow-up time
						the trial. The investigator's assessments of the prurigo activity score and the investigator's global assessment of disease severity were recorded at baseline; at weeks 4, 8, and 12; and at the follow-up visit at week 18.
OLYMPIA 1, NCT04501666 [3, 38, 39]	Randomized, double-blind, placebo-controlled, phase III study to assess the efficacy and safety of nemolizumab versus placebo.	Screening period (up to 4 weeks), a 24-week treatment period, and an 8-week follow-up period (12 weeks after their last study drug injection).	Adults with moderate-to-severe prurigo nodularis.	Nemolizumab monotherapy (subcutaneous administration), every 4 weeks for 24 weeks. At baseline, patients weighing less than 90 kg received an initial dose of nemolizumab, 60 mg, followed by nemolizumab, 30mg, every 4 weeks, and patients weighing 90 kg or more received nemolizumab, 60 mg, every 4 weeks.	Placebo matching nemolizumab monotherapy (subcutaneous administration).	The primary endpoints were the proportion of patients with a clinically meaningful itch response, defined as a 4-point or more improvement from baseline in weekly average PP-NRS score at week 16, and the proportion of patients with IGA success at week 16 (defined as IGA score of 0/1 [clear/almost clear] and a ≥2-point improvement from baseline). The key secondary endpoints included the proportion of patients with itch response at week 4; proportion of patients with weekly average PP-NRS score of less than 2 at weeks 4 and 16 (qualifying as an itch-free or nearly itch-free state); and proportion of patients with a clinically meaningful improvement in sleep disturbance, defined as an improvement of at least 4 points from baseline on the Sleep Disturbance Numerical Rating Scale (SD-NRS; scores range from 0 [no sleep loss] to 10 [I did not sleep at all]), at weeks 4 and 16. The study also had secondary endpoints evaluating outcomes in Prurigo Activity and Severity score, Dermatology Life Quality Index and EuroQoL Group 5-Dimensions (EQ-5D) questionnaire, Hospital Anxiety and Depression Scale (HADS), PN-associated pain frequency and intensity, and Patient Global Assessment of Disease and Patient Global Assessment of Treatment through week 24.

Trial name, NCT-number (reference)	Study design	Study duration	Patient population	Intervention	Comparator	Outcomes and follow-up time
OLYMPIA 2, NCT04501679 [40-42]	Randomized, double-blind, placebo-controlled, phase III study to assess the efficacy and safety of nemolizumab versus placebo.	Screening period (up to 4 weeks), a 16-week treatment period, and an 8-week follow-up period (12 weeks after their last study drug injection).	Adults with moderate-to-severe prurigo nodularis.	Initial 60-mg dose of nemolizumab followed by subcutaneous injections of 30 mg or 60 mg (depending on baseline weight) every 4 weeks for 16 weeks.	Placebo matching the initial 60-mg dose of nemolizumab followed by subcutaneous injections of 30 mg or 60 mg (depending on baseline weight) every 4 weeks for 16 weeks.	There were two primary efficacy endpoints at week 16: itch response, defined as an improvement from baseline of 4 points or more on the PP-NRS, and an IGA response, defined as a score of 0 (clear) or 1 (almost clear) plus a reduction of at least 2 points from baseline. There were five key secondary endpoints included in the hierarchical plan, to adjust for multiple testing: a reduction from baseline of 4 points or more on the PP-NRS score at week 4, a weekly average PP-NRS score of less than 2 at weeks 4 and 16, and a reduction from baseline of 4 or more points on the sleep disturbance numerical rating scale (SD-NRS; range, 0 [no sleep loss] to 10 [unable to sleep at all]) at weeks 4 and 16. A reduction from baseline of 4 points or more on the PP-NRS and on the SD-NRS represents a clinically meaningful improvement. Other secondary endpoints included additional aspects of skin lesions, patient-reported pruritus, sleep disturbance, pain frequency and intensity, global assessment of disease and treatment, health-related quality of life (assessed by the Dermatology Life Quality Index and EuroQoL Group 5-Dimensions [EQ-5D] questionnaire), and symptoms of anxiety and depression (assessed by the Hospital Anxiety and Depression Scale [HADS]).
LIBERTY-PN PRIME, NCT04183335 [44, 46]	Randomized, double blind, placebo-controlled, multi-center, parallel group, phase	The duration of study for each participant included 2-4 weeks of screening	Patients with prurigo nodularis who are inadequatel y controlled on topical	Participants received dupilumab at a loading dose of 600 milligrams (mg), subcutaneously (SC) on Day 1 followed by dupilumab 300 mg	Participants received placebo matched to dupilumab 600 mg (loading dose), SC on Day 1 followed by placebo matched to dupilumab 300 mg Q2W for 24 weeks added	The primary endpoint was the proportion of patients with a ≥4-point reduction in Worst Itch Numeric Rating Scale (WI-NRS) score (range 0 (‘no itch’) to 10 (‘worst imaginable itch’)) at week 24 (PRIME). WI-NRS is validated in PN, with research to date supporting a four-point reduction as clinically meaningful.

Trial name, NCT-number (reference)	Study design	Study duration	Patient population	Intervention	Comparator	Outcomes and follow-up time
	III study to evaluate the efficacy and safety of dupilumab versus placebo.	period, 24 weeks of treatment period and 12 weeks of post treatment period.	prescription therapies or when those therapies are not advisable.	once every 2 weeks (Q2W) for 24 weeks added to background therapy of topical corticosteroids/topical calcineurin inhibitors (TCS/TCI) at stable dose.	to background therapy of TCS/TCI at stable dose.	Key secondary end points included proportion of patients with reduction in skin lesion number to an Investigator Global Assessment for PN-Stage (IGA PN-S) score of 0 or 1 at week 24. IGA PN-S is also validated in PN, with scores ranging from 0 to 4 (0, 'clear' (no nodules); 1, 'almost clear' (≤5 nodules); 2, 'mild' (6–19 nodules); 3, 'moderate' (20–99 nodules); 4, 'severe' (≥100 nodules)). Other pre-specified secondary and tertiary endpoints included assessment of QoL, skin pain, sleep and mental health.
PRIME2, NCT04202679 [44, 47]	Randomized, double blind, placebo-controlled, multi-center, parallel group, phase III study to evaluate the efficacy and safety of dupilumab versus placebo.	The duration of study for each participant included 2-4 weeks of screening period, 24 weeks of treatment period and 12 weeks of post treatment period.	Patients with prurigo nodularis who are inadequatel y controlled on topical prescription therapies or when those therapies are not advisable.	Participants received dupilumab at a loading dose of 600 mg, SC on Day 1 followed by dupilumab 300 mg Q2W for 24 weeks added to background therapy of TCS/TCI at stable dose.	Participants received placebo matched to dupilumab 600 milligrams (mg) (loading dose), subcutaneously (SC) on Day 1 followed by placebo matched to dupilumab 300 mg once every 2 weeks (Q2W) for 24 weeks added to background therapy of topical corticosteroids/topical calcineurin inhibitors (TCS/TCI) at stable dose.	The primary endpoint was the proportion of patients with a ≥4-point reduction in Worst Itch Numeric Rating Scale (WI-NRS) score (range 0 ('no itch') to 10 ('worst imaginable itch')) at week 12 (PRIME2). WI-NRS is validated in PN, with research to date supporting a four-point reduction as clinically meaningful. Key secondary end points included proportion of patients with reduction in skin lesion number to an Investigator Global Assessment for PN-Stage (IGA PN-S) score of 0 or 1 at week 24. IGA PN-S is also validated in PN, with scores ranging from 0 to 4 (0, 'clear' (no nodules); 1, 'almost clear' (≤5 nodules); 2, 'mild' (6–19 nodules); 3, 'moderate' (20–99 nodules); 4, 'severe' (≥100 nodules)). Other pre-specified secondary and tertiary endpoints included assessment of QoL, skin pain, sleep and mental health.

6.1.2 Comparability of studies

6.1.2.1 Study design

Studies varied in terms of phase (phase 2 vs. phase 3), sample size (50-295 patients), and wash-out period duration (1-4 weeks). This highlights the potential for bias and will be acknowledged as the analysis limitation. Studies utilised parallel design.

6.1.2.2 Outcome measurement

The following efficacy outcomes relevant for this application were evaluated in similar manners and reported across the trials: DLQI change from baseline, IGA response, PP/Worst Itch Numeric Rating Scale (WI-NRS) ≥4 and change from baseline in PP/WI-NRS, PP NRS/WI-NRS and IGA composite endpoint. The comparability between PP-NRS and WI-NRS outcomes is supported by the literature [51]. The trials consistently analysed IGA success as proportion of participants with IGA 0 or 1 on a 5-point scale ranging from 0 (clear) to 4 (severe).

6.1.2.3 Comparability of patients across studies

The included studies were broadly similar in most aspects of patient characteristics. Some differences across trials were observed in the following characteristics: treatment-refractory status, use of concomitant TCS/TCI, proportion of Asian patients enrolled, duration of PN, background of atopy, and disease severity.

Dupilumab trials required to include patients with a history of failing TCS and tended to include a higher proportion of patients with Asian origin, atopy background, and lower duration of PN and disease severity scores when compared with nemolizumab trials.

The dupilumab trials (LIBERTY-PN PRIME, PRIME2) allowed the use of TCI/TCS (56-61% of patients used TCI/TCS during the study), while the nemolizumab trials did not.

Severity was not defined in the inclusion criteria of the dupilumab trials but is assumed to be moderate-to-severe based on baseline characteristics (see Table 11).

Table 11 Baseline characteristics of patients in studies included for the comparative analysis of efficacy and safety – ITT population

	NCT03181503 [35]		OLYMPIA 1 [38]		OLYMPIA 2 [42]		LIBERTY-PN PRIME [44]		PRIME2 [44]	
	Nemolizumab (N=34)	Placebo (N=36)	Nemolizumab (N=190)	Placebo (N=96)	Nemolizumab (N=183)	Placebo (N=91)	Dupilumab (n=75)	Placebo (N=76)	Dupilumab (N=78)	Placebo (N=82)
Mean age (SD), years	59.7 (13.2)	52.4 (17.5)	57.5 (12.8)	57.6 (13.4)	53.7 (14.4)	50.8 (15.0)	49.2 (17.4)	51.1 (15.8)	51.0 (15.8)	46.7 (15.2)
Gender, no. of females (%)	19 (56)	22 (61)	110(57.9)	56(58.3)	113 (61.7)	55 (60.4)	52 (69.3)	48 (63.2)	52 (66.7)	51 (62.2)
Race										
White, no. (%)	33 (97)	35 (97)	160(84.2)	81(84.4)	147 (80.3)	68 (74.7)	35 (46.7)	45 (59.2)	48 (61.5)	48 (58.5)
Black, no. (%)	1 (3)	1 (3)	18(9.5)	10(10.4)	5 (2.7)	7 (7.7)	8 (10.7)	3 (3.9)	3 (3.8)	5 (6.1)
Asian, no. (%)	–	–	10(5.3)	2(2.1)	23 (12.6)	14 (15.4)	29 (38.7)	25 (32.9)	25 (32.1)	27 (32.9)
Other, no. (%)	–	–	2(1.0)	2(2.1)	8 (4.4)	2 (2.2)	3 (4.0)	3 (4.0)	2 (2.6)	2 (2.4)
Not reported, no. (%)	–	–	0	1(1.0)						
Mean body weight (SD), kg	81.6 (21.8)	80.3 (20.7)	87.1(21.8)	80.8(17.8)	79.7 (17.8)	80.8 (22.3)	75.2 (17.3)	71.4 (17.0)	73.9 (17.5)	75.0 (19.7)

	NCT03181503 [35]		OLYMPIA 1 [38]		OLYMPIA 2 [42]		LIBERTY-PN PRIME [44]		PRIME2 [44]	
	Nemolizumab (N=34)	Placebo (N=36)	Nemolizumab (N=190)	Placebo (N=96)	Nemolizumab (N=183)	Placebo (N=91)	Dupilumab (n=75)	Placebo (N=76)	Dupilumab (N=78)	Placebo (N=82)
Weekly average PP-NRS, mean (SD)[1]	8.4 (1.2)	8.4 (1.2)	8.5(0.9)(n=184)	8.4(1.0)(n=96)	8.5 (0.9)	8.4 (1.0)	8.6 (0.9)	8.3 (1.1)	8.5 (1.0)	8.5 (1.0)
Weekly average SD-NRS[2], mean (SD)	–	–	7.0 (2.4)	6.9(2.3)	7.2 (2.2)	7.3 (2.2)	4.4 (2.4)	4.3 (2.2)	4.4 (2.3)	4.2 (2.5)
Main duration of PN, (SD)[3]	–	–	86.9 (85.3)	100.6 (98.6)	104.2 (100.7)	108.6 (114.9)	6.0 (7.6)	5.4 (6.2)	5.4 (6.9)	5.5 (7.0)
History of atopy n (%)[4]	5 (15)	6 (17)	60 (31.6)	33 (34.3)	57 (31.1)	31 (34.1)	33 (44.0)	28 (38.6)	34 (43.6)	40 (48.8)
Previous therapy reported										
Topical	–	–	106 (55.8)	54 (56.3)	144 (78.7)	72 (79.1)	74 (98.7)	76 (100)	78 (100)	82 (100)
Systemic	–	–	81 (42.6)	33 (34.4)	104 (56.8)	57 (62.6)	53 (70.7)	52 (68.4)	49 (62.8)	52 (63.4)
Other	–	–	22 (11.6)	5 (5.2)	–	–	–	–	–	–
Intralesional corticosteroid	–	–	5 (2.6)	2 (2.1)	8 (4.4)	5 (5.5)	–	–	–	–

	NCT03181503 [35]		OLYMPIA 1 [38]		OLYMPIA 2 [42]		LIBERTY-PN PRIME [44]		PRIME2 [44]	
	Nemolizumab (N=34)	Placebo (N=36)	Nemolizumab (N=190)	Placebo (N=96)	Nemolizumab (N=183)	Placebo (N=91)	Dupilumab (n=75)	Placebo (N=76)	Dupilumab (N=78)	Placebo (N=82)
Mean DLQI score (SD)	16.9 (7.5)	15.8 (6.0)	17.1 (7.0)	16.9 (6.7)	16.5 (6.8)	17.1 (6.6)	17.8 (7.1)	15.7 (7.3)	18.2 (6.5)	18.2 (7.0)
Mean HADS score (SD)										
Anxiety	–	–	7.8 (4.5)	7.3 (4.4)	8.1 (4.5)	7.2 (4.2)	8.5 (5.2)	8.3 (4.6)	9.3 (4.2)	9.5 (5.1)
Depression	–	–	6.7 (4.7)	6.5 (4.7)	6.6 (4.2)	5.4 (4.0)	6.0 (3.8)	6.0 (4.1)	6.9 (4.0)	6.3 (4.0)
Investigator's Global Assessment score, no. (%)										
3	16 (47)	22 (61)	107 (56.3)	62(64.6)	108 (59.0)	48 (52.7)	54 (72.0)	53 (70.7)	49 (62.8)	49 (60.5)
4	18 (53)	14 (39)	83 (43.7)	34(35.4)	75 (41.0)	43 (47.3)	21 (28.0)	22 (29.3)	29 (37.2)	32 (39.5)

Abbreviations: BSC, best supportive care; DLQI, Dermatology Life Quality Index; PP-NRS, Peak Pruritus Numerical Rating Scale; SD, standard deviation; SD-NRS, Sleep Disturbance Numerical Rating Scale.

[1]In LIBERTY-PN PRIME and PRIME2: Mean WI-NRS (0–10) score.

[2]In LIBERTY-PN PRIME and PRIME2: Mean Sleep-NRS (0–10) score.

[3]OLYMPIA 1, OLYMPIA 2: months; LIBERTY-PN PRIME, PRIME2: years.

[4] NCT03181503, OLYMPIA 1, OLYMPIA 2: defined as a medical history of atopic dermatitis, asthma, or allergic rhinoconjunctivitis.; LIBERTY-PN PRIME, PRIME2: defined as having a medical history of AD, allergic rhinitis/rhinoconjunctivitis, asthma or food allergy.

Sources: Ständer, et al. 2020 [35], Ständer, et al. 2024 [38], Kwatra, et al. 2023 [42], Yosipovitch, et al. 2023 [44].

6.1.3 Comparability of the study population(s) with Danish patients eligible for treatment

No input related to patient characteristics was included in the cost comparison analysis. Therefore, Table 12 is not applicable.

Table 12 Characteristics in the relevant Danish population and in the health economic model (N/A)

	Value in Danish population (reference)	Value used in health economic model (reference if relevant)
N/A	N/A	N/A

6.1.4 Efficacy – results per NCT03181503

Detailed information about the results of all outcomes included in the comparative analysis is presented in Appendix B.

6.1.4.1 PP-NRS absolute change from baseline at week 12

At week 12, the absolute change from baseline in the PP-NRS was a reduction by 5.1 points in the nemolizumab group, as compared with a reduction by 2.1 points in the placebo group (difference, −3.0 points; 95% confidence interval [CI], (−4.4−(−1.7)) [35].

6.1.5 Efficacy – results per OLYMPIA 1

In this section, the efficacy endpoints (non-responder imputation [NRI] data) that were included in the ITC are described. The safety endpoints are presented in section 9 and the HRQoL endpoints in section 10. Detailed information about the results of all outcomes included in the comparative analysis as well as the observed cases (OC) data is presented in Appendix B.

6.1.5.1 PP-NRS improvement ≥4 points at week 16

At week 16, itch response was achieved in 111 of 190 patients (58.4%) treated with nemolizumab and 16 of 96 patients (16.7%) receiving placebo (strata adjusted difference, 41.8% [95% CI, 31.5%–52.0%]; P < 0.001) [38].

6.1.5.2 PP-NRS improvement ≥4 points at week 24

[redacted]

6.1.5.3 PP-NRS absolute change from baseline at week 16

At week 16, the absolute change from baseline in the PP-NRS was a reduction by 4.7 points in the nemolizumab group, as compared with a reduction by 1.6 points in the placebo group (difference, −3.1 points; 95% confidence interval [CI], −3.9–(−2.4); [redacted] [32, 38].

6.1.5.4 PP-NRS absolute change from baseline at week 24

At week 24, the absolute change from baseline in the PP-NRS was a reduction by 4.9 points in the nemolizumab group, as compared with a reduction by 1.5 points in the placebo group (difference, −3.4 points; 95% confidence interval [CI], −4.2–(−2.7); [redacted] [32, 38].

6.1.5.5 IGA success at week 16

At week 16, the IGA success occurred in 50 of 190 patients (26.3%) treated with nemolizumab and 7 of 96 patients (7.3%) receiving placebo (strata-adjusted difference, 14.6% [95% CI, 6.7%-22.6%]; P = 0.003) [38].

6.1.5.6 IGA success at week 24

[redacted]

6.1.5.7 PP-NRS improvement ≥4 points and IGA success at week 16

[redacted]

6.1.5.8 PP-NRS improvement ≥4 points and IGA success at week 24

[redacted]

6.1.6 Efficacy – results per OLYMPIA 2

In this section, the efficacy endpoints (NRI data) that were included in the ITC are described. The HRQoL endpoints are presented in section 10, the safety endpoints in section 9. Detailed information about the results of all outcomes included in the comparative analysis as well as the OC data is presented in Appendix B.

6.1.6.1 PP-NRS improvement ≥4 points at week 16

At week 16, PP-NRS improvement ≥4 points occurred in 103 of 190 patients (56.3%) treated with nemolizumab and 19 of 91 patients (20.9%) receiving placebo (strata adjusted difference, 37.4% [95% CI, 26.3%-48.5%]; P <0.001) [42].

6.1.6.2 PP-NRS absolute change from baseline at week 16

The PP-NRS absolute change from baseline was a reduction by 4.8 points in the nemolizumab group, compared with a reduction by 1.7 points in the placebo group (difference, −3.1 points; 95% CI, −26.3 to −48.5; P<0.001) (week 16) [42].

6.1.6.3 IGA success at week 16

At week 16, IGA success occurred in 69 of 183 patients (37.7%) treated with nemolizumab and 10 of 91 patients (11.0%) receiving placebo (strata adjusted difference, 28.5% [95% CI, 18.8%-28.2%]; P < 0.001) [42].

6.1.7 Efficacy – results per LIBERTY-PN PRIME

In this section, the efficacy endpoints (NRI data for the ITT population) that were included in the ITC are described. The safety endpoints are presented in section 9 and the HRQoL endpoints in section 10. Detailed information about the results of all outcomes included in the comparative analysis as well as the data for the subgroup of patients with no TCS use are presented in Appendix B.

6.1.7.1 WI-NRS improvement ≥4 points at week 24

In the ITT population at week 24, WI-NRS improvement ≥4 points occurred in 45 of 75 patients (60.0%) treated with dupilumab and 14 of 76 patients (18.4%) receiving placebo (strata adjusted difference, 42.7% [95% CI, 27.8%-57.7%]; P < 0.001). When restricting the dupilumab population to those patients without stable use of TCS or TCI, WI-NRS improvement ≥4 points occurred in 16 of 28 patients (57.1%) treated with dupilumab and 8 of 31 patients (25.8%) receiving placebo (response rate difference, 33.5% [95% CI, 5.71%-61.4%] [44].

6.1.7.2 IGA success at week 24

In the ITT population at week 24, IGA success occurred in 36 of 75 patients (48.0%) treated with dupilumab and 14 of 76 patients (18.4%) receiving placebo (strata adjusted difference, 28.3% [95% CI, 13.4%-43.2%]; P < 0.001).

6.1.7.3 WI-NRS improvement ≥4 points and IGA success at week 12

WI-NRS improvement ≥4 points and IGA success occurred in 33 of 75 patients (44.0%) treated with dupilumab and 12 of 76 patients (15.8%) receiving placebo (strata adjusted difference, 29.2% [95% CI, 27.8%-57.7%]; P < 0.001) (week 12, ITT population) [44].

6.1.7.4 WI-NRS improvement ≥4 points and IGA success at week 24

WI-NRS improvement ≥4 points and IGA success occurred in 45 of 75 patients (60.0%) treated with dupilumab and 14 of 76 patients (18.4%) receiving placebo (strata adjusted difference, 42.7% [95% CI, 27.8%-57.7%]; P < 0.001) (week 24, ITT population).

6.1.8 Efficacy – results per PRIME2

In this section, the efficacy endpoints (NRI data for the ITT population) that were included in the ITC are described. The safety endpoints are presented in section 9 and the HRQoL endpoints in section 10. Detailed information about the results of all outcomes included in the comparative analysis as well as the data for the subgroup of patients with no TCS use are presented in Appendix B.

6.1.8.1 WI-NRS improvement ≥4 points at week 24

At week 24, WI-NRS improvement ≥4 points occurred in 45 of 78 patients (57.7%) treated with dupilumab and 16 of 82 patients (19.5%) receiving placebo (strata adjusted difference, 42.6% [95% CI, 29.1%-56.1%]; P < 0.001) [44].

6.1.8.2 IGA success at week 24

At week 24, IGA success occurred in 35 of 78 patients (44.9%) treated with dupilumab and 13 of 82 patients (15.9%) receiving placebo (strata adjusted difference, 30.8% [95% CI, 16.4%-45.2%]; P < 0.001) [44].

6.1.8.3 WI-NRS improvement ≥4 points at week 24 and IGA success at week 24

In the ITT population at week 24, WI-NRS improvement ≥4 points and IGA success occurred in 25 of 78 patients (32.1%) treated with dupilumab and 7 of 82 patients (8.5%) receiving placebo (strata adjusted difference, 25.5% [95% CI, 13.1%-37.9%]; P < 0.001) [44].

7. Comparative analyses of efficacy

7.1.1 Differences in definitions of outcomes between studies

In the nemolizumab studies, the itch response was evaluated by using the PP-NRS, whereas in dupilumab studies, it was WI-NRS. Both scores are considered comparable.

7.1.2 Method of synthesis

A clinical SLR was conducted according to the standards of established guidelines. The included studies were reviewed to assess uniformity among the included trials and determine potential sources of heterogeneity of an evidence network for analysis. The feasibility assessment findings confirmed that the studies proposed to be included in the networks can be considered sufficiently comparable with respect to study design, patient demography (e.g., age, race/ethnicity, etc.), disease severity, and trial outcome measurements. However, the following heterogeneity was observed and should be acknowledged as limitations:

- Differences in patient characteristics, such as duration of PN, disease severity, race, previous treatments, and history of failing TCS.

- Specific concerns regarding the comparison between nemolizumab and dupilumab, especially concerning the use of TCS during the trial.
- Varying timepoints in the conducted studies.
- Limited availability of as observed analyses, including outcomes after the receipt of rescue treatments.

The outcomes found feasible at one or more timepoints included change from baseline (CFB) in Dermatology Life Quality Index (DLQI) and Peak Pruritus (PP) Numerical Rating Scale (NRS)/Worst Itch (WI) NRS (PP-NRS and WI-NRS scores are considered comparable), the proportion of responders of Investigator Global Assessment (IGA) (0 or 1), PP NRS/ WI-NRS response (>=4 points improvement) and composite outcome of PP NRS/WI-NRS (>=4 points improvement) and IGA (0 or 1), and proportion of patients experiencing a treatment-emergent adverse event (TEAE).

Nemolizumab and dupilumab were compared on different efficacy and safety outcomes under Bayesian NMA framework. Data for continuous outcomes of CFB in DLQI and PP NRS/WI-NRS were analysed under normal assumption (with identify link) and binary outcome data of the proportions of responders of IGA 0/1, PP NRS/ WI-NRS ≥4-point improvement, the composite outcome of PP NRS/WI-NRS (≥4-point improvement) and IGA (0/1), and the proportion of patients experiencing TEAEs were analysed in binomial framework (with logit link).

- 12/16 weeks (CFB in DLQI, PP NRS/WI-NRS and IGA composite)
- 16 weeks (PP NRS/ WI-NRS improvement of ≥4 from baseline, absolute CFB in PP NRS/WI-NRS)
- 24 weeks (CFB in DLQI, IGA 0/1, PP NRS/ WI-NRS improvement of ≥4 from baseline, PP NRS/WI-NRS and IGA composite, absolute CFB in PP NRS/WI-NRS)

Fixed-effects (FE) and Random-effects (RE) Bayesian NMAs were conducted for the outcomes listed in Table 13.

7.1.2.1 Sensitivity analysis 1 – Imputation method

Observed cases (OC) data from trials was prioritized for analyses given NICE recommendations. However, there were limited OC data in dupilumab trials and heterogeneity across trials with respect to analytic techniques. Given a lack of OC data in comparator trials, a separate sensitivity analysis was conducted using NRI data for nemolizumab when all comparator data resulted from NRI analyses. Results were found to be consistent with the base case analyses [52].

7.1.2.2 Sensitivity analysis 2 – No TCS/TCI use

Given the lack of definitive evidence for TCS/TCI use as an effect modifier, ITT population from dupilumab trials (TCS/TCI allowed) were pooled with ITT population from nemolizumab trials (TCS/TCI not allowed) and analysed as a base-case scenario. However, for the outcomes and timepoints where dupilumab trial reported results for subgroup of patients with no TCS use, a sensitivity analysis was conducted [52].

7.1.3 Results from the comparative analysis

[redacted]

[redacted]

[redacted]

Table 13 Results from the comparative analysis of nemolizumab vs. dupilumab in PN

Outcome measure	Nemolizumab trials – data input	Dupilumab trials – data input	Result
PP-NRS/WI-NRS improvement ≥4 points at week 16 Base case scenario	[redacted]		
PP-NRS/WI-NRS improvement ≥4 points at week 16 Sensitivity analysis 1 – imputation method	[redacted]		

Outcome measure	Nemolizumab trials – data input	Dupilumab trials – data input	Result
PP-NRS/WI-NRS improvement ≥4 points at week 24 Base case	[redacted]		
PP-NRS/WI-NRS improvement ≥4 points at week 24 Sensitivity analysis 2 – no TCS/TCI use	[redacted]		
PP-NRS/WI-NRS absolute change from baseline at week 16 Base case	[redacted]		
PP-NRS/WI-NRS absolute change from baseline at week 24 Base case	[redacted]		
IGA success at week 24	[redacted]		

Outcome measure	Nemolizumab trials – data input	Dupilumab trials – data input	Result
Base case	[redacted]		
IGA success at week 24 Sensitivity analysis 2 – no TCS/TCI use	[redacted]		
Composite PP-NRS/WI-NRS improvement ≥4 points and IGA success at week 12/16 Base case	[redacted]		
Composite PP-NRS/WI-NRS improvement ≥4 points and IGA success at week 12/16 Sensitivity analysis 1 – imputation method	[redacted]		
Composite PP-NRS/WI-NRS improvement ≥4 points and IGA success at week 24 Base case	[redacted]		
Composite PP-NRS/WI-NRS improvement ≥4 points and IGA success at week 24 Sensitivity analysis 2 – no TCS/TCI use	[redacted]		

Abbreviations: CrI, credible interval; Dupi, dupilumab; MD, Mean difference; Nemo, nemolizumab; NRI, non-responder imputation; OC, observed case; Pbo, placebo; PP/WI-NRS, Peak Pruritus/Worst Itch Numerical Rating Scale; TCI, topical calcineurin inhibitor; TCS, topical corticosteroid; WOCF, worst observation carried forward. Note: Two main observed cases-like analyses were available. "As observed" analysis was available from PRIME trials and it was defined as "data collected after study intervention discontinuation and/or after

taking the selected prohibited medications/procedures and/or rescue medications were included, and missing data at week 12/24 were considered non-responders". "Observed case" analysis was available from OLYMPIA trials, and it was defined as "no data were imputed. For this analysis, if any rescue medication was received, data on or post rescue therapy were analysed as observed (i.e., not treated as non-responders).Source: [52]

7.1.4 Efficacy – results per PP-NRS improvement ≥4 points at week 16

[redacted]

Figure 2 PP-NRS improvement ≥4 points at week 16, base case

[redacted]

[redacted]

Figure 3 PP-NRS improvement ≥4 points at week 16, sensitivity analysis 1 – imputation method

[redacted]

7.1.5 Efficacy – results per PP-NRS absolute change from baseline at week 16

[redacted]

Figure 4 PP-NRS absolute change from baseline at week 16, base case

7.1.6 Efficacy – results per PP-NRS absolute change from baseline at week 24

[redacted]

Figure 5 PP-NRS absolute change from baseline at week 24, base case

7.1.7 Efficacy – results per IGA success at week 24

[redacted]

Figure 6 IGA success at week 24, base case

Figure 7 IGA success at week 24, sensitivity analysis 2 – no TCS/TCI use

No sensitivity analysis using NRI data was performed at 24 weeks for the ITT population as observed case data for IGA success for dupilumab was available.

7.1.8 Efficacy – results per composite PP-NRS improvement ≥4 points and IGA success at week 12/16

Figure 8 Composite PP-NRS improvement ≥4 points and IGA success at week 12/16, base case

Figure 9 Composite PP-NRS improvement ≥4 points and IGA success at week 16, sensitivity analysis 1 – imputation method

7.1.9 Efficacy – results per composite PP-NRS improvement ≥4 points and IGA success at week 24

Figure 10 Composite PP-NRS improvement ≥4 points and IGA success at week 24, base case

Figure 11 Composite PP-NRS improvement ≥4 points and IGA success at week 24, sensitivity analysis 2 – no TCS/TCI use

8. Modelling of efficacy in the health economic analysis

8.1 Presentation of efficacy data from the clinical documentation used in the model

8.1.1 Extrapolation of efficacy data

Not applicable.

8.1.1.1 Extrapolation of [effect measure 1]

Not applicable.

Table 14 Summary of assumptions associated with extrapolation of [effect measure] (N/A)

Method/approach	Description/assumption
Data input	N/A
Model	N/A
Assumption of proportional hazards between intervention and comparator	N/A
Function with best AIC fit	N/A
Function with best BIC fit	N/A
Function with best visual fit	N/A
Function with best fit according to evaluation of smoothed hazard assumptions	N/A
Validation of selected extrapolated curves (external evidence)	N/A
Function with the best fit according to external evidence	N/A
Selected parametric function in base case analysis	N/A
Adjustment of background mortality with data from Statistics Denmark	N/A
Adjustment for treatment switching/cross-over	N/A
Assumptions of waning effect	N/A
Assumptions of cure point	N/A

8.1.1.2 Extrapolation of [effect measure 2]

Not applicable.

8.1.2 Calculation of transition probabilities

Table 15 Transitions in the health economic model (N/A)

Health state (from)	Health state (to)	Description of method	Reference
N/A	N/A	N/A	N/A

8.2 Presentation of efficacy data from [additional documentation]

Not applicable.

8.3 Modelling effects of subsequent treatments

Not applicable.

8.4 Other assumptions regarding efficacy in the model

Not applicable.

8.5 Overview of modelled average treatment length and time in model health state

Table 16 Estimates in the model (N/A)

	Modelled average [effect measure] (reference in Excel)	Modelled median [effect measure] (reference in Excel)	Observed median from relevant study
N/A	N/A	N/A	N/A

Table 17 Overview of modelled average treatment length and time in model health state, undiscounted and not adjusted for half cycle correction (adjust the table according to the model)

Treatment	Treatment length [months]	Health state 1 [months]
Nemolizumab	24	N/A
Dupilumab	24	N/A

9. Safety

9.1 Safety data from the clinical documentation

The safety analyses were performed for the safety population. In case of NCT03181503 [35], OLYMPIA 1 [38], and OLYMPIA 2 [42], the safety population comprised patients who underwent randomization and received at least one dose of nemolizumab or placebo. Safety assessments were performed through week 18 in the NCT03181503 trial [35]. Safety results presented in this application for OLYMPIA 1 and OLYMPIA 2 correspond to adverse events that occurred during the treatment period (16 weeks) and were defined as adverse events with onset date on or after the first dose date till 4 weeks after the last treatment or early discontinuation, whichever was earlier [38, 42].

In the NCT03181503 trial [35], adverse events are reported and included in this application. Regarding adverse drug reactions, they are not reported in the trial, since in the study protocol it is mentioned that according to International Council for Harmonisation (ICH) E6, an unexpected adverse drug reaction is defined as an adverse reaction, the nature or severity of which is not consistent with the applicable study drug information [35]. In OLYMPIA 1 and OLYMPIA 2, the safety results are presented as treatment-emergent adverse events and in this application are included as adverse events.

In NCT03181503 trial [35], the percentage of patients with adverse events (AEs) was 68% in the nemolizumab group and 67% in the placebo group (Table 18). Four patients in the nemolizumab group and three in the placebo group had serious adverse events. The only serious adverse events with frequency of ≥ 5% recorded was atopic dermatitis in the placebo group (Table 20). Two patients in each group discontinued nemolizumab or placebo owing to adverse events; one of the patients in the placebo group who discontinued had a serious adverse event.

In OLYMPIA 1 [38], a total of 134 patients (71.7%) treated with nemolizumab and 62 (65.3%) receiving placebo experienced at least 1 AE during the treatment period (Table 18), and the majority of AEs were of mild or moderate severity. There were no clinically meaningful differences in the incidence of SAEs, and AE leading to study discontinuation, between the nemolizumab and placebo groups. The most common AEs (occurring in ≥5% of the patients) were headache and eczema that occurred with a higher frequency in the nemolizumab group during the treatment period. These events were mostly mild or moderate in severity, managed with simple analgesics (headache) or topical treatments (eczema); none led to study discontinuation. The majority of AEs resolved by the end of the study. There were no serious adverse events with frequency of ≥ 5% recorded in the trial.

In OLYMPIA 2 [42], a total of 112 patients (61.2%) receiving nemolizumab and 48 (52.7%) receiving placebo had at least one adverse event during the treatment period (Table 18). Serious adverse events that emerged during the treatment period occurred in more patients in the placebo group than in the nemolizumab group. One patient in each group

had a serious adverse event during the treatment period that was considered to be a result of the trial regimen: bullous pemphigoid in a patient in the nemolizumab group and generalized exfoliative dermatitis in a patient in the placebo group. There were no serious adverse events with frequency of ≥ 5% recorded in the trial. No deaths occurred during the trial. The percentage of patients who withdrew from the trial because of adverse events that emerged during the treatment period was similar in the two groups (2.2% each). The most common individual adverse events (occurring in ≥5% of the patients) that emerged during the treatment period in the nemolizumab group and were reported with higher frequency than in the placebo group were atopic dermatitis and headache. The events coded as “atopic dermatitis” (e.g., “exacerbation of atopic dermatitis”) were distinct from worsening of prurigo nodularis events, which were coded as “neurodermatitis”. Most of the atopic dermatitis events were mild in severity and were managed with topical treatments without discontinuation of nemolizumab.

In the dupilumab-related trials, LIBERTY-PN PRIME and PRIME2 [44], all safety analyses were also performed on the safety population, which included all randomized patients who received ≥1 dose of dupilumab or placebo. Results are reported for the 24 weeks of treatment. In these two trials, the AEs were analysed in three categories: pre-treatment AEs, TEAEs, and post-treatment AEs [44]. The safety data in this application focuses on the TEAEs, which were defined as AEs that developed, worsened or became serious during the treatment-emergent period, and in this application are included as adverse events.

In both LIBERTY-PN PRIME and PRIME2 [44], dupilumab was well tolerated and had an overall safety profile consistent with its known profile (Table 19). Treatment-emergent serious adverse events were reported in five (6.7%) and six (8.0%) patients in the dupilumab and placebo groups, respectively, in PRIME, and two (2.6%) and two (2.4%), respectively, in PRIME2. Except for two events of mesenteritis and sepsis experienced by one patient in the placebo group in PRIME, none were considered related to the study intervention. Two placebo-treated patients (2.7%) in LIBERTY-PN PRIME and one placebo-treated patient (1.2%) in PRIME2 discontinued treatment due to a TEAE; no dupilumab-treated patients discontinued treatment. Conjunctivitis occurred equally in the dupilumab and placebo groups in PRIME (two (2.7%) in each) and was more frequent with dupilumab in PRIME2 (three (3.9%) versus zero). None were serious or severe, and none led to study drug discontinuation. Herpes viral infections were also more common with dupilumab in PRIME2: four (5.2%) versus zero, whereas no herpes infections occurred in either group in PRIME. Skin infections occurred less in dupilumab-treated patients than placebo-treated patients in both trials: PRIME, two (2.7%) versus seven (9.3%); PRIME2, four (5.2%) versus five (6.1%). There were no serious adverse events with frequency of ≥ 5% recorded in the trial.

The overview of safety events for each of the studies used to document the efficacy of the intervention (nemolizumab) and the comparator (dupilumab) in this application is presented in Table 18 and Table 19, respectively. A list of all serious adverse events observed in the five studies is reported in Appendix E.

Table 18 Overview of safety events (nemolizumab trials). The time period the table covers is specified for each trial in the table.

	NCT03181503 (time period: up to 18 weeks) [35]			OLYMPIA 1 (time period: during treatment period [16 weeks]†) [38]			OLYMPIA 2 (time period: during treatment period [16 weeks]†)[42]		
	Nemolizumab (N=34) [35]	Placebo (N=36) [35]	Difference, % (95 % CI)	Nemolizumab (N=187) [38]	Placebo (N=95) [38]	Difference, % (95 % CI)	Nemolizumab (N=183) [42]	Placebo (N=91) [42]	Difference, % (95 % CI)
Number of adverse events, n	77	69	8	N/A	N/A	N/A	264	106	158
Number and proportion of patients with ≥1 adverse events, n (%)	23 (68)	24 (67)	1.0 (-21.0, 23.0)	134 (71.7)	62 (65.3)	6.4 (-5.2, 17.9)	112 (61.2)	48 (52.7)	8.5 (-4.0, 20.9)
Number of serious adverse events*, n	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Number and proportion of patients with ≥ 1 serious adverse events, n (%)	4 (11.76)	3 (8.33)	3.4 (-10.7, 17.5)	16 (8.6)	10 (10.5)	-2.0 (-9.3, 5.4)	4 (2.2)	5 (5.5)	-3.3 (-8.4, 1.8)
Number of CTCAE grade ≥ 3 events, n	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Number and proportion of patients with ≥ 1	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A

	NCT03181503 (time period: up to 18 weeks) [35]			OLYMPIA 1 (time period: during treatment period [16 weeks]†) [38]			OLYMPIA 2 (time period: during treatment period [16 weeks]†)[42]		
	Nemolizumab (N=34) [35]	Placebo (N=36) [35]	Difference, % (95 % CI)	Nemolizumab (N=187) [38]	Placebo (N=95) [38]	Difference, % (95 % CI)	Nemolizumab (N=183) [42]	Placebo (N=91) [42]	Difference, % (95 % CI)
CTCAE grade ≥ 3 events, n (%)									
Number of adverse reactions, n	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Number and proportion of patients with ≥ 1 adverse reactions, n (%)	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Number and proportion of patients who had a dose reduction, n (%)	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Number and proportion of patients who discontinue treatment regardless of reason*, n (%)	3 (8.8)	7 (19.4)	-10.6 (-26.7, 5.4)	N=190, 24 (12.6)	N=96, 13 (13.5)	-0.9 (-9.2, 7.4)	9 (4.9)	3 (3.3)	1.6 (-3.2, 6.4)
Number and proportion of patients who discontinue treatment	2 (6)	2 (6)	0.3 (-10.6, 11.2)	9 (4.8)	4 (4.2)	0.6 (-4.5, 5.7)	4 (2.2)	2 (2.2)	0.0 (-3.7, 3.7)

	NCT03181503 (time period: up to 18 weeks) [35]			OLYMPIA 1 (time period: during treatment period [16 weeks]†) [38]			OLYMPIA 2 (time period: during treatment period [16 weeks]†)[42]		
	Nemolizumab (N=34) [35]	Placebo (N=36) [35]	Difference, % (95 % CI)	Nemolizumab (N=187) [38]	Placebo (N=95) [38]	Difference, % (95 % CI)	Nemolizumab (N=183) [42]	Placebo (N=91) [42]	Difference, % (95 % CI)
due to adverse events, n (%)									

Note: †Treatment-emergent adverse events (TEAEs) during treatment period were defined as adverse events with onset date on or after the first dose date till 4 weeks after the last treatment or early discontinuation, whichever was earlier. *These values correspond to the intent-to-treat population (all randomised patients).

Abbreviations: CI, confidence interval.

Table 19 Overview of safety events (dupilumab trials). Results are reported for the 24 weeks of treatment.

	LIBERTY-PN PRIME [44]			PRIME2 [44]		
	Dupilumab (N=75) [44]	Placebo (N=75) [44]	Difference, % (95 % CI)	Dupilumab (N= 77) [44]	Placebo (N= 82) [44]	Difference, % (95 % CI)
Number of adverse events, n	N/A	N/A	N/A	N/A	N/A	N/A
Number and proportion of patients with ≥1 adverse events, n (%)	49 (65.3)	42 (56.0)	9.3 (-6.2, 24.9)	42 (54.5)	38 (46.3)	8.2 (-7.3, 23.7)
Number of serious adverse events*, n	N/A	N/A	N/A	N/A	N/A	N/A

	LIBERTY-PN PRIME [44]			PRIME2 [44]		
	Dupilumab (N=75) [44]	**Placebo (N=75) [44]**	**Difference, % (95 % CI)**	**Dupilumab (N= 77) [44]**	**Placebo (N= 82) [44]**	**Difference, % (95 % CI)**
Number and proportion of patients with ≥ 1 serious adverse events*, n (%)	5 (6.7)	6 (8.0)	-1.3 (-9.7, 7.0)	2 (2.6)	2 (2.4)	0.2 (-4.7, 5.0)
Number of CTCAE grade ≥ 3 events, n	N/A	N/A	N/A	N/A	N/A	N/A
Number and proportion of patients with ≥ 1 CTCAE grade ≥ 3 events§, n (%)	N/A	N/A	N/A	N/A	N/A	N/A
Number of adverse reactions, n	N/A	N/A	N/A	N/A	N/A	N/A
Number and proportion of patients with ≥ 1 adverse reactions, n (%)	N/A	N/A	N/A	N/A	N/A	N/A
Number and proportion of patients who had a dose reduction, n (%)	N/A	N/A	N/A	N/A	N/A	N/A
Number and proportion of patients who discontinue treatment regardless of reason, n (%)	1 (1.3)	16 (21.3)	-20.0 (-29.6, -10.4)	2 (2.6)	25 (30.5)	-27.9 (-38.5, -17.3)
Number and proportion of patients who discontinue treatment due to adverse events, n (%)	0 (0)	2 (2.7)	-2.7 (-6.3, 1.0)	0 (0)	1 (1.2)	-1.2 (-3.6, 1.2)

Abbreviations: CI, confidence interval.

Table 20 Serious adverse events with frequency of ≥ 5% recorded in the NCT03181503 trial [35] (time frame: up to 18 weeks)

Adverse events	Nemolizumab 0.5 mg/kg (N=34)		Placebo (N=36)	
	Number of patients with adverse events	Number of adverse events	Number of patients with adverse events	Number of adverse events
Atopic dermatitis, n (%)	0 (0.0)	N/A	3 (8.3)	N/A

Table 21 Adverse events used in the health economic model (N/A)

Adverse events	Intervention	Comparator		
	Frequency used in economic model for intervention	Frequency used in economic model for comparator	Source	Justification
Adverse event, n (%)	N/A	N/A	N/A	N/A

9.1.1 Comparative analysis of the safety data

A comparative analysis of the safety data was also performed in the ITC. Table 22 presents the safety data input from the individual studies used in the ITC and the results of the ITC for the TEAEs at the end of the study.

Table 22 Results from the comparative analysis of the safety results of nemolizumab vs. dupilumab in PN

Outcome measure	Nemolizumab trials – data input	Dupilumab trials – data input	Result
TEAEs end of study	[redacted]		

Abbreviations: CrI, credible interval; Dupi, dupilumab; MD, Mean difference; Nemo, nemolizumab; Pbo, placebo; TEAE, treatment-emergent adverse event.

[redacted]

Figure 12 Results per TEAEs at the end of study, base case

9.2 Safety data from external literature applied in the health economic model

This section is not applicable since a cost comparison is presented in the current application and no AEs were included in the analysis.

Table 23 Adverse events that appear in more than X % of patients (N/A)

Adverse events	Intervention (N=x)			Comparator (N=x)			Difference, % (95 % CI)	
	Number of patients with adverse events	Number of adverse events	Frequency used in economic model for intervention	Number of patients with adverse events	Number of adverse events	Frequency used in economic model for comparator	Number of patients with adverse events	Number of adverse events
Adverse event, n	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A

Abbreviation: N/A, not applicable.

10. Documentation of health-related quality of life (HRQoL)

A cost comparison is performed in the application, therefore, the focus of this section is on comparing the intervention and the comparator's effect on HRQoL measured in the clinical studies.

The DLQI questionnaire was used to collect HRQoL data in the NCT03181503, OLYMPIA 1, and OLYMPIA 2 trials for the intervention, nemolizumab. The DLQI questionnaire was also used in the comparator, dupilumab, trials LIBERTY-PN PRIME, PRIME2. The HADS questionnaire was used in OLYMPIA 1, OLYMPIA 2, LIBERTY-PN PRIME, and PRIME2. The EQ-5D questionnaire was used in OLYMPIA 1 and OLYMPIA 2 studies. An overview of the

included HRQoL instruments in the studies informing clinical effectiveness in this application is presented in Table 24.

Table 24 Overview of included HRQoL instruments

Measuring instrument	Source	Utilization
EQ-5D	OLYMPIA 1, OLYMPIA 2	Comparative analysis
DLQI	NCT03181503, OLYMPIA 1, OLYMPIA 2, LIBERTY-PN PRIME, PRIME2	Comparative analysis
HADS	OLYMPIA 1, OLYMPIA 2, LIBERTY-PN PRIME, PRIME2	Comparative analysis

Abbreviations: DLQI, Dermatology Life Quality Index; EQ-5D, EuroQoL Group 5-Dimensions; HADS, Hospital Anxiety and Depression Scale.

Information on all HRQoL instruments included from the studies informing clinical effectiveness are described in the following sections. Since a cost comparison is carried out in this application, sections 10.4 and 10.5 are not applicable.

10.1 Presentation of the health-related quality of life EQ-5D – OLYMPIA 1 and OLYMPIA 2

In LIBERTY-PN PRIME, and PRIME2 studies, the endpoints “change from baseline in EQ-5D-5L single index score to week 24” and “change from baseline in EQ-5D visual analog scale to week 24” were included as tertiary/exploratory endpoints. However, results for this endpoint are not publicly available and are therefore not presented in this application. This section focuses on EQ-5D data from OLYMPIA 1 and OLYMPIA 2 trials.

10.1.1 Study design and measuring instrument

The EQ-5D instrument is a validated questionnaire, completed by the subject, that consists of 2 parts. The first part consists of 5 multiple choice QoL questions and the second is a 100 point VAS scale with 0 being “Worst imaginable health state” and 100 being “Best imaginable health state” [32, 33, 53].

10.1.2 Data collection

Data collection via EQ-5D VAS questionnaire for the endpoint “change from baseline in EQ-5D for each subscale at each visit” was performed at baseline, week 16 and week 24 in OLYMPIA 1 trial [32] and at baseline and week 16 in OLYMPIA 2 trial [33]. EQ-5D VAS score was summarized as a continuous variable using OC for baseline, Week 16, and Week 24 in OLYMPIA 1 and for baseline and Week 16 in OLYMPIA 2, for the ITT population. The absolute change from baseline in EQ-5D VAS score was also summarized using OC. The absolute change from baseline in EQ-5D VAS score at Week 16 and Week 24 (OLYMPIA 1) and at week 16 (OLYMPIA 2) was analysed using ANCOVA and OC, including treatment group (in OLYMPIA 1), analysis center, and body weight at randomization cut-off (<90 kg and ≥90 kg) as factors and baseline as a covariate [32, 33].

Baseline was defined as the last non-missing value before the first dose of study drug. All observed data even after use of rescue therapy were included. There were no imputations for missing data [32, 33]. Five dimensions of EQ-5D VAS (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression) were summarized as a categorical variable using OC. Number of patients that completed the EQ-5D questionnaire at each time point is available and presented in Table 25, Table 26, Table 27, and Table 28. However, data about patients expected to complete the EQ-5D questionnaire are not available.

Table 25 Pattern of missing data and completion, EQ-5D (nemolizumab) from OLYMPIA 1 study

Time point	HRQoL population N	Missing N (%)	Expected to complete N	Completion N (%)
	Number of patients at randomization	Number of patients for whom data is missing (% of patients at randomization)	Number of patients "at risk" at time point X	Number of patients who completed (% of patients expected to complete)
Baseline	[redacted]			
Week 16				
Week 24				

Abbreviations: HRQoL, health-related quality of life; N/A, not available. Source: OLYMPIA 1 CSR, Data on file [32].

Table 26 Pattern of missing data and completion, EQ-5D (placebo) from OLYMPIA 1 study

Time point	HRQoL population N	Missing N (%)	Expected to complete N	Completion N (%)
	Number of patients at randomization	Number of patients for whom data is missing (% of patients at randomization)	Number of patients "at risk" at time point X	Number of patients who completed (% of patients expected to complete)
Baseline	[redacted]			
Week 16				
Week 24				

Abbreviations: HRQoL, health-related quality of life; N/A, not available. Source: OLYMPIA 1 CSR, Data on file [32].

Table 27 Pattern of missing data and completion, EQ-5D (nemolizumab) from OLYMPIA 2 study

Time point	HRQoL population N	Missing N (%)	Expected to complete N	Completion N (%)
	Number of patients at randomization	Number of patients for whom data is missing (% of patients at randomization)	Number of patients "at risk" at time point X	Number of patients who completed (% of patients expected to complete)
Baseline	[redacted]			
Week 16				

Abbreviations: HRQoL, health-related quality of life; N/A, not available. Source: OLYMPIA 2 CSR, Data on file [33].

Table 28 Pattern of missing data and completion, EQ-5D (placebo) from OLYMPIA 2 study

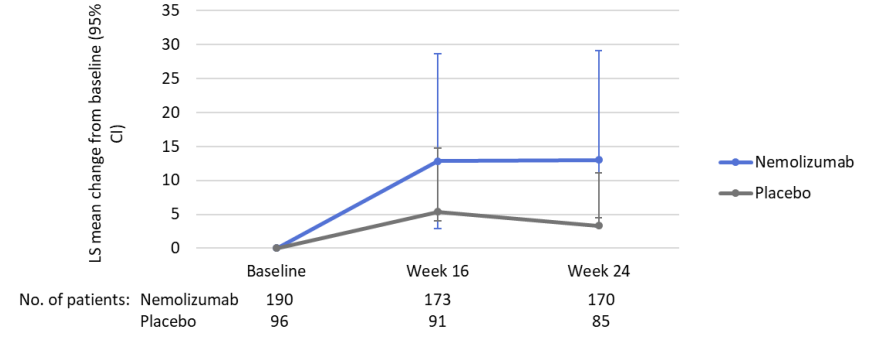
Time point	HRQoL population N	Missing N (%)	Expected to complete N	Completion N (%)
	Number of patients at randomization	Number of patients for whom data is missing (% of patients at randomization)	Number of patients "at risk" at time point X	Number of patients who completed (% of patients expected to complete)
Baseline	[redacted]			
Week 16				

Abbreviations: HRQoL, health-related quality of life; N/A, not available. Source: OLYMPIA 2 CSR, Data on file [33].

10.1.3 HRQoL results

The EQ-5D HRQoL available results correspond to the EQ-5D VAS questionnaire. The EQ-5D VAS results for OLYMPIA 1 and OLYMPIA 2 are presented below. In OLYMPIA 1, nemolizumab was more efficacious than placebo in increasing the EQ-5D VAS score compared with baseline at week 16 (LS mean difference 7.49; 95% CI 2.71, 12.27; [redacted] and at week 24 (LS mean difference 9.65; 95% CI 4.39, 14.92; [redacted] (Figure 13) [32, 38].

Figure 13 LS mean change from baseline of EQ-5D VAS at week 16 and week 24 for both the intervention (nemolizumab) and comparator (placebo) – OLYMPIA 1



Abbreviations: CI, confidence interval; LS, least squares; SE, standard error. Source: Adapted from OLYMPIA 1 CSR, Data on file [32].

Table 29 HRQoL EQ-5D VAS summary statistics – OLYMPIA 1

	Intervention (nemolizumab)	Comparator (placebo)	Intervention vs. comparator
	[redacted]		
Baseline			
Week 16			
Week 24			

Note: Baseline is defined as the last non-missing value before the first dose of study drug. All observed data even after use of rescue therapy included; No imputations for missing data. Abbreviations: CI, confidence interval. Source: Adapted from OLYMPIA 1 CSR, Data on file [32].

In OLYMPIA 2, at week 16, nemolizumab was more efficacious than placebo in Increasing the EQ-5D VAS score compared with baseline (LS mean difference 11.06; 95% CI 6.53, 15.59; [redacted] Figure 14).

Figure 14 LS mean change from baseline of EQ-5D VAS at week 16 for both the intervention (nemolizumab) and comparator (placebo) – OLYMPIA 2

[redacted]

Abbreviations: CI, confidence interval; LS, least squares; SE, standard error. Source: Adapted from OLYMPIA 2 CSR, Data on file [33].

Table 30 HRQoL EQ-5D VAS summary statistics – OLYMPIA 2

	Intervention (nemolizumab)	Comparator (placebo)	Intervention vs. comparator
	[redacted]		
Baseline			
Week 16			

Note: Baseline is defined as the last non-missing value before the first dose of study drug. All observed data even after use of rescue therapy included; No imputations for missing data. Abbreviations: CI, confidence interval. Source: Adapted from OLYMPIA 2 CSR, Data on file [33].

10.2 Presentation of the health-related quality of life DLQI

HRQoL DLQI data is available from the NCT03181503, OLYMPIA 1 and OLYMPIA 2 studies (nemolizumab studies) as well as for the LIBERTY-PN PRIME and PRIME2 studies (dupilumab studies).

10.2.1 NCT03181503

10.2.1.1 Study design and measuring instrument

DLQI is a validated 10-item questionnaire, covering domains including symptoms/feelings, daily activities, leisure, work/school, personal relationships and treatment. Subject will rate each question ranging from 0 (not at all) to 3 (very much), and the total score ranges from 0 to 30, with a higher score indicating a poorer QoL. DLQI was given only to the subset of subjects who fluently speak a language in which the questionnaire was available (based on availability of validated translations in participating countries).

10.2.1.2 Data collection

DLQI assessment was performed by the subject at baseline, week 4 and week 12 and in case of early termination visit or unscheduled visit, if applicable. DLQI response was defined as a reduction in score of at least 5 points [35]. Pattern of missing data and completion is not available for the NCT03181503 study.

Table 31 Pattern of missing data and completion (NCT03181503)

Time point	HRQoL population N	Missing N (%)	Expected to complete N	Completion N (%)
	Number of patients at randomization	Number of patients for whom data is missing (% of patients at randomization)	Number of patients "at risk" at time point X	Number of patients who completed (% of patients expected to complete)

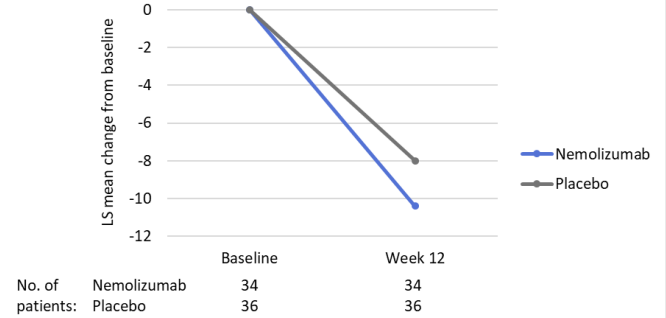
Time point	HRQoL population N	Missing N (%)	Expected to complete N	Completion N (%)
Baseline	N/A	N/A	N/A	N/A
Week 4	N/A	N/A	N/A	N/A
Week 12	N/A	N/A	N/A	N/A

Abbreviation: N/A, not available.

10.2.1.3 HRQoL results

The DLQI results available for the NCT03181503 trial are limited. At week 12, the LS mean change from baseline in the DLQI was -10.4 in the nemolizumab group and -8.0 in the placebo group (Figure 15 and Table 32) [35]. In a post hoc analysis, the percentage of patients with a response according to the DLQI, defined as a reduction of 4 points or more (minimal clinically important difference), was higher in the nemolizumab group than in the placebo group both at week 4 and at week 12 (59% vs. 31% at both time points) [35].

Figure 15 LS mean change from baseline of DLQI at week 12 for both the intervention (nemolizumab) and comparator (placebo) – NCT03181503



Source: [35].

Table 32 HRQoL DLQI summary statistics - NCT03181503

	Intervention (nemolizumab)		Comparator (placebo)		Intervention vs. comparator
	N	LS mean	N	LS mean	Difference
Change from baseline in DLQI at week 12	34	-10.4	36	-8.0	-2.4

Abbreviations: DLQI, Dermatology Life Quality Index; LS, least squares; SE, standard error. Source: [35].

10.2.2 OLYMPIA 1 and OLYMPIA 2

10.2.2.1 Study design and measuring instrument

The DLQI is a validated 10-item questionnaire covering domains including symptoms/feelings, daily activities, leisure, work/school, personal relationships, and treatment [54]. Patients rated each question ranging from 0 (not at all) to 3 (very much). A higher total score indicates a poorer QoL.

10.2.2.2 Data collection

DLQI data was collected at baseline, week 4, week 16, and week 24 in OLYMPIA 1 [32] and at baseline, week 4 and week 16 in OLYMPIA 2 [33]. Patient-reported outcome assessments, including DLQI, were to occur before Investigator assessments, laboratory sample collections, and study drug administration. The DLQI total score was summarized as a continuous variable using OC for the ITT population at baseline, Week 4, Week 16, and Week 24 in OLYMPIA 1 and at baseline, week 4, and week 16 in OLYMPIA 2. The absolute change from baseline in DLQI total score was also summarized. The absolute change from baseline in DLQI total score at Week 4, Week 16, and Week 24 in OLYMPIA 1 and at baseline, week 4, and week 16 in OLYMPIA 2 was analysed using ANCOVA with multiple imputation (MI) assuming missing at random (MAR) and using mixed effects model for repeated measures (MMRM) approach, including treatment group (OLYMPIA 1), analysis center, and body weight at randomization cut-off (<90 kg and ≥90 kg) as factors and baseline as a covariate. Improvement of ≥4 in DLQI total score was calculated using baseline as the reference point for change in DLQI total score. The proportion of subjects with an improvement of ≥4 was summarized for the ITT population using OC and non-responder imputation [32, 33]. Number of patients that completed the DLQI questionnaire at each time point is available and presented in Table 33, Table 34, Table 35, and Table 36. However, data about patients expected to complete the questionnaire are not available.

Table 33 Pattern of missing data and completion, DLQI (nemolizumab) from OLYMPIA 1 study

Time point	HRQoL population N	Missing N (%)	Expected to complete N	Completion N (%)
	Number of patients at randomization	Number of patients for whom data is missing (% of patients at randomization)	Number of patients "at risk" at time point X	Number of patients who completed (% of patients expected to complete)
Baseline	[redacted]			
Week 4				
Week 16				
Week 24				

Abbreviations: DLQI, Dermatology Life Quality Index; HRQoL, health-related quality of life; N/A, not available.
Source: OLYMPIA 1 CSR, Data on file [32].

Table 34 Pattern of missing data and completion, DLQI (placebo) from OLYMPIA 1 study

Time point	HRQoL population N	Missing N (%)	Expected to complete N	Completion N (%)
	Number of patients at randomization	Number of patients for whom data is missing (% of patients at randomization)	Number of patients "at risk" at time point X	Number of patients who completed (% of patients expected to complete)
Baseline	[redacted]			
Week 4				
Week 16				
Week 24				

Abbreviations: DLQI, Dermatology Life Quality Index; HRQoL, health-related quality of life; N/A, not available.
Source: OLYMPIA 1 CSR, Data on file [32].

Table 35 Pattern of missing data and completion, DLQI (nemolizumab) from OLYMPIA 2 study

Time point	HRQoL population N	Missing N (%)	Expected to complete N	Completion N (%)
	Number of patients at randomization	Number of patients for whom data is missing (% of patients at randomization)	Number of patients "at risk" at time point X	Number of patients who completed (% of patients expected to complete)
Baseline	[redacted]			
Week 4				
Week 16				

Abbreviations: DLQI, Dermatology Life Quality Index; HRQoL, health-related quality of life; N/A, not available.
Source: OLYMPIA 2 CSR, Data on file [33].

Table 36 Pattern of missing data and completion, DLQI (placebo) from OLYMPIA 2 study

Time point	HRQoL population N	Missing N (%)	Expected to complete N	Completion N (%)
	Number of patients at randomization	Number of patients for whom data is missing (% of patients at randomization)	Number of patients "at risk" at time point X	Number of patients who completed (% of patients expected to complete)
Baseline	[redacted]			

Time point	HRQoL population N	Missing N (%)	Expected to complete N	Completion N (%)
Week 4	[redacted]			
Week 16				

Abbreviations: DLQI, Dermatology Life Quality Index; HRQoL, health-related quality of life; N/A, not available.
Source: OLYMPIA 2 CSR, Data on file [33].

10.2.2.3 HRQoL results

The HRQoL endpoints related to the DLQI questionnaire are "Change from baseline in DLQI" and "Proportion of patients with ≥4-point improvement in DLQI". Here "Change from baseline in DLQI" results are presented for OLYMPIA 1 and OLYMPIA 2. In OLYMPIA 1, nemolizumab was more effective than placebo in reducing the mean DLQI total score compared with baseline at week 4 (LS mean difference -4.80; 95% CI -6.31, -3.29; XXX x [redacted], week 16 (LS mean difference -6.39; 95% CI -8.43, -4.35 [redacted], and week 24 (LS mean difference -8.43; 95% CI -10.54, -6.31; [redacted] (Figure 16). In this analysis, subjects were considered treatment failures on or after receiving rescue therapy [32, 38].

Figure 16 LS mean change from baseline of DLQI at week 4, week 16 and week 24 for both the intervention (nemolizumab) and comparator (placebo) – OLYMPIA 1

[redacted]

Note: Analysis of covariance using multiple imputation missing at random (intent-to-treat population) was performed. Baseline was defined as the last non-missing value before the first dose of study drug. If a subject received any rescue therapy, composite variable strategy was applied, the data at/after receipt of rescue therapy were set as worst possible value. The estimates were from 50 complete datasets by MI with MAR assumption. Subjects with missing baseline data were excluded since there was no imputation at baseline. Analysis of covariance model was used for the change from baseline as the dependent variable including treatment group and randomized stratification variables (analysis center and body weight at randomization [<90 kg, ≥90 kg]) as factors and the baseline value as a covariate. Abbreviations: CI, confidence interval. Source: OLYMPIA 1 CSR, Data on file [32].

Table 37 HRQoL DLQI summary statistics – OLYMPIA 1

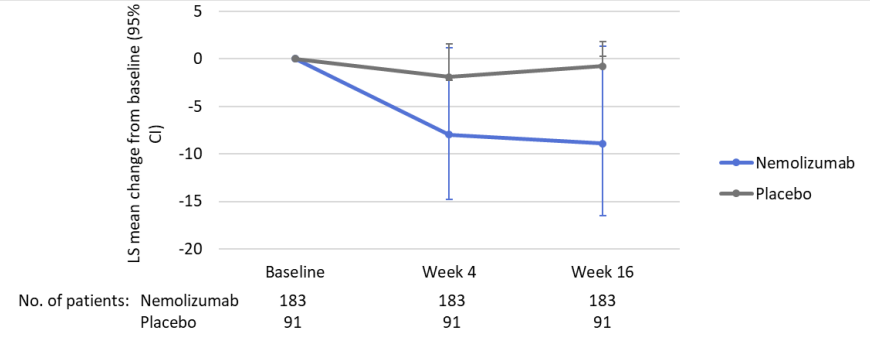
	Intervention (nemolizumab)		Comparator (placebo)		Intervention vs. comparator
	N	Mean (SD)	N	Mean (SD)	Difference (95% CI)
Baseline	[redacted]				

	Intervention (nemolizumab)	Comparator (placebo)	Intervention vs. comparator
Week 4	[redacted]		
Week 16			
Week 24			

Note: Baseline is defined as the last non-missing value before the first dose of study drug. All observed data even after use of rescue therapy included; No imputations for missing data. Abbreviations: CI, confidence interval; SD, standard deviation. Source: OLYMPIA 1 CSR, Data on file [32].

In OLYMPIA 2, In a post hoc exploratory analysis, when subjects were considered treatment failures on or after receiving rescue therapy, nemolizumab was more effective than placebo in reducing the mean DLQI total score compared with baseline at Week 4 (LS mean difference -6.05; 95% CI -7.77, -4.32; [redacted] and Week 16 (LS mean difference -8.15; 95% CI -10.16, -6.14; [redacted] (Figure 17) [33, 42].

Figure 17 LS mean change from baseline of DLQI at week 4 and week 16 for both the intervention (nemolizumab) and comparator (placebo) – OLYMPIA 2



Note: Analysis of covariance using multiple imputation missing at random (intent-to-treat population) was performed. Baseline was defined as the last non-missing value before the first dose of study drug. If a subject received any rescue therapy, composite variable strategy was applied, the data at/after receipt of rescue therapy were set as worst possible value. The estimates were from 50 complete datasets by MI with MAR assumption. Subjects with missing baseline data were excluded since there was no imputation at baseline. Analysis of covariance model was used for the change from baseline as the dependent variable including treatment group and randomized stratification variables (analysis center and body weight at randomization [<90 kg, ≥90 kg]) as factors and the baseline value as a covariate. Abbreviations: CI, confidence interval. Source: OLYMPIA 2 CSR, Data on file [33].

Table 38 HRQoL DLQI summary statistics – OLYMPIA 2

	Intervention (nemolizumab)		Comparator (placebo)		Intervention vs. comparator
	N	Mean (SD)	N	Mean (SD)	Difference (95% CI)
Baseline	[redacted]				

	Intervention (nemolizumab)	Comparator (placebo)	Intervention vs. comparator
Week 4	[redacted]		
Week 16			

Note: Baseline is defined as the last non-missing value before the first dose of study drug. All observed data even after use of rescue therapy included; No imputations for missing data. Abbreviations: CI, confidence interval; SD, standard deviation. Source: OLYMPIA 2 CSR, Data on file [33].

10.2.3 LIBERTY-PN PRIME and PRIME 2

10.2.3.1 Study design and measuring instrument

The instrument comprises 10 items assessing the impact of skin disease on patients' HRQoL over the previous week. The items cover symptoms, leisure activities, work/school or holiday time, personal relationships including intimate, the side effects of treatment, and emotional reactions to having a skin disease. It is a validated questionnaire used in clinical practice and clinical trials [55]. Response scale is a 4-point Likert scale (0 = "not at all" and 3 = "very much") for nine items. The remaining one item about work/studying asks whether work/study has been prevented and then (if "No") to what degree the skin condition has been a problem at work/study; the item is rated on a 3-point Likert scale ("Not at all" to "A lot"). Overall scoring ranges from 0 to 30, with a high score indicative of a poor HRQoL. Even though not validated in PN specifically, the DLQI is well established and widely used to assess HRQoL in patients with skin conditions in clinical trials [55].

10.2.3.2 Data collection

Data collection of the DLQI questionnaire was performed at baseline, week 4, 8, 12, and 24 in LIBERTY-PN PRIME and PRIME 2 studies [44]. Pattern of missing data and completion is not publicly available for LIBERTY-PN PRIME and PRIME 2 studies.

Table 39 Pattern of missing data and completion (LIBERTY-PN PRIME and PRIME 2)

Time point	HRQoL population N	Missing N (%)	Expected to complete N	Completion N (%)
	Number of patients at randomization	Number of patients for whom data is missing (% of patients at randomization)	Number of patients "at risk" at time point X	Number of patients who completed (% of patients expected to complete)
Baseline	N/A	N/A	N/A	N/A
Week 4	N/A	N/A	N/A	N/A
Week 8	N/A	N/A	N/A	N/A

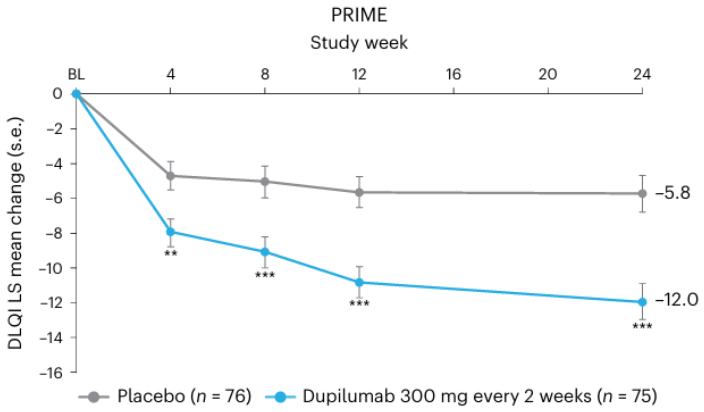
Time point	HRQoL population N	Missing N (%)	Expected to complete N	Completion N (%)
Week 12	N/A	N/A	N/A	N/A
Week 24	N/A	N/A	N/A	N/A

Abbreviation: N/A, not available.

10.2.3.3 HRQoL results

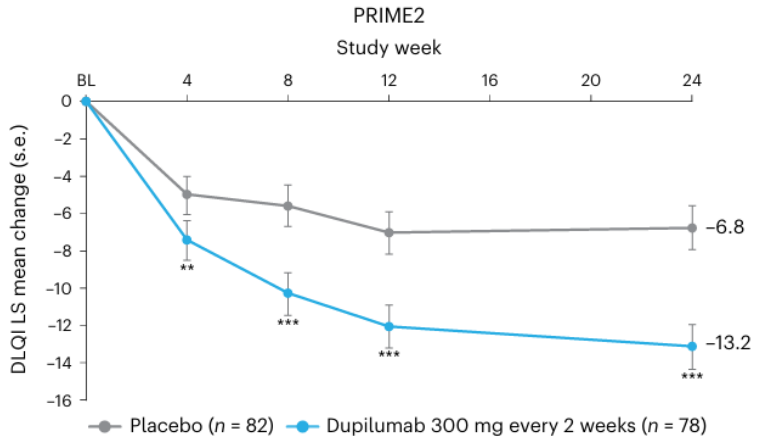
The DLQI LS mean change from baseline at week 4, 8, 12 and 24 for LIBERTY-PN PRIME is presented in Figure 18 and for PRIME2 in Figure 19.

Figure 18 LS mean change (SE) in DLQI from baseline (LIBERTY-PN PRIME)



Note: *P < 0.05, **P < 0.01, ***P < 0.001. Data were presented as mean ± SE. The imputed complete data were analysed by fitting an analysis of covariance (ANCOVA) model with the corresponding BL value, intervention group, documented history of atopy (atopic or non-atopic), stable use of TCS/TCI (yes or no), region and BL antidepressant use (yes or no) as covariates. P values at week 24 are multiplicity-controlled. P values for all the other timepoints are non-multiplicity-controlled. Abbreviations: BL, baseline; DLQI, Dermatology Life Quality Index; LS, least squares; SE, standard error. Source: [44].

Figure 19 LS mean change (SE) in DLQI from baseline (PRIME2)



Note: *P < 0.05, **P < 0.01, ***P < 0.001. Data were presented as mean ± SE. The imputed complete data were analysed by fitting an analysis of covariance (ANCOVA) model with the corresponding BL value, intervention group, documented history of atopy (atopic or non-atopic), stable use of TCS/TCI (yes or no), region and BL antidepressant use (yes or no) as covariates. P values at week 24 are multiplicity-controlled. P values for all the

other timepoints are non-multiplicity-controlled. Abbreviations: BL, baseline; DLQI, Dermatology Life Quality Index; LS, least squares; SE, standard error. Source: [44].

The DLQI results available with specific values from LIBERTY-PN PRIME and PRIME2 correspond to the endpoint “change from baseline in DLQI at week 24”. Dupilumab-treated patients showed significant improvements in QoL compared to placebo-treated patients, as measured by LS mean change (±SE) in DLQI score from baseline at week 24: PRIME, −12.0 (1.0) versus −5.8 (1.0); PRIME2, −13.2 (1.2) versus −6.8 (1.2) (95% CI, −8.3 to −4.0 and −8.4 to −4.4 for the difference, respectively; both P < 0.001) (Table 40 and Table 41) [44].

Table 40 HRQoL DLQI summary statistics - LIBERTY-PN PRIME

	Intervention (dupilumab)		Comparator (placebo)		Intervention vs. comparator
	N	LS mean (SE)	N	LS mean (SE)	Difference (95% CI) p-value
Change from baseline in DLQI at week 24	75	−12.0 (1.0)	76	−5.8 (1.0)	−6.1 (−8.3 to −4.0) p<0.001

Note: Unless otherwise indicated, efficacy analyses were performed in the full analysis set, which included all patients who underwent randomization. For continuous efficacy endpoints, P values and difference versus placebo were derived by an analysis of covariance (ANCOVA) model. P values were derived from the Cox proportional hazard model. Abbreviations: DLQI, Dermatology Life Quality Index; LS, least squares; SE, standard error. Source: [44].

Table 41 HRQoL DLQI summary statistics - PRIME2

	Intervention		Comparator		Intervention vs. comparator
	N	LS mean (SE)	N	LS mean (SE)	Difference (95% CI) p-value
Change from baseline in DLQI at week 24	78	−13.2 (1.2)	82	−6.8 (1.2)	−6.4 (−8.4 to −4.4) p<0.001

Note: Unless otherwise indicated, efficacy analyses were performed in the full analysis set, which included all patients who underwent randomization. For continuous efficacy endpoints, P values and difference versus placebo were derived by an analysis of covariance (ANCOVA) model. P values were derived from the Cox proportional hazard model. Abbreviations: DLQI, Dermatology Life Quality Index; LS, least squares; SE, standard error. Source: [44].

10.2.4 Comparative analysis of DLQI data

[redacted]

Table 42 Results from the comparative analysis of the HRQoL DLQI results of nemolizumab vs. dupilumab in PN

Outcome measure	Nemolizumab trials – data input	Dupilumab trials – data input	Result
DLQI absolute change from baseline at week 12/16 **Base case**	[redacted]		
DLQI absolute change from baseline at week 24 **Base case**	[redacted]		
DLQI absolute change from baseline at week 24 **Sensitivity analysis 2 – no TCS/TCI use**	[redacted]		

Abbreviations: CrI, credible interval; DLQI, Dermatology Life Quality Index; Dupi, dupilumab; MD, Mean difference; Nemo, nemolizumab; OC, observed case; Pbo, placebo; TCI, topical calcineurin inhibitor; TCS, topical corticosteroid; WOCF, worst observation carried forward.

Note: Two main observed cases-like analyses were available. “As observed” analysis was available from PRIME trials and it was defined as “data collected after study intervention discontinuation and/or after taking the selected prohibited medications/procedures and/or rescue medications were included, and missing data at week 12/24 were considered non-responders”. “Observed case” analysis was available from OLYMPIA trials, and it was defined as “no data were imputed. For this analysis, if any rescue medication was received, data on or post rescue therapy were analysed as observed (i.e., not treated as non-responders).’

10.2.4.1 Efficacy – results per DLQI absolute change from baseline at week 12/16

[redacted]

Figure 20 DLQI absolute change from baseline at week 12/16, base case

10.2.4.2 Efficacy – results per DLQI absolute change from baseline at week 24

Figure 21 DLQI absolute change from baseline at week 24, base case

Figure 22 DLQI absolute change from baseline at week 24, sensitivity analysis 2 – no TCS/TCI use

10.3 Presentation of the health-related quality of life HADS

10.3.1 OLYMPIA 1 and OLYMPIA 2

10.3.1.1 Study design and measuring instrument

The HADS is a 14-question questionnaire completed by the subject [56]. Each question had a multiple choice answer that is scored between 0 and 3. Questions are identified as relating to anxiety (A) or depression (D) and a summation for each area is performed leading to a total score of 0 to 21 for each area. Scores of 0 to 7 are considered normal, 8 to 10 are borderline, and ≥11 indicates clinical effects.

10.3.1.2 Data collection

Each HADS score subscale (Total Score Anxiety and Total Score Depression) was summarized as continuous variables using OC for baseline, Week 16, and Week 24 in OLYMPIA 1 and for baseline and week 16 for OLYMPIA 2, for the ITT population. The absolute change from baseline in HADS subscale scores was also summarized. The absolute change from baseline in HADS subscale scores was analysed for Week 16 and Week 24 (OLYMPIA 1) and for week 16 (OLYMPIA 2) using ANCOVA and OC, including treatment group (OLYMPIA 1), analysis center, and body weight at randomization cut-off (<90 kg and ≥90 kg) as factors and baseline as a covariate [32, 33].

Table 43 Pattern of missing data and completion, HADS – total score anxiety and depression (nemolizumab) from OLYMPIA 1 study

Time point	HRQoL population N	Missing N (%)	Expected to complete N	Completion N (%)
	Number of patients at randomization	Number of patients for whom data is missing (% of patients at randomization)	Number of patients "at risk" at time point X	Number of patients who completed (% of patients expected to complete)
Baseline	[redacted]			
Week 16				
Week 24				

Abbreviations: HADS, Hospital Anxiety and Depression Scale; HRQoL, health-related quality of life; N/A, not available. Source: OLYMPIA 1 CSR, Data on file [32].

Table 44 Pattern of missing data and completion, HADS – total score anxiety and depression (placebo) from OLYMPIA 1 study

Time point	HRQoL population N	Missing N (%)	Expected to complete N	Completion N (%)
	Number of patients at randomization	Number of patients for whom data is missing (% of patients at randomization)	Number of patients "at risk" at time point X	Number of patients who completed (% of patients expected to complete)
Baseline	[redacted]			
Week 16				
Week 24				

Abbreviations: HADS, Hospital Anxiety and Depression Scale; HRQoL, health-related quality of life; N/A, not available. Source: OLYMPIA 1 CSR, Data on file [32].

Table 45 Pattern of missing data and completion, HADS – total score anxiety and depression (nemolizumab) from OLYMPIA 2 study [33]

Time point	HRQoL population N	Missing N (%)	Expected to complete N	Completion N (%)
	Number of patients at randomization	Number of patients for whom data is missing (% of patients at randomization)	Number of patients "at risk" at time point X	Number of patients who completed (% of patients expected to complete)
Baseline	[redacted]			
Week 16				

Abbreviations: HADS, Hospital Anxiety and Depression Scale; HRQoL, health-related quality of life; N/A, not available. Source: OLYMPIA 2 CSR, Data on file [33].

Table 46 Pattern of missing data and completion, HADS – total score anxiety and depression (placebo) from OLYMPIA 2 study

Time point	HRQoL population N	Missing N (%)	Expected to complete N	Completion N (%)
	Number of patients at randomization	Number of patients for whom data is missing (% of patients at randomization)	Number of patients "at risk" at time point X	Number of patients who completed (% of patients expected to complete)
Baseline	[redacted]			
Week 16				

Abbreviations: HADS, Hospital Anxiety and Depression Scale; HRQoL, health-related quality of life; N/A, not available. Source: OLYMPIA 2 CSR, Data on file [33].

10.3.1.3 HRQoL results

Results for the endpoint "Change from baseline in hospital anxiety and depression scale score for each subscale" are presented here. In OLYMPIA 1, nemolizumab was more effective than placebo in reducing the HADS total anxiety score compared with baseline at week 16 (LS mean difference -1.18; 95% CI -2.06, -0.30; [redacted] (Figure 23), and HADS total depression score (LS mean difference -1.32; 95% CI -2.16, -0.47; [redacted] (Figure 24). At week 24, nemolizumab was more effective than placebo in reducing the HADS total anxiety score compared with baseline week 24 (LS mean difference -1.58; 95% CI -2.46, -0.71; [redacted] (Figure 23), and HADS total depression score (LS mean difference -1.86; 95% CI -2.78, -0.94; [redacted] (Figure 24) [32, 38].

Figure 23 LS mean change from baseline in HADS (total score anxiety) at week 16 and week 24 for both the intervention (nemolizumab) and comparator (placebo) – OLYMPIA 1

Note: Analysis of covariance - observed cases (intent-to-treat population). Baseline was defined as the last non-missing value before the first dose of study drug. All observed data even after use of rescue therapy were included. There were no imputations for missing data. Analysis of covariance model was used for the change from baseline as the dependent variable including treatment group and randomized stratification variables (analysis center and body weight at randomization [<90 kg, ≥90 kg]) as factors and the baseline value as a covariate. Abbreviations: CI, confidence interval; LS, least squares. Source: OLYMPIA 1 CSR, Data on file [32].

Figure 24 LS mean change from baseline in HADS (total score depression) at week 16 and week 24 for both the intervention (nemolizumab) and comparator (placebo) – OLYMPIA 1

Note: Analysis of covariance - observed cases (intent-to-treat population). Baseline was defined as the last non-missing value before the first dose of study drug. All observed data even after use of rescue therapy were included. There were no imputations for missing data. Analysis of covariance model was used for the change from baseline as the dependent variable including treatment group and randomized stratification variables (analysis center and body weight at randomization [<90 kg, ≥90 kg]) as factors and the baseline value as a covariate. Abbreviations: CI, confidence interval; LS, least squares. Source: OLYMPIA 1 CSR, Data on file [32].

Table 47 HRQoL HADS (total score anxiety) summary statistics – OLYMPIA 1

	Intervention (Nemolizumab)		Comparator (placebo)		Intervention vs. comparator
	N	Mean (SD)	N	Mean (SD)	Difference (95% CI)
Baseline	[redacted]				
Week 16					
Week 24					

Note: Baseline is defined as the last non-missing value before the first dose of study drug. All observed data even after use of rescue therapy included; No imputations for missing data. Abbreviations: HADS, Hospital Anxiety and Depression Scale; SD, standard deviation. Source: OLYMPIA 1 CSR, Data on file [32].

Table 48 HRQoL HADS (total score depression) summary statistics – OLYMPIA 1

	Intervention (Nemolizumab)		Comparator (placebo)		Intervention vs. comparator
	N	Mean (SD)	N	Mean (SD)	Difference (95% CI)
Baseline	[redacted]				
Week 16					
Week 24					

Note: Baseline is defined as the last non-missing value before the first dose of study drug. All observed data even after use of rescue therapy included; No imputations for missing data. Abbreviations: HADS, Hospital Anxiety and Depression Scale; SD, standard deviation. Source: OLYMPIA 1 CSR, Data on file [32].

In OLYMPIA 2, at week 16, nemolizumab was more effective than placebo in reducing the HADS total anxiety score compared with baseline (LS mean difference -1.18; 95% CI -1.98, -0.38; [redacted] (Figure 25), and HADS total depression score (LS mean difference -1.55; 95% CI -2.34, -0.75; [redacted] (Figure 26) [33, 42].

Figure 25 LS mean change from baseline in HADS (total score anxiety) at week 16 for both the intervention (nemolizumab) and comparator (placebo) – OLYMPIA 2

Note: Analysis of covariance - observed cases (intent-to-treat population). Baseline was defined as the last non-missing value before the first dose of study drug. All observed data even after use of rescue therapy were included. There were no imputations for missing data. Analysis of covariance model was used for the change from baseline as the dependent variable including treatment group and randomized stratification variables (analysis center and body weight at randomization [<90 kg, ≥90 kg]) as factors and the baseline value as a covariate. Abbreviations: CI, confidence interval; LS, least squares. Source: OLYMPIA 2 CSR, Data on file [33].

Figure 26 LS mean change from baseline in HADS (total score depression) at week 16 for both the intervention (nemolizumab) and comparator (placebo) – OLYMPIA 2

Note: Analysis of covariance - observed cases (intent-to-treat population). Baseline was defined as the last non-missing value before the first dose of study drug. All observed data even after use of rescue therapy were included. There were no imputations for missing data. Analysis of covariance model was used for the change from baseline as the dependent variable including treatment group and randomized stratification variables (analysis center and body weight at randomization [<90 kg, ≥90 kg]) as factors and the baseline value as a covariate. Abbreviations: CI, confidence interval; LS, least squares. Source: OLYMPIA 2 CSR, Data on file [33].

Table 49 HRQoL HADS (total score anxiety) summary statistics – OLYMPIA 2

	Intervention (Nemolizumab)		Comparator (placebo)		Intervention vs. comparator
	N	Mean (SD)	N	Mean (SD)	Difference (95% CI)
Baseline					
Week 16					

Note: Baseline is defined as the last non-missing value before the first dose of study drug. All observed data even after use of rescue therapy included; No imputations for missing data. Abbreviations: HADS, Hospital Anxiety and Depression Scale; SD, standard deviation. Source: OLYMPIA 2 CSR, Data on file [33].

Table 50 HRQoL HADS (total score depression) summary statistics – OLYMPIA 2

	Intervention (Nemolizumab)		Comparator (placebo)		Intervention vs. comparator
	N	Mean (SD)	N	Mean (SD)	Difference (95% CI)
Baseline					
Week 16					

Note: Baseline is defined as the last non-missing value before the first dose of study drug. All observed data even after use of rescue therapy included; No imputations for missing data. Abbreviations: HADS, Hospital Anxiety and Depression Scale; SD, standard deviation. Source: OLYMPIA 2 CSR, Data on file [33].

10.3.2 LIBERTY-PN PRIME and PRIME 2

10.3.2.1 Study design and measuring instrument

The HADS is a PRO instrument for screening anxiety and depression in non-psychiatric populations; repeated administration also provides information about changes to a patient's emotional state [56, 57]. The HADS consists of 14 items, 7 each for anxiety and depression symptoms; possible scores range from 0 to 21 for each subscale. The following cut-off scores are recommended for both subscales: 0 to 7 equals to normal, 8 to 10 equals to borderline abnormal (borderline case), and 11 to 21 equals to abnormal.

10.3.2.2 Data collection

Data collection of the HADS questionnaire was performed at baseline, week 12, and 24 in LIBERTY-PN PRIME and PRIME 2 studies [44]. Pattern of missing data and completion is not publicly available for LIBERTY-PN PRIME and PRIME 2 studies.

Table 51 Pattern of missing data and completion (LIBERTY-PN PRIME and PRIME 2)

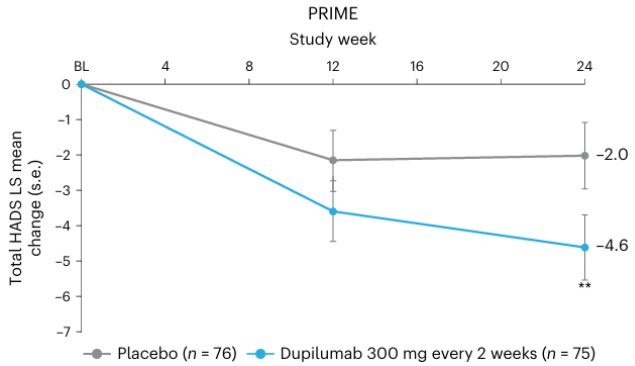
Time point	HRQoL population N	Missing N (%)	Expected to complete N	Completion N (%)
	Number of patients at randomization	Number of patients for whom data is missing (% of patients at randomization)	Number of patients "at risk" at time point X	Number of patients who completed (% of patients expected to complete)
Baseline	N/A	N/A	N/A	N/A
Week 12	N/A	N/A	N/A	N/A
Week 24	N/A	N/A	N/A	N/A

Abbreviation: N/A, not available.

10.3.2.3 HRQoL results

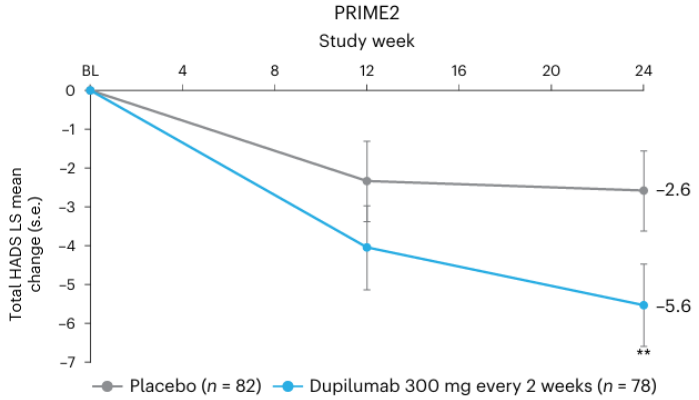
The HADS LS mean change from baseline at week 12 and 24 for LIBERTY-PN PRIME is presented in Figure 27 and for PRIME2 in Figure 28.

Figure 27 LS mean change (SE) in HADS from baseline (LIBERTY-PN PRIME)



Note: *P < 0.05, **P < 0.01, ***P < 0.001. Data were presented as mean ± SE. The imputed complete data were analysed by fitting an analysis of covariance (ANCOVA) model with the corresponding BL value, intervention group, documented history of atopy (atopic or non-atopic), stable use of TCS/TCI (yes or no), region and BL antidepressant use (yes or no) as covariates. P values at week 24 are multiplicity-controlled. P values for all the other timepoints are non-multiplicity-controlled. Abbreviations: BL, baseline; HADS, Hospital Anxiety and Depression Scale; LS, least squares; SE, standard error. Source: [44].

Figure 28 LS mean change (SE) in DLQI from baseline (PRIME2)



Note: *P < 0.05, **P < 0.01, ***P < 0.001. Data were presented as mean ± SE. The imputed complete data were analysed by fitting an analysis of covariance (ANCOVA) model with the corresponding BL value, intervention group, documented history of atopy (atopic or non-atopic), stable use of TCS/TCI (yes or no), region and BL antidepressant use (yes or no) as covariates. P values at week 24 are multiplicity-controlled. P values at week 24 are multiplicity-controlled except for LS mean change in total HADS in PRIME2. P values for all the other timepoints are non-multiplicity-controlled. Abbreviations: BL, baseline; HADS, Hospital Anxiety and Depression Scale; LS, least squares; SE, standard error. Source: [44].

The HADS results available with numerical data from LIBERTY-PN PRIME and PRIME2 correspond to the endpoint “Change from baseline in total HADS score to week 24”. Statistical (PRIME) or non-multiplicity-controlled (PRIME2) significant improvements in anxiety and depression, as measured by LS mean change from baseline in total HADS at week 24, were observed in both studies (Table 52 and Table 53).

Table 52 HRQoL HADS summary statistics – LIBERTY-PN PRIME

	Intervention (dupilumab)		Comparator (placebo)		Intervention vs. comparator
	N	LS Mean (SE)	N	LS mean (SE)	Difference (95% CI) p-value

	Intervention (dupilumab)		Comparator (placebo)		Intervention vs. comparator
Change from baseline in total HADS score to week 24	75	−4.6 (0.9)	76	−2.0 (0.9)	−2.6 (−4.5 to −0.7) p= 0.008

Note: Unless otherwise indicated, efficacy analyses were performed in the full analysis set, which included all patients who underwent randomization. For continuous efficacy endpoints, P values and difference versus placebo were derived by an analysis of covariance (ANCOVA) model. P values were derived from the Cox proportional hazard model. Abbreviations: BL, baseline; HADS, Hospital Anxiety and Depression Scale; LS, least squares; SE, standard error. Source: [44].

Table 53 HRQoL HADS summary statistics – PRIME2

	Intervention (dupilumab)		Comparator (placebo)		Intervention vs. comparator
	N	Mean (SE)	N	Mean (SE)	Difference (95% CI) p-value
Change from baseline in total HADS score to week 24	78	−5.6 (1.1)	82	−2.6 (1.0)	−3.0 (−4.7 to −1.2) p=0.001

Note: Unless otherwise indicated, efficacy analyses were performed in the full analysis set, which included all patients who underwent randomization. For continuous efficacy endpoints, P values and difference versus placebo were derived by an analysis of covariance (ANCOVA) model. P values were derived from the Cox proportional hazard model. Abbreviations: BL, baseline; HADS, Hospital Anxiety and Depression Scale; LS, least squares; SE, standard error. Source: [44].

10.4 Health state utility values (HSUVs) used in the health economic model (N/A)

Since a cost comparison is carried out in the application, this section is not applicable.

10.4.1 HSUV calculation

Not applicable.

10.4.1.1 Mapping

Not applicable.

10.4.2 Disutility calculation

Not applicable.

10.4.3 HSUV results

Not applicable.

Table 54 Overview of health state utility values [and disutilities] (N/A)

	Results [95% CI]	Instrument	Tariff (value set) used	Comments
HSUV A	N/A	N/A	N/A	N/A

10.5 Health state utility values measured in other trials than the clinical trials forming the basis for relative efficacy (N/A)

Since a cost comparison is carried out in the application, this section is not applicable.

10.5.1 Study design

Not applicable.

10.5.2 Data collection

Not applicable.

10.5.3 HRQoL Results

Not applicable.

10.5.4 HSUV and disutility results

Not applicable.

Table 55 Overview of health state utility values [and disutilities] (N/A)

	Results [95% CI]	Instrument	Tariff (value set) used	Comments
HSUV A	N/A	N/A	N/A	N/A

Table 56 Overview of literature-based health state utility values (N/A)

	Results [95% CI]	Instrument	Tariff (value set) used	Comments
Study 1	N/A	N/A	N/A	N/A

11. Resource use and associated costs

11.1 Medicines - intervention and comparator

The economic analysis compares the treatment costs of the intervention, nemolizumab, with the comparator dupilumab, taking into account the use of concomitant treatment,

TCS and TCI for dupilumab. The medicines used in the model are listed in Table. The use of TCS/TCI is modelled after the latest DMC recommendation [1], which prescribed 100 g every 2 weeks of any TCS and 100 g every 2 weeks of TCI (tacrolimus).

Table 57 Medicines used in the model

Medicine	Dose	Relative dose intensity	Frequency	Patient population
Nemolizumab	30 mg	1 injection	Q4W	BW≤90 kg
Nemolizumab	30 mg	2 injections	Q4W	BW>90 kg
Dupilumab	300 mg	1 injection	Q2W	Patients treated with dupilumab
Betamethason	N/A*	100 g	Q2W	Patients treated with dupilumab
Clobetasol	N/A*	100 g	Q2W	Patients treated with dupilumab
Mometason	N/A*	100 g	Q2W	Patients treated with dupilumab
Tacrolimus	N/A*	100 g	Q2W	Patients treated with dupilumab
Pimecrolimus	N/A*	100 g	Q2W	Patients treated with dupilumab

* Patients treated with TCS or TCI are assumed to use 100 g every 2 weeks, in line with the DMC assessment for dupilumab in PN [1].

11.2 Medicines– co-administration

The cost of concomitant treatment is accounted for the patients receiving dupilumab, based on the DMC assessment of dupilumab in PN [1], of 100 g of TCI and TCS every 2 weeks. The cost is calculated by using the average prices of the different TCS treatments available in Denmark (all topical preparations considered), plus the price of TCIs (tacrolimus and pimecrolimus). The drugs with their costs are described in Table 58.

Table 58 Concomitant treatments

Substance	Pharmaceutical form	Strength	Unit cost AIP [DKK]	ATC code	Reference
Betamethason	Cutaneous solution	1.0 mg/g	66.07 per 100 g	D07AC01	Medicinpriser.dk
Clobetasol	Ointment	1.0 mg/g	57.00 per 100 g	D07AD01	Medicinpriser.dk
Mometason	Cream	0.5 mg/g	60.00 per 100 g	D07AC13	Medicinpriser.dk

Substance	Pharmaceutical form	Strength	Unit cost AIP [DKK]	ATC code	Reference
Tacrolimus	Ointment	1.0 mg/g	284.00 per 60 g	D11AH01	Medicinpriser.dk
Pimecrolimus	Ointment	0.1 mg/g	224.0 per 30 g	D11AH02	Medicinpriser.dk

11.3 Administration costs

Both dupilumab and nemolizumab are administered as a subcutaneous injection, which can be self-administered. The administration costs are assumed the same for both drugs and are therefore not included in the cost comparison.

Table 59 Administration costs used in the model (N/A)

Administration type	Frequency	Unit cost [DKK]	DRG code	Reference
N/A	N/A	N/A	N/A	N/A

11.4 Disease management costs

Not applicable since they are assumed to be the same.

Table 60 Disease management costs used in the model (N/A)

Activity	Frequency	Unit cost [DKK]	DRG code	Reference
N/A	N/A	N/A	N/A	N/A

11.5 Costs associated with management of adverse events

Not applicable.

Table 61 Cost associated with management of adverse events (N/A)

	DRG code	Unit cost/DRG tariff
N/A	N/A	N/A

11.6 Subsequent treatment costs

Not applicable since they are assumed to be the same.

Table 62 Medicines of subsequent treatments (N/A)

Medicine	Dose	Relative dose intensity	Frequency	Vial sharing
N/A	N/A	N/A	N/A	N/A

11.7 Patient costs

Not applicable since they are assumed to be the same.

Table 63 Patient costs used in the model (N/A)

Activity	Time spent [minutes, hours, days]
N/A	N/A

11.8 Other costs (e.g. costs for home care nurses, out-patient rehabilitation and palliative care cost)

Not applicable since they are assumed to be the same.

12. Results

12.1 Base case overview

The health economic analysis is based on a cost comparison between nemolizumab and dupilumab. A complete overview of the base aspects is presented in Table 64.

Table 64 Base case overview

Feature	Description
Comparator	Dupilumab
Type of model	Cost comparison
Time horizon	2 years
Treatment line	1L. Subsequent treatment lines not included.
Measurement and valuation of health effects	Not applicable
Costs included	Medicine costs Concomitant treatment cost
Dosage of medicine	Based on weight

Feature	Description
Average time on treatment	Intervention: 24 months Comparator: 24 months
Parametric function for PFS	Not applicable
Parametric function for OS	Not applicable
Inclusion of waste	No
Average time in model health state	Not applicable

12.1.1 Base case results

The results of the cost comparison are presented in Table 65. The costs reported are the yearly cost calculated as the average between the first year of treatment and the second year of treatment. The costs for the first and second year are also reported separately in the model. Nemolizumab is expected to accumulate more cost per year, however it has been tested as the only monotherapy treatment in the largest global clinical development program for patients with PN to date and has a unique mechanism of action that targets directly the IL-31Rα.

There is substantial need for additional targeted therapies in PN, since many treatments are prescribed off-label and the only treatment currently approved for the treatment of PN reports limitations linked primarily to the time to itch relief and complete remission. Furthermore, ITC data indicates a statistically significant improvement in itch when comparing nemolizumab with dupilumab, an effect that is difficult to quantify and capture into a simple cost comparison, but that could improve the patient's quality of life.

Table 65 Base case results, discounted estimates

	Nemolizumab	Dupilumab	Difference
Medicine costs	106,394.40 kr	60,853.84 kr	45,540.55 kr
Medicine costs – co-administration	0	17,190.00 kr	-17,190.00 kr
Administration	0	0	0
Disease management costs	0	0	0
Costs associated with management of adverse events	0	0	0
Subsequent treatment costs	0	0	0
Patient costs	0	0	0

	Nemolizumab	Dupilumab	Difference
Palliative care costs	0	0	0
Cost comparison	**106,394.40 kr**	**78,043.84 kr**	**28,350.55 kr**

12.2 Sensitivity analyses

The model and results uncertainty were assessed through deterministic and probabilistic sensitivity analysis.

12.2.1 Deterministic sensitivity analyses

A one-way sensitivity analysis was performed changing the base case parameters with a relative 20% increase or decrease, to assess the effect on the cost comparison. Due to the simplicity of the model, only the five parameters with the largest effect from the base case cost comparison are shown in

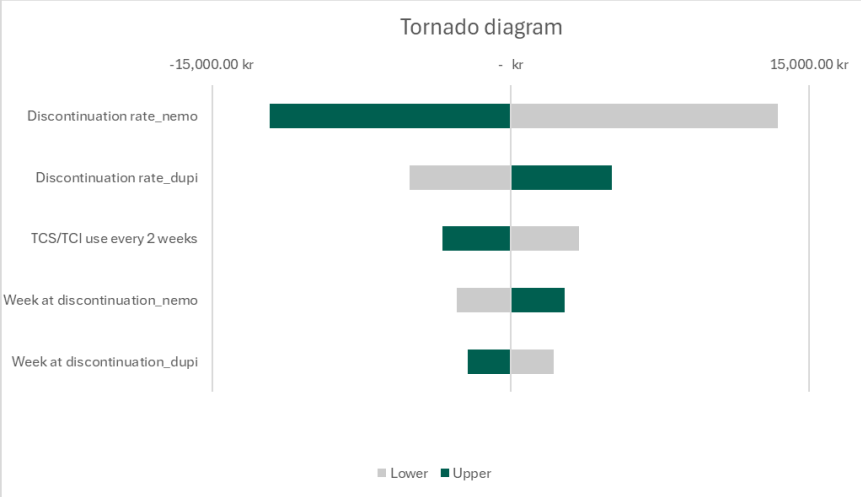
Table 66. A tornado diagram is illustrated in Figure 29.

Table 66 One-way sensitivity analyses results

	Change	Reason / Rational / Source	Incremental cost (DKK) – Lower value	Incremental cost (DKK) – Upper value	ICER (DKK/ QALY)
Base case	-	-	N/A	N/A	N/A
Discontinuation rate nemolizumab	Increase and decrease of 20% base case value	To test different discontinuation rate	13,455.85 kr	-12,123.96 kr	N/A
TCS/TCI use every 2 weeks	Increase and decrease of 20% base case value	To test a different quantity of TCS/TCI	-5,077.69 kr	5,077.70 kr	N/A
Tacrolimus price	Increase and decrease of 20% base case value	To test a different price for Tacrolimus	3,438.00 kr	-3,438.00 kr	N/A
Discontinuation rate dupilumab	Increase and decrease of 20% base case value	To test different discontinuation rate	-2,714.28 kr	2,714.29 kr	N/A
Week at discontinuation nemolizumab	Increase and decrease of 20% base case value	To test a different time, point in which patients discontinue	2,166.66 kr	-2,166.66 kr	N/A

Abbreviations: N/A, not applicable; QALY, quality-adjusted life years.

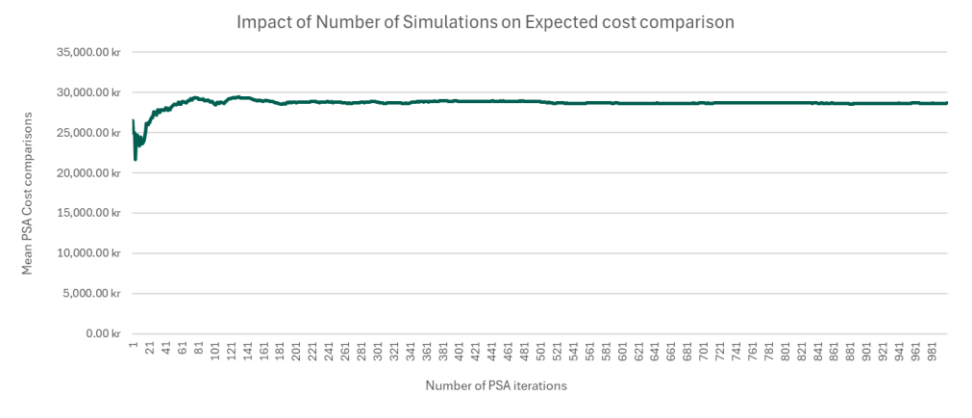
Figure 29 Tornado diagram



12.2.2 Probabilistic sensitivity analyses

A probabilistic sensitivity analysis (PSA) was performed to test the parametric uncertainty while changing them at once. When standard errors were unknown, they were calculated as 10% from the mean deterministic value. A number of 1,000 simulations were run, and a final average of the probabilistic cost comparison was calculated. Compared to the base case cost comparison of 28,350 DKK, the probabilistic result is 28,662 DKK which highlights the relatively low uncertainty. A convergence plot for the estimated mean cost comparison value is presented in Figure 30. A summary of the distribution tested for each parameter included in the PSA is shown in Table 87.

Figure 30 Convergence plot



13. Budget impact analysis

Number of patients (including assumptions of market share)

Table 67 present the rounded number of patients eligible for treatment on a yearly basis and the relevant market share assumed for nemolizumab. The budget impact is shown in

Table 68. With the recommendation of nemolizumab, it is estimated that 5-year budget impact will account for 42,841 DKK.

Table 67 Number of new patients expected to be treated over the next five-year period if the medicine is introduced (adjusted for market share)

	Year 1	Year 2	Year 3	Year 4	Year 5
			Recommendation		
Nemolizumab	5	2	2	2	2
Dupilumab	5	2	2	2	2
			Non-recommendation		
Nemolizumab	0	0	0	0	0
Dupilumab	10	3	3	3	3

Note: The patient numbers are rounded up in the table, but not in the calculations.

Budget impact

Table 68 Expected budget impact of recommending the medicine for the indication

	Year 1	Year 2	Year 3	Year 4	Year 5
The medicine under consideration is recommended	932,657 kr	279,797 kr	279,797 kr	279,797 kr	279,797 kr
The medicine under consideration is NOT recommended	789,854 kr	236,956 kr	236,956 kr	236,956 kr	236,956 kr
Budget impact of the recommendation	**142,802 kr**	**42,841 kr**	**42,841 kr**	**42,841 kr**	**42,841 kr**

14. List of experts (N/A)

Not applicable.

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Appendix A. Main characteristics of studies included

The main characteristics of the studies included in the assessment are presented in the tables below.

Table 69 Main characteristics of studies included (NCT03181503)

Trial name: NCT03181503	**NCT number: NCT03181503**
Objective	To assess the efficacy and safety of nemolizumab as compared with placebo in the treatment of prurigo nodularis.
Publications – title, author, journal, year	Full paper – Ständer S, Yosipovitch G, Legat FJ, Lacour JP, Paul C, Narbutt J, Bieber T, Misery L, Wollenberg A, Reich A, Ahmad F, Piketty C. Trial of Nemolizumab in Moderate-to-Severe Prurigo Nodularis. N Engl J Med. 2020 Feb 20;382(8):706-716. [35] Full paper – Ständer S, Yosipovitch G, Lacour JP, Legat FJ, Paul C, Reich A, Chaouche K, Ahmad F, Piketty C. Nemolizumab efficacy in prurigo nodularis: onset of action on itch and sleep disturbances. J Eur Acad Dermatol Venereol. 2022 Oct;36(10):1820-1825. doi: 10.1111/jdv.18377. Epub 2022 Jul 4. PMID: 35766128; PMCID: PMC9796585. [36]
Study type and design	This is a multicenter, randomized, placebo-controlled, double-blind, parallel-group, phase 2 trial that involved patients with moderate-to-severe prurigo nodularis and was conducted at centers in Austria, France, Germany, Poland, and the United States. Treatment was assigned centrally via Interactive Response Technology (IRT). All eligible subjects will be randomly assigned to one of the two treatment groups (0,5mg/kg or placebo) in a 1:1 ratio at baseline. Randomization will be stratified according to presence or absence of background of atopy.
Sample size (n)	A total of 70 patients were randomly assigned to a trial group (34 patients to the nemolizumab group and 36 to the placebo group).
Main inclusion criteria	1. Male or female of at least 18 years at screening 2. Clinical diagnosis of PN for at least 6 months with: o Prurigo lesions on upper limbs with or without lesions on the trunk or lower limbs o 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;

  NOTE: NRS score should be measured on at least 5 days during the week preceding the baseline visit.

4. Female subjects must fulfill one of the criteria below:
   - Female subjects of non-childbearing potential (postmenopausal [absence of menstrual bleeding for 1 year prior to screening, without any other medical reason], hysterectomy or bilateral oophorectomy);
   - Female subjects of childbearing potential who agree to a true abstinence (when in line with the preferred and usual lifestyle of the subject), or to use an effective method of contraception throughout the clinical trial and for 120 days after the last study drug administration:

     NOTE: Effective and highly effective methods of contraception are defined below:
   - Effective methods of contraception include:
     - Progestogen-only oral hormonal contraception
     - Male or female condom
     - Cap, diaphragm or sponge with spermicide
     - Combination of male or female condom with cap, diaphragm or sponge with spermicide
   - Highly effective methods of contraception include:
     - Combined (estrogen and progestogen containing) hormonal contraception, oral, or intra-vaginal, or transdermal
     - Injectable or implants hormonal contraception
     - Intra-uterine devices
     - Bilateral tubal ligation, or tube insert (such as Essure system) provided it has

	been inserted at least 3 months before the study ▪ Vasectomized partner (for at least 3 months) 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 electronic devices will be properly used. 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. 9. Subject agrees that his/her samples (blood and skin) collected for PD analysis will be kept at GALDERMA R&D after analysis as part of a long-term research (Program (2) – "Physiopathological study on skin disease to identify new dermatological medications; Initial declaration CP ECOH : DC-2008-315, 31/01/2009)
Main exclusion criteria	1. Chronic pruritus resulting from another condition than PN such as scabies, insect bite, lichen simplex chronicus, psoriasis, acne, folliculitis, habitual picking, lymphomatoid papulosis, chronic actinic dermatitis, dermatitis herpetiformis, sporotrichosis, bullous disease 2. Unilateral lesions of prurigo (e.g only one arm affected) 3. Cutaneous bacterial or viral infection within 1 week before the baseline visit. 4. Infection requiring treatment with oral or parenteral antibiotics, antivirals, antiparasitics or antifungals within 1 week before the screening visit, or during the screening period, unless completely resolved at the screening/ baseline visits respectively, 5. Any uncontrolled or serious disease, or any medical or surgical condition, that may either interfere with the interpretation of the clinical trial results and/or put the subject at significant risk according to Investigator's judgment (e.g. solid cancer, AIDS, serious or uncontrolled cardiac disease…) at Screening or Baseline. NOTE: Patients with controlled diseases such as diabetes mellitus, thyroid disorders and psychiatric disorders (such as depression and anxiety) are eligible

6. Any active dermatoses that would need immediate therapy.
7. Subject with active atopic dermatitis or known with recurrent flares of atopic dermatitis

   NOTE: patients with atopic diathesis, as diagnosed by the medical history and/or laboratory analysis (i.e. specific IgE), are eligible for the study
8. Neuropathic and psychogenic pruritus (notalgia paresthetica, brachioradial pruritus, dilutional parasitosis, pathomimia)
9. Positive serology results hepatitis B surface antigen [HBsAg] or hepatitis B core antibody [HBcAb], hepatitis C antibody or Human Immunodeficiency virus [HIV] antibody) at the screening visit

   NOTE : Subject with a positive HBcAb and a negative HBsAg can be included in this trial if HBsAb is positive (considered immune after a natural infection)
10. Subject having any of the abnormal lab criteria listed below, at the screening visit:
    - Elevated ALT / AST ≥ 3 ULN
    - Elevated CPK > 1.5 ULN, unless not confirmed on a repeat assessment to be performed at least 72h after the first one
    - Neutrophil count < 1.5 x $10^3/\mu l$
    - Creatinine clearance <60ml/min/1.73m² calculated with the CKD-EPI formula (Levey et al 2009)
    - Any other abnormal lab result that would be considered as clinically significant by the investigator
11. Subjects with a medical history of asthma that fulfill any or more of the conditions below
    - Had an asthma exacerbation requiring hospitalization in the last 12 months before screening visit
    - Whose asthma has not been well-controlled (i.e. symptoms >2 days per week, nighttime awakenings >1-3 times per week, or some interference with normal activities) during the last 3 months before the screening visit
    - PEF <80% of the predicted value at screening or baseline visit
12. Latent or active TB, as determined by a positive Quantiferon-based TB test result at screening visit.

Trial name: NCT03181503		NCT number: NCT03181503
	NOTE: In case of indeterminate result, the test should be repeated in local laboratory at screening 2(only one retest is allowed). If the test is still indeterminate, the subject will not be included. 13. Having received any of the following treatments within the specified time frame prior to the baseline visit: 14. Calcineurin inhibitors (tacrolimus, pimecrolimus), TCS, vitamin D analogs , PDE-4 inhibitors: 2 weeks 15. Any topical treatment other than moisturizer (e.g capsaicin, cryotherapy): 2 weeks 16. Emollients or moisturizer with menthol, capsaicine, polidocanol or other having “anti-itch” claim Systemic treatments 1 week	
Intervention	Nemolizumab administered subcutaneously at a dose of 0.5 mg per kilogram of body weight. A total of three subcutaneous injections were administered — at baseline, at week 4, and at week 8. A total of 34 patients received the intervention (nemolizumab).	
Comparator(s)	Matching placebo administered subcutaneously. A total of three subcutaneous injections were administered — at baseline, at week 4, and at week 8. A total of 36 patients received the comparator (placebo).	
Follow-up time	The week 12 trial visit was specified as the end of the intervention period. Patients had follow-up visits at 16 and 18 weeks.	
Is the study used in the health economic model?	Yes.	
Primary, secondary and exploratory endpoints	The primary outcome was the percent change from baseline in the peak pruritus score on the numerical rating scale at week 4. Secondary outcomes were the changes from baseline in the peak and mean pruritus scores on the numerical rating scale at week 12 (endpoint included in this application), in the verbal rating scale score for itch (on a scale from 0 [no pruritus] to 4 [very severe pruritus]) at week 12, in the dynamic pruritus score for the change in itch (on a scale from 0 [strongly worsened pruritus] to 8 [almost no pruritus or no pruritus], with a score of 4 indicating no change) at week 4, in the investigator’s global assessment of disease severity on the basis of the appearance of lesions (on a scale from 0 [clear] to 4 [severe]), and in a multi-dimensional, 7-item prurigo activity score to monitor the stage of disease (number, distribution, and activity of prurigo lesions) at week 12.	

Trial name: NCT03181503	NCT number: NCT03181503
	Exploratory outcomes included changes in the Dermatology Life Quality Index (scores range from 0 to 30, with 30 representing the worst possible quality of life due to pruritus; a change in the score of ≥4 points is considered to be clinically important) and in the numerical rating scale score for sleep disturbance to determine sleep quality (on a scale from 0 to 10, with higher scores indicating worse sleep quality). Patients' assessments of the numerical rating scale score for pruritus, the verbal rating scale score for pruritus, and the numerical rating scale score for sleep disturbance were performed daily by the patients at home in the evening using a handheld device. The dynamic pruritus score was assessed 24 hours, 48 hours, and 72 hours after the first injection and at week 4 before the second injection. The Dermatology Life Quality Index was assessed at baseline and at weeks 4 and 12 or at early discontinuation of the trial. The investigator's assessments of the prurigo activity score and the investigator's global assessment of disease severity were recorded at baseline; at weeks 4, 8, and 12; and at the follow-up visit at week 18.
Method of analysis	The intent-to-treat (ITT) Population was defined as comprising all subjects who are randomized. All primary efficacy variables and secondary efficacy variables will be analysed based on the ITT Population. The per-protocol (PP) Population was defined as comprising the ITT subjects who have no major protocol deviations. This was the primary population for this study. PP analysis was conducted only up to Week 4. The percent change from baseline to any visits of the weekly average of the peak and of the average pruritus NRS, were analysed separately via an ANOVA including the Treatment group as factor, presence and absence of background of atopy and country as a cofactors. The absolute change was analysed via an ANCOVA, same factors as the percent change but with including baseline NRS as a covariate. IGA, DPS and PAS were analysed at any visits by the CMH test stratified by background of atopy and by country with the ridit transformation and the row mean difference statistic (FREQ procedure from SAS). Proportion of subjects achieving success (IGA=0[clear] or IGA=1[Almost clear] with two point improvement from baseline) were analysed at each evaluation visit using the Cochran-Mantel Haenszel (CMH) test stratified by background of atopy and by country with the ridit transformation and the general association statistic (FREQ procedure from SAS). PP and ITT (Criteria will be set to missing after rescue medication is used and imputed to LOCF, for continuous outcomes and to failure for binary outcomes) were conducted on secondary endpoints. DLQI data were analysed on observed cases by CMH test stratified by background of atopy and by country with the ridit transformation and the row mean difference statistic (FREQ procedure from SAS) on the data in categories and also in terms change from baseline via an

Trial name: NCT03181503	NCT number: NCT03181503
	ANCOVA including treatment, baseline DLQI as a covariate, background of atopy and country as cofactors. The absolute and the percent change in weekly average sleep disturbance NRS from baseline up to week 4 were analysed by CMH test stratified by background of atopy and by country with the ridit transformation and the row mean difference statistic (FREQ procedure from SAS).
Subgroup analyses	To evaluate the consistency of treatment effects, subgroup analyses were explored for the primary and selected secondary efficacy endpoints based on: • Age (18-65 or >65) • Gender (Male, Female) • Country (Austria, France, Germany, and Poland) • Presence or absence of background of atopy (the stratification factor for randomization to the treatments) • Baseline number of prurigo nodularis nodule (< median vs ≥ median), if exact counts are not available in the database then use (20-100 vs. >100) categories as classes. Subgroup analyses were explored for safety endpoints (e.g., AEs) based on: • Age (18-65 or >65) • Gender (Male, Female) • Country (Austria, France, Germany, and Poland) • Presence or absence of background of atopy (the stratification factor for randomization to the treatments) If the number of subjects in a subgroup was too small, subgroups may be pooled for analyses. Decisions regarding merging subgroups or eliminating some subgroups were made at the blinded review before treatment unblinding and database lock. Summary statistics were provided for each of the subgroups by time points. The estimated mean change of treatment groups and 95% CI were calculated and displayed graphically using forest plots for subgroup.
Other relevant information	

Table 70 Main characteristics of studies included (OLYMPIA 1)

Trial name: OLYMPIA 1	NCT number: NCT04501666
Objective	To assess the efficacy and occurrence of adverse events in adults with moderate to severe prurigo nodularis (PN) treated with nemolizumab vs those receiving placebo.
Publications – title, author, journal, year	Conference abstract – Ständer S, Yosipovitch G, Legat FJ, Reich A, Paul C, Simon D, Naldi L, Chen X, Jabbar Lopez ZK, Piketty C, Kwatra SG. Nemolizumab monotherapy improves itch and skin lesions in patients with moderate-to-severe prurigo nodularis: Results from a global Phase 3 trial (OLYMPIA 1). Presented at European Academy of Dermatology and Venereology (2023). [3] Full paper – Ständer S, Yosipovitch G, Legat FJ, Reich A, Paul C, Simon D, Naldi L, Metz M, Tsianakas A, Pink A, Fage S, Micali G, Weisshaar E, Sundaram H, Metelitsa A, Augustin M, Wollenberg A, Homey B, Fargnoli MC, Sofen H, Korman NJ, Skov L, Chen X, Jabbar-Lopez ZK, Piketty C, Kwatra SG; OLYMPIA 1 Investigators. Efficacy and Safety of Nemolizumab in Patients With Moderate to Severe Prurigo Nodularis: The OLYMPIA 1 Randomized Clinical Phase 3 Trial. JAMA Dermatol. 2024 Nov 27. [38]
Study type and design	Phase 3, multicenter, double-blind, placebo-controlled, randomized, parallel-group study. Patients were randomized 2:1 using an interactive response technology and stratified by baseline body weight (<90 kg and ≥90 kg) to receive subcutaneous injections of nemolizumab or placebo.
Sample size (n)	A total of 286 patients were randomised 2:1 to receive subcutaneous injections of nemolizumab monotherapy once every 4 weeks (190 patients) or matching placebo (96 patients).
Main inclusion criteria	Individuals must meet all of the following criteria to be included in the study: 1. Male or female and aged ≥18 years at the time of screening 2. Clinical diagnosis of PN for at least 6 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 is moderate and 4 is severe) at both the screening and baseline visits 3. Severe pruritus defined as follows on the PP NRS: a. At the screening visit (Visit 1): PP-NRS score is ≥ 7.0 for the 24-hour period immediately preceding the screening visit

b. At the baseline visit (Visit 2): Mean of the daily intensity of the PP-NRS score is ≥ 7.0 over the previous week;

Note: PP-NRS score should be measured on at least 4 days during the week preceding the baseline visit. Rounding of the mean NRS score is not permitted.

4. Female subjects of childbearing potential (ie, fertile, following menarche and until becoming post-menopausal unless permanently sterile) must agree to use at least 1 adequate and approved method of contraception throughout the study and for 12 weeks after the last study drug injection. Adequate and approved methods of contraception applicable for the subject and/or her partner are defined below:

   a. True abstinence, when in line with the preferred and usual lifestyle of the subject. Periodic abstinence (eg, calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception

   b. Progestogen-only oral hormonal contraception

   c. Combination of male condom with cap, diaphragm, or sponge with spermicide (double barrier methods) (*In Germany only, double barrier methods are not considered an adequate and approved method of contraception)

      Note: “Double barrier methods” refers to simultaneous use of a physical barrier by each partner. Use of a single barrier method (eg, condom) together with a spermicide is not acceptable.

   d. Combined (estrogen- and progestogen-containing) oral, intravaginal, or transdermal hormonal contraception

   e. Injectable or implanted hormonal contraception

   f. Intrauterine devices or intrauterine hormone releasing system

   g. Bilateral tubal ligation or tube insert (such as the Essure system) at least 3 months before the study

   h. Bilateral vasectomy of male partner at least 3 months before the study

5. Female subjects of non-childbearing potential must meet 1 of the following criteria:

   a. 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

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

6. Subject is willing and able to comply with all of the time commitments and procedural requirements of the clinical study

Trial name: OLYMPIA 1		NCT number: NCT04501666
	protocol, including daily diary recordings by the subject using an electronic handheld device provided for this study 7. Read, understood and signed an informed consent form (ICF) before any investigational procedure(s) are performed.	
Main exclusion criteria	Individuals meeting any of the following criteria at screening or baseline are ineligible to participate in this study: 1. Body weight < 30 kg 2. Chronic pruritus resulting from another active condition other than PN, such as but not limited to scabies, lichen simplex chronicus, psoriasis, atopic dermatitis, contact dermatitis, acne, folliculitis, lichen planus, habitual picking/excoriation disorder, sporotrichosis, bullous autoimmune disease, end-stage renal disease, cholestatic liver disease (eg, primary biliary cirrhosis), or diabetes mellitus or thyroid disease that is not adequately treated, as per standard of care 3. Unilateral lesions of prurigo (eg, only one arm affected) 4. History of or current confounding skin condition (eg, Netherton syndrome, cutaneous T-cell lymphoma [mycosis fungoides or Sezary syndrome], chronic actinic dermatitis, dermatitis herpetiformis) 5. Subjects meeting 1 or more of the following criteria at screening or baseline: a. Had an exacerbation of asthma requiring hospitalization in the preceding 12 months b. Reporting asthma that has not been well-controlled (ie, 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 c. Asthma Control Test (ACT) ≤ 19 (only for subjects with a history of asthma) d. Peak expiratory flow (PEF) < 80% of the predicted value Note: In the event that PEF is < 80% of the predicted value at the screening visit in subjects without any history of asthma or in subjects with history of asthma but with the ACT score > 19, PEF testing can be repeated once within 48 hours. 6. Subjects with a current medical history of chronic obstructive pulmonary disease and/or chronic bronchitis 7. Cutaneous infection within 1 week before the baseline visit, any infection requiring treatment with oral or parenteral antibiotics, antivirals, antiparasitics, 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

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

   Note: Subjects with a positive HBcAb and a negative HBsAg can be included in this clinical study if hepatitis B surface antibody is positive (considered immune after a natural infection). Subjects with negative confirmatory test for HCV can be included in this clinical study.

   In the event of rescreening, the serology tests results (eg, HBV, HCV, HIV) from the first screening can be used by the investigator to assess the eligibility of rescreened subjects if those tests were performed within 6 weeks prior to the baseline visit.

9. Requiring rescue therapy for PN during the screening period or expected to require rescue therapy within 4 weeks following the baseline visit

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

    Note: Subjects with atopic diathesis, as diagnosed by the medical history and/or laboratory analysis (ie, specific immunoglobulin E), are eligible for the study.

11. Neuropathic and psychogenic pruritus such as but not limited to notalgia paresthetica, brachioradial pruritus, small fiber neuropathy, skin picking syndrome, or delusional parasitosis

12. Having received any of the following treatments in the table below within the specified timeframe before the baseline visit:

    a. Topical calcineurin inhibitors (tacrolimus, pimecrolimus), and topical corticosteroids: 2 weeks

    b. Vitamin D analogs and PDE-4 inhibitors: 2 weeks

    c. Any other topical treatment other than moisturizer (eg, capsaicin, cryotherapy for treatment of PN): 2 weeks

    d. Emollients or moisturizers with menthol, polidocanol or other having “anti-itch” claim: 1 week

    e. Systemic or intralesional corticosteroids (corticosteroid inhalers are permitted): 4 weeks

    f. Oral antihistamines (unless these treatments were taken at a stable dose for 3 months prior to screening or for a seasonal allergy): 1 week

g. Drugs with sedative effect such as benzodiazepines, imidazopyridines, barbiturates, sedative anti depressants (eg, amitriptyline), SSRIs (eg, paroxetine), or SNRIs, except if these treatments were taken at a stable dose for at least 3 months before screening: 1 week

h. Phototherapy or tanning beds: 4 weeks

i. Immunosuppressive or immunomodulatory drugs (eg, cyclosporine, methotrexate, thalidomide, oral tacrolimus, cyclophosphamide, azathioprine, mycophenolate mofetil, JAK inhibitors): 8 weeks or 5 half-lives (whichever is longer)

j. Biologics and their biosimilars (eg, dupilumab, etanercept, adalimumab, infliximab, omalizumab): 8 weeks or 5 half-lives (whichever is longer)

k. Systemic retinoids: 8 weeks or 5 half-lives (whichever is longer)

l. Systemic roxithromycin, erythromycin: 1week

m. Opioid antagonists (eg, naltrexone, naloxone), opioid partial/mixed agonists (eg, nalbuphine, butorphanol), or opioid agonists (except when used for short term/acute pain);NK1 receptor antagonists (eg, aprepitant, serlopitant): 4 weeks or 5 half-lives (whichever is longer)

n. Gabapentinoids, unless used at a stable dose for at least 6 months or used for non-prurigo conditions: 4 weeks

o. Cannabinoids (eg, dronabinol): 2 weeks

p. Alternative medicine for PN (eg, traditional Chinese medicine): 2 weeks

q. Live vaccines: 12 weeks

r. Non-live vaccines: 4 weeks

Note: Subjects should not interrupt ongoing treatment with medications important for the subject's health for the sole purpose of participating in this study.

13. Previous participation in a clinical study with nemolizumab

14. Pregnant women (positive serum pregnancy test result at the screening visit or positive urine pregnancy test at the baseline visit), breastfeeding women, or women planning a pregnancy during the clinical study

15. History of lymphoproliferative disease or history of malignancy of any organ system within the last 5 years, except for:

a. 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;

b. Actinic keratoses that have been treated

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

17. 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

    Note: Subjects who have a documented history of completion of an appropriate TB treatment regimen for latent or active TB with no history of re-exposure to TB since their treatment was completed are eligible to participate in the study.

    In the event of rescreening, the TB tests result from the first screening can be used by the investigator to assess the eligibility of rescreened subjects if the test was performed within 6 weeks prior to the baseline visit.

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

19. Any medical or psychological condition or any clinically relevant laboratory abnormalities, such as but not limited to elevated alanine aminotransferase (ALT) or aspartate aminotransferase (AST) (> 3 × upper limit of normal [ULN]) in combination with elevated bilirubin (> 2 × ULN), 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, or may interfere with study assessments (eg, poor venous access or needle-phobia)

20. History of alcohol or substance abuse within 6 months of the screening visit

21. Planned or expected major surgical procedure during the clinical study

22. Subject is unwilling to refrain from using prohibited medications during the clinical study (see Section 9.10.3)

23. 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

    For subjects accepting optional biopsy sampling (by signing an additional consent), the following exclusion criteria also apply. If any of the below criteria are met, biopsy samples must not be collected:

24. History of coagulation disorders

25. Known sensitivity to local anesthetics

Trial name: OLYMPIA 1		NCT number: NCT04501666
	26. Using platelet aggregation inhibitors, or anticoagulants (sporadic intake or continuous low-dose intake of aspirin or other non-steroidal anti-inflammatory drugs is allowed) 27. History or physical evidence of keloids or hypertrophic scarring resulting from skin trauma. The clinical examination will include the observation of scars.	
Intervention	Patients were randomized 2:1 using an interactive response technology and stratified by baseline body weight (<90kg vs ≥90 kg) to receive subcutaneous injections of nemolizumab monotherapy every 4 weeks for 24 weeks. At baseline, patients weighing less than 90 kg received an initial dose of nemolizumab, 60 mg, followed by nemolizumab, 30mg, every 4 weeks, and patients weighing 90 kg or more received nemolizumab, 60 mg, every 4 weeks. Patients in the placebo group received matching placebo injections. 190 patients received the intervention (nemolizumab).	
Comparator(s)	Patients were randomized 2:1 using an interactive response technology and stratified by baseline body weight (<90kg vs ≥90 kg) to receive subcutaneous injections of matching placebo every 4 weeks for 24 weeks. Patients in the placebo group received matching placebo injections to nemolizumab as following: at baseline, patients weighing less than 90 kg received an initial dose of nemolizumab, 60 mg, followed by nemolizumab, 30mg, every 4 weeks, and patients weighing 90 kg or more received nemolizumab, 60 mg, every 4 weeks. 96 patients received the comparator (placebo).	
Follow-up time	The study consisted in a screening period (1 to 4 weeks), followed by 24 weeks' treatment period and 8 weeks' follow-up period. After the treatment period, patients were eligible to enter an ongoing open-label, 184-week long-term extension study (OLYMPIA LTE). These patients were not required to complete the follow-up visit.	
Is the study used in the health economic model?	Yes.	
Primary, secondary and exploratory endpoints	The primary endpoints were the proportion of patients with a clinically meaningful itch response, defined as a 4-point or more improvement from baseline in weekly average PP-NRS score at week 16, and the proportion of patients with IGA success at week 16 (defined as IGA score of 0/1 [clear/almost clear] (endpoints included in this application) and a ≥2-point improvement from baseline). The key secondary endpoints included the proportion of patients with itch response at week 4; proportion of patients with weekly average PP-NRS score of less than 2 at weeks 4 and 16 (qualifying as an itch-free or nearly itch-free state); and proportion of patients with a clinically meaningful improvement in sleep disturbance, defined as an	

Trial name: OLYMPIA 1	NCT number: NCT04501666
	improvement of at least 4 points from baseline on the Sleep Disturbance Numerical Rating Scale (SD-NRS; scores range from 0 [no sleep loss] to 10 [I did not sleep at all]), at weeks 4 and 16. The study also had secondary endpoints evaluating outcomes in Prurigo Activity and Severity score, Dermatology Life Quality Index and EuroQoL Group 5-Dimensions (EQ-5D) questionnaire, Hospital Anxiety and Depression Scale (HADS), PN-associated pain frequency and intensity, and Patient Global Assessment of Disease and Patient Global Assessment of Treatment through week 24. These endpoints are also included in this application.
Method of analysis	The intent-to-treat (ITT) population consisted of all randomized subjects. The safety population included all randomized subjects who receive at least 1 dose of study drug. The Per-Protocol (PP) population consisted of all subjects in the ITT population who had no major protocol deviations that would have a significant effect on the efficacy of the study treatment. The ITT population was the primary population for all efficacy analyses, and all safety data was summarized based on the safety population. The PP population was used as the population for sensitivity analyses of the primary and key secondary efficacy endpoints. Both primary endpoints were analysed using a Cochran-Mantel-Haenszel (CMH) test adjusted for randomized stratification variable analysis center and baseline body weight (<90 kg and ≥90kg). The estimate of the treatment difference (nemolizumab minus placebo), p-value and 2-sided 95% confidence interval is presented. Missing data at Week 16, and any data for subjects in receipt of rescue medication up to Week 16, were regarded as a non-responder for the primary analysis of the endpoint. All binary key secondary efficacy endpoints were analysed as per the primary endpoint. Additionally, sensitivity analyses using multiple-imputation assuming missing at random (MAR)and observed case (OC) analysis were performed for key secondary endpoints Binary secondary endpoints were analysed in the same manner as the primary endpoint; missing values were imputed as non-responder. Continuous secondary endpoints (except EQ-5D, HADS) were analysed using multiple-imputation assuming MAR and using mixed effect model for repeated measure (MMRM)approach, including analysis center as factor and baseline as 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 analysis of covariance (ANCOVA)including analysis center as factor and baseline as covariate. All secondary endpoints were presented descriptively using OC.
Subgroup analyses	Descriptive summary and analysis for primary and key secondary endpoints were produced for the following subgroups:

Trial name: OLYMPIA 1	NCT number: NCT04501666
	• Region (Europe, North America, Asia-Pacific) • Age groups (18-65, and > 65) • Sex (Male, Female) • Race (White, Black, Asian, Other) • Baseline weight (< 90 kg, ≥ 90 kg)
Other relevant information	

Table 71 Main characteristics of studies included (OLYMPIA 2)

Trial name: OLYMPIA 2	NCT number: NCT04501679
Objective	To assess the efficacy of nemolizumab compared to placebo in subjects ≥18 years of age with PN after a 16-week treatment period.
Publications – title, author, journal, year	Conference abstract – Ständer S YG, Lacour JP, et al. Patients with prurigo nodularis treated with nemolizumab achieved itch-free state: results from a phase 3 trial (OLYMPIA 2). Abstract presented at: 25th World Congress of Dermatology; July 3-8, 2023; Singapore. [40] Conference abstract – Reich A, Legat F, Paul C, et al. Nemolizumab modulates prurigo nodularis-associated skin pain and markedly improves patient reported outcomes in patients with moderate-to-severe prurigo nodularis in a phase 3 study (OLYMPIA 2). 32nd European Academy of Dermatology and Venereology Congress; October 11-14; Berlin, Germany 2023. [41] Full paper – Kwatra SG, Yosipovitch G, Legat FJ, Reich A, Paul C, Simon D, Naldi L, Lynde C, De Bruin-Weller MS, Nahm WK, Sauder M, Gharib R, Barbarot S, Szepietowski JC, Conrad C, Fleischer A, Laquer VT, Misery L, Serra-Baldrich E, Lapeere H, Ahmad F, Jabbar Lopez ZK, Piketty C, Ständer S; OLYMPIA 2 Investigators. Phase 3 Trial of Nemolizumab in Patients with Prurigo Nodularis. N Engl J Med. 2023 Oct 26;389(17):1579-1589. [42]
Study type and design	Double-blind, multicenter, phase 3, randomized trial of nemolizumab monotherapy as compared with placebo at 68 sites across nine countries. Patients were enrolled from September 2020 through November 2021 and participated in a 16-week treatment period and an 8-week follow-up period. Using an interactive response technology, patients were randomly assigned, in a 2:1 ratio, to receive subcutaneous injections of nemolizumab monotherapy or matching placebo for 16 weeks. Randomization was stratified according to baseline body weight (<90 kg

Trial name: OLYMPIA 2		NCT number: NCT04501679
	vs. ≥90 kg). Blinded, coded trial regimen kits were used to mask the assigned regimen.	
Sample size (n)	A total of 274 patients underwent randomization; 183 were assigned to the nemolizumab group, and 91 to the placebo group.	
Main inclusion criteria	Individuals must meet all of the following criteria to be included in the study: 1. Male or female and aged ≥18 years at the time of screening 2. Clinical diagnosis of PN for at least 6 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 is moderate and 4 is severe) at both the screening and baseline visits 3. Severe pruritus defined as follows on the PP NRS: a. At the screening visit (Visit 1): PP-NRS score is ≥ 7.0 for the 24-hour period immediately preceding the screening visit b. At the baseline visit (Visit 2): Mean of the daily intensity of the PP-NRS score is ≥ 7.0 over the previous week; Note: PP-NRS score should be measured on at least 4 days during the week preceding the baseline visit. Rounding of the mean NRS score is not permitted. 4. Female subjects of childbearing potential (ie, fertile, following menarche and until becoming post-menopausal unless permanently sterile) must agree to use at least 1 adequate and approved method of contraception throughout the study and for 12 weeks after the last study drug injection. Adequate and approved methods of contraception applicable for the subject and/or her partner are defined below: a. True abstinence, when in line with the preferred and usual lifestyle of the subject. Periodic abstinence (eg, calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception b. Progestogen-only oral hormonal contraception c. Combination of male condom with cap, diaphragm, or sponge with spermicide (double barrier methods) (*In Germany only, double barrier methods are not considered an adequate and approved method of contraception) Note: “Double barrier methods” refers to simultaneous use of a physical barrier by each partner. Use of a single barrier	

	method (eg, condom) together with a spermicide is not acceptable. d. Combined (estrogen- and progestogen-containing) oral, intravaginal, or transdermal hormonal contraception e. Injectable or implanted hormonal contraception f. Intrauterine devices or intrauterine hormone releasing system g. Bilateral tubal ligation or tube insert (such as the Essure system) at least 3 months before the study h. Bilateral vasectomy of male partner at least 3 months before the study 5. Female subjects of non-childbearing potential must meet 1 of the following criteria: a. 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 b. Documented hysterectomy, bilateral salpingectomy, or bilateral oophorectomy at least 3 months before the study 6. Subject is 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 subject using an electronic handheld device provided for this study 7. Read, understood and signed an informed consent form (ICF) before any investigational procedure(s) are performed.
Main exclusion criteria	Individuals meeting any of the following criteria at screening or baseline are ineligible to participate in this study: 1. Body weight < 30 kg 2. Chronic pruritus resulting from another active condition other than PN, such as but not limited to scabies, lichen simplex chronicus, psoriasis, atopic dermatitis, contact dermatitis, acne, folliculitis, lichen planus, habitual picking/excoriation disorder, sporotrichosis, bullous autoimmune disease, end-stage renal disease, cholestatic liver disease (eg, primary biliary cirrhosis), or diabetes mellitus or thyroid disease that is not adequately treated, as per standard of care 3. Unilateral lesions of prurigo (eg, only one arm affected) 4. History of or current confounding skin condition (eg, Netherton syndrome, cutaneous T-cell lymphoma [mycosis fungoides or Sezary syndrome], chronic actinic dermatitis, dermatitis herpetiformis) 5. Subjects meeting 1 or more of the following criteria at screening or baseline:

a. Had an exacerbation of asthma requiring hospitalization in the preceding 12 months

b. Reporting asthma that has not been well-controlled (ie, 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

c. Asthma Control Test (ACT) ≤ 19 (only for subjects with a history of asthma)

d. Peak expiratory flow (PEF) < 80% of the predicted value

Note: In the event that PEF is < 80% of the predicted value at the screening visit in subjects without any history of asthma or in subjects with history of asthma but with the ACT score > 19, PEF testing can be repeated once within 48 hours.

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

7. Cutaneous infection within 1 week before the baseline visit, any infection requiring treatment with oral or parenteral antibiotics, antivirals, antiparasitics, 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

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

   Note: Subjects with a positive HBcAb and a negative HBsAg can be included in this clinical study if hepatitis B surface antibody is positive (considered immune after a natural infection). Subjects with negative confirmatory test for HCV can be included in this clinical study.

   In the event of rescreening, the serology tests results (eg, HBV, HCV, HIV) from the first screening can be used by the investigator to assess the eligibility of rescreened subjects if those tests were performed within 6 weeks prior to the baseline visit.

9. Requiring rescue therapy for PN during the screening period or expected to require rescue therapy within 4 weeks following the baseline visit

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

Note: Subjects with atopic diathesis, as diagnosed by the medical history and/or laboratory analysis (ie, specific immunoglobulin E), are eligible for the study.

11. Neuropathic and psychogenic pruritus such as but not limited to notalgia paresthetica, brachioradial pruritus, small fiber neuropathy, skin picking syndrome, or delusional parasitosis
12. Having received any of the following treatments in the table below within the specified timeframe before the baseline visit:
    a. Topical calcineurin inhibitors (tacrolimus, pimecrolimus), and topical corticosteroids: 2 weeks
    b. Vitamin D analogs and PDE-4 inhibitors: 2 weeks
    c. Any other topical treatment other than moisturizer (eg, capsaicin, cryotherapy for treatment of PN): 2 weeks
    d. Emollients or moisturizers with menthol, polidocanol or other having “anti-itch” claim: 1 week
    e. Systemic or intralesional corticosteroids (corticosteroid inhalers are permitted): 4 weeks
    f. Oral antihistamines (unless these treatments were taken at a stable dose for 3 months prior to screening or for a seasonal allergy): 1 week
    g. Drugs with sedative effect such as benzodiazepines, imidazopyridines, barbiturates, sedative anti depressants (eg, amitriptyline), SSRIs (eg, paroxetine), or SNRIs, except if these treatments were taken at a stable dose for at least 3 months before screening: 1 week
    h. Phototherapy or tanning beds: 4 weeks
    i. Immunosuppressive or immunomodulatory drugs (eg, cyclosporine, methotrexate, thalidomide, oral tacrolimus, cyclophosphamide, azathioprine, mycophenolate mofetil, JAK inhibitors): 8 weeks or 5 half-lives (whichever is longer)
    j. Biologics and their biosimilars (eg, dupilumab, etanercept, adalimumab, infliximab, omalizumab): 8 weeks or 5 half-lives (whichever is longer)
    k. Systemic retinoids: 8 weeks or 5 half-lives (whichever is longer)
    l. Systemic roxithromycin, erythromycin: 1week
    m. Opioid antagonists (eg, naltrexone, naloxone), opioid partial/mixed agonists (eg, nalbuphine, butorphanol), or opioid agonists (except when used for short term/acute pain);NK1 receptor antagonists (eg, aprepitant, serlopitant): 4 weeks or 5 half-lives (whichever is longer)

n. Gabapentinoids, unless used at a stable dose for at least 6 months or used for non-prurigo conditions: 4 weeks

o. Cannabinoids (eg, dronabinol): 2 weeks

p. Alternative medicine for PN (eg, traditional Chinese medicine): 2 weeks

q. Live vaccines: 12 weeks

r. Non-live vaccines: 4 weeks

Note: Subjects should not interrupt ongoing treatment with medications important for the subject's health for the sole purpose of participating in this study.

13. Previous participation in a clinical study with nemolizumab

14. Pregnant women (positive serum pregnancy test result at the screening visit or positive urine pregnancy test at the baseline visit), breastfeeding women, or women planning a pregnancy during the clinical study

15. History of lymphoproliferative disease or history of malignancy of any organ system within the last 5 years, except for:

    a. 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;

    b. Actinic keratoses that have been treated

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

17. 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

    Note: Subjects who have a documented history of completion of an appropriate TB treatment regimen for latent or active TB with no history of re-exposure to TB since their treatment was completed are eligible to participate in the study.

    In the event of rescreening, the TB tests result from the first screening can be used by the investigator to assess the eligibility of rescreened subjects if the test was performed within 6 weeks prior to the baseline visit.

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

19. Any medical or psychological condition or any clinically relevant laboratory abnormalities, such as but not limited to elevated alanine aminotransferase (ALT) or aspartate aminotransferase (AST)

Trial name: OLYMPIA 2	NCT number: NCT04501679
	(> 3 × upper limit of normal [ULN]) in combination with elevated bilirubin (> 2 × ULN), 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, or may interfere with study assessments (eg, poor venous access or needle-phobia) 20. History of alcohol or substance abuse within 6 months of the screening visit 21. Planned or expected major surgical procedure during the clinical study 22. Subject is unwilling to refrain from using prohibited medications during the clinical study (see Section 9.10.3) 23. 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 For subjects accepting optional biopsy sampling (by signing an additional consent), the following exclusion criteria also apply. If any of the below criteria are met, biopsy samples must not be collected: 24. History of coagulation disorders 25. Known sensitivity to local anesthetics 26. Using platelet aggregation inhibitors, or anticoagulants (sporadic intake or continuous low-dose intake of aspirin or other non-steroidal anti-inflammatory drugs is allowed) History or physical evidence of keloids or hypertrophic scarring resulting from skin trauma. The clinical examination will include the observation of scars.
Intervention	In the nemolizumab (intervention) 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. 183 patients received the intervention (nemolizumab).
Comparator(s)	Patients in the placebo (comparator) group received matching placebo injections according to their weight. 91 patients received the comparator (placebo).
Follow-up time	The study consisted in a 16-week treatment period and an 8-week follow-up period. After the 16-week treatment period, patients were eligible to enter the ongoing long-term extension trial (OLYMPIA LTE; ClinicalTrials.gov number, NCT04204616).

Trial name: OLYMPIA 2	NCT number: NCT04501679
Is the study used in the health economic model?	Yes.
Primary, secondary and exploratory endpoints	**Primary endpoints (endpoints included in this application):** • Proportion of patients with an improvement of ≥4 points from baseline in PP-NRS at week 16 • Proportion of patients with an Investigator Global Assessment (IGA success (defined as an IGA of 0 [Clear] or 1 [Almost clear] and a ≥ 2-point improvement from baseline) at week 16. **Key secondary endpoints:** • Proportion of patients with an improvement of ≥4 points from baseline in PP-NRS at week 4 • Proportion of patients with PP-NRS score <2 at week 16 • Proportion of patients with an improvement of ≥4 points from baseline in SD NRS at week 16 • Proportion of patients with an improvement of ≥4 points from baseline in SD NRS at week 4 • Proportion of patients with PP-NRS score <2 at week 4. **Other secondary endpoints:** IGA success rate at each visit through week 16 (endpoints included in this application) Percentage of pruriginous lesions with excoriations/crusts (PAS item 5a) at each visit through week 16 Percentage of healed prurigo lesions (PAS item 5b) at each visit through week 16 Change from baseline in number of lesions in representative area (PAS item 4) at each visit through week 16 Proportion of patients with an improvement of ≥ 4 from baseline in PP-NRS through week 16 Proportion of patients with PP-NRS < 2 from baseline through week 16 Proportion of patients with PP-NRS < 3 from baseline through week 16 Absolute change from baseline in PP-NRS through week 16 Percent change from baseline in PP-NRS through week 16 Proportion of patients with an improvement of ≥ 4 from baseline in AP NRS through week 16 Proportion of patients with PP-NRS improvement ≥ 4 from baseline and IGA success at week 16

Trial name: OLYMPIA 2	NCT number: NCT04501679
	Proportion of patients with AP NRS < 2 from baseline through week 16 Absolute change from baseline in AP NRS through week 16 Percent change from baseline in AP NRS through week 16 Proportion of patients with an improvement of ≥ 4 from baseline in SD NRS through week 16 Absolute change from baseline in SD NRS through week 16 Percent change from baseline in SD NRS through week 16 Change from baseline in sleep diary endpoints (sleep onset latency, WASO, total awake time, total sleep time, sleep efficiency, WASO related to PN, number of WASO related to PN based on recordings from subject sleep diary through week 16 Proportion of patients reporting low disease activity (clear, almost clear, or mild) based on PGAD at week 16 Proportion of patients satisfied with study treatment (good, very good, or excellent) based on PGAT at Week 16 Proportion of patients with an improvement of ≥ 4 in DLQI at week 4 and week 16 Change from baseline in DLQI through week 16 Change from baseline in HADS for each subscale (ie, depression and anxiety) at week 16 Change from baseline in EQ-5D at week 16
Method of analysis	The intent-to-treat (ITT) population consisted of all randomized patients and was the primary population for efficacy analyses. The per protocol (PP) population included all patients in the ITT population who had no major protocol deviations that could have a significant effect on the efficacy of study treatment. The PP population was used for analyses of primary and key secondary endpoints. The safety population consisted of all randomized patients who received at least one administration of the study drug and was used for analysis of safety. Both primary endpoints were analysed using a Cochran-Mantel-Haenszel (CMH) test adjusted for the randomization strata analysis center and body weight at randomization (<90 kg, ≥90 kg), in order to test the difference between nemolizumab and placebo for the proportion of subjects achieving success in each endpoint. The estimate of the treatment difference and corresponding 2 sided 95% CI and p-values were presented. The CIs were based on the Wald statistic controlling for stratification variables. Strata-adjusted proportion differences were obtained using a weighted average of stratum-specific proportion using CMH. In addition, an unadjusted CMH test was performed.

Trial name: OLYMPIA 2	NCT number: NCT04501679

	Sensitivity analyses for both primary endpoints were conducted in order to test for the robustness of the primary analyses. Key secondary endpoints were tested only if both primary endpoints were successful at a 5% level of significance. All key secondary endpoints were analysed for the ITT population similarly to the primary endpoint analysis including graphical presentation. Additionally, the same sensitivity analyses as for the primary endpoints were performed, including bar charts for the key secondary endpoints or PP population. Binary secondary endpoints were analysed as described for primary endpoints if not specified otherwise. Missing values were imputed as a non-responder except for OC analysis. If a subject received rescue medication at any point, continuous data on or after receipt of rescue medication were set to worse case except for OC analysis; binary responses were derived from the underlying value. Continuous secondary endpoints (except EQ-5D, HADS, and PN intensity) were analysed using MI assuming MAR, including treatment group, analysis center, and body weight at randomization cut-off (<90 kg and ≥90 kg) as factors and baseline as a covariate, and using an MMRM approach, including visit, treatment group, analysis center, and body weight at randomization cut-off (<90 kg and ≥90 kg) as factors, and baseline, the interaction term between baseline and visit, and the interaction term between treatment group and visit as covariates, 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. EuroQoL 5-Dimension and HADS endpoints were analysed using an analysis of covariance (ANCOVA), including treatment group, analysis center, and body weight at randomization cut-off (<90 kg and ≥90 kg) as factors and baseline as a covariate. Prurigo nodularis intensity was analysed using an MMRM approach, including visit, treatment group, analysis center, and body weight at randomization cut-off (<90 kg and ≥90 kg) as factors, and 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.
Subgroup analyses	Descriptive summary and analysis for primary and key secondary endpoints will be produced for the following subgroups: • Region (Europe, North America, Asia-Pacific) • Age groups (18-65, and > 65) • Sex (Male, Female) • Race (White, Black, Asian, Other) • Baseline weight (< 90 kg, ≥ 90 kg)
Other relevant information	

Table 72 Main characteristics of studies included (LIBERTY-PN PRIME)

Trial name: LIBERTY-PN PRIME	NCT number: NCT04183335
Objective	To evaluate the use of dupilumab in patients with PN inadequately controlled on topical prescription therapies or when those therapies are not advisable.
Publications – title, author, journal, year	Full paper – Yosipovitch G, Mollanazar N, Ständer S, Kwatra SG, Kim BS, Laws E, Mannent LP, Amin N, Akinlade B, Staudinger HW, Patel N, Yancopoulos GD, Weinreich DM, Wang S, Shi G, Bansal A, O'Malley JT. Dupilumab in patients with prurigo nodularis: two randomized, double-blind, placebo-controlled phase 3 trials. Nat Med. 2023 May;29(5):1180-1190. [44] Full paper – Yosipovitch G, Kim BS, Kwatra SG, Mollanazar NK, Ständer S, Satoh T, Mendes-Bastos P, Tsai TF, Laws E, Nivens MC, Maloney J, Shi G, Bansal A, Dubost-Brama A. Dupilumab improves pruritus and skin lesions in patients with prurigo nodularis: Pooled results from 2 phase 3 trials (LIBERTY-PN PRIME and PRIME2). JAAD Int. 2024 Apr 10;16:163-174. [45]
Study type and design	This study is a Phase 3, multi-center, 24-week treatment, parallel, double-blind, randomized, placebo controlled study to evaluate the use of dupilumab in patients with PN inadequately controlled on topical prescription therapies or when those therapies are not advisable. All participants will be centrally assigned to randomized study intervention using an Interactive Response Technology (IRT). Patients were randomized 1:1 to receive subcutaneous dupilumab 300 mg or matching placebo every 2 weeks for 24 weeks. Randomization will be stratified by the following factors: • documented history of atopy (atopic or non-atopic) • stable use of TCS/TCI (yes or no) • country/territory code
Sample size (n)	A total of 200 patients were screened and 151 were randomized (75 dupilumab and 76 placebo) at 58 study sites in eight countries/regions.
Main inclusion criteria	Participants are eligible to be included in the study only if all of the following criteria apply: **Age** 1. Participants must be 18 to 80 years of age, at the time of signing the informed consent. **Type of participant and disease characteristics**

Patients with a clinical diagnosis of PN, as defined by all of the following:

2. Diagnosed by a dermatologist for at least 3 months before the Screening visit.

3. On the WI-NRS ranging from 0 to 10, patients must have an average worst itch score of ≥7 in the 7 days prior to Day 1.

   NOTE: Baseline pruritus NRS average score for maximum itch intensity will be determined based on the average of daily NRS scores for maximum intensity (the daily score ranges from 0 to 10) during the 7 days immediately preceding randomization. A minimum of 4 daily scores out of the 7 days is required to calculate the baseline average score. For patients who do not have at least 4 daily scores reported during the 7 days immediately preceding the planned randomization date, randomization should be postponed until this requirement is met, but without exceeding the 28-day maximum duration of the screening period.

4. Patients must have a minimum of 20 PN lesions in total on both legs, and/or both arms and/or trunk, at Screening visit and on Day 1.

   NOTE: Patients need to have bilaterally symmetrical lesions on the extremities. The presence of lesions on at least 2 body surface areas is required.

5. History of failing a 2-week course of medium-to-superpotent TCS or when TCS are not medically advisable.

   NOTE: Failure is defined as patients who are unable to achieve and/or maintain remission and low disease activity (similar to IGA PN-S score of ≤2 [≤19 nodules]) despite treatment with a daily regimen of medium-to-superpotent TCS (±TCI as appropriate), applied for at least 14 days, or for the maximum duration recommended by the product prescribing information, whichever is shorter.

6. Have applied a stable dose of topical emollient (moisturizer) once or twice daily for at least 5 out of the 7 consecutive days immediately before Day 1 (NOTE: See exclusion criterion 20 for limitations regarding emollients).

7. Participants must be willing and able to complete a daily symptom eDiary for the duration of the study.

Sex

8. Male or Female

   Contraceptive use by women should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies.

   a) Female participants

Trial name: LIBERTY-PN PRIME		NCT number: NCT04183335
	- A female participant is eligible to participate if she is not pregnant or breastfeeding, and at least one of the following conditions applies: Is not a WOCBP. - OR: - Is a WOCBP and agrees to use a contraceptive method during the study (at a minimum until 12 weeks after the last dose of study intervention). - A WOCBP must have a negative highly sensitive pregnancy test (urine or serum as required by local regulations) on Day 1 before the first dose of study intervention. - If a urine test cannot be confirmed as negative (eg, an ambiguous result), a serum pregnancy test is required. In such cases, the participant must be excluded from participation if the serum pregnancy result is positive. - The investigator is responsible for review of medical history, menstrual history, and recent sexual activity to decrease the risk for inclusion of a woman with an early undetected pregnancy. **Informed Consent** 9. Capable of giving signed informed consent of the protocol which includes compliance with the requirements and restrictions listed in the informed consent form (ICF) and in this protocol. In countries where legal age of majority is above 18 years, a specific ICF must also be signed by the participant's legally authorized representative.	
Main exclusion criteria	Participants are excluded from the study if any of the following criteria apply: **Medical conditions** 1. Presence of skin morbidities other than PN and mild AD that may interfere with the assessment of the study outcomes. Conditions such as, but not limited to, the following: scabies, insect bite, lichen simplex chronicus, psoriasis, acne, folliculitis, habitual picking, lymphomatoid papulosis, chronic actinic dermatitis, dermatitis herpetiformis, sporotrichosis, bullous disease. NOTE: patients with mild active AD will represent up to 10% of the atopic PN study population.	

2. PN secondary to medications (eg, opioids, angiotensin converting enzyme [ACE] inhibitors).
3. PN secondary to medical conditions such as neuropathy or psychiatric disease (eg, notalgia paresthetica, brachioradial pruritus, neurotic excoriations, obsessive compulsive disorder, delusions of parasitosis, etc).
4. Patients with a documented AD severity moderate to severe within 6 months before the screening visit, or documented diagnosis of moderate to severe AD from screening visit to randomization visit (eg, IGA AD of 3 or 4, eczema area and severity index [EASI] ≥16, scoring atopic dermatitis [SCORAD] ≥25).
5. Severe concomitant illness(es) under poor control that, in the investigator's judgment, would adversely affect the patient's participation in the study. Examples include, but are not limited to patients with life expectancy shorter than 1 year, patients with uncontrolled diabetes (hemoglobin A1c ≥9% according to the laboratory results within 3 months before screening visit), patients with cardiovascular conditions (eg, Class III or IV heart failure according to the New York Heart Association classification), hepato-biliary conditions (eg, Child-Pugh Class B or C), neurological conditions (eg, demyelinating diseases), active major autoimmune diseases (eg, lupus, inflammatory bowel disease, rheumatoid arthritis, etc), other severe endocrinological, gastrointestinal, metabolic, pulmonary, or lymphatic diseases. The specific justification for patients excluded under this criterion will be noted in study documents (chart notes, eCRF, etc).
6. Severe renal conditions (eg, patients with uremia and/or on dialysis).
7. Participants with uncontrolled thyroid disease.
8. Active TB or non-tuberculous mycobacterial infection, or a history of incompletely treated TB will be excluded from the study unless it is well documented by a specialist that the participant has been adequately treated and can now start treatment with dupilumab in the medical judgment of the investigator and/or infectious disease specialist. Tuberculosis testing will be performed on a country-by-country basis, according to local guidelines if required by regulatory authorities or ethics boards.
9. Diagnosed active endoparasitic infections; suspected or high risk of endoparasitic infection, unless clinical and (if necessary) laboratory assessment have ruled out active infection before randomization.
10. Active chronic or acute infection (except HIV infection) requiring treatment with systemic antibiotics, antivirals, antiprotozoals, or antifungals within 2 weeks before screening visit or during the screening period.
11. Known or suspected immunodeficiency, including history of invasive opportunistic infections (eg, TB, histoplasmosis, listeriosis,

coccidioidomycosis, pneumocystosis, aspergillosis) despite infection resolution, or otherwise recurrent infections of abnormal frequency or prolonged duration suggesting an immune-compromised status, as judged by the investigator.

12. Active malignancy or history of malignancy within 5 years before the baseline visit, except completely treated in situ carcinoma of the cervix, completely treated and resolved non-metastatic squamous or basal cell carcinoma of the skin.

13. History of systemic hypersensitivity or anaphylaxis to any biologic therapy, including any excipients.

14. Any other medical or psychological condition including relevant laboratory abnormalities at screening that, in the opinion of the investigator, suggest a new and/or insufficiently understood disease, may present an unreasonable risk to the study patient as a result of his/her participation in this clinical trial, may make patient's participation unreliable, or may interfere with study assessments. The specific justification for patients excluded under this criterion will be noted in study documents (chart notes, eCRF, etc).

15. History of substance and/or alcohol abuse.

16. Planned major surgical procedure during the patient's participation in this study.

Prior/concomitant therapy

17. Exposure to another systemic or topical investigative drug (monoclonal antibodies as well as small molecules) within a certain time period prior to Visit 1 (screening), as follows: an interval of less than 6 months or <5 PK half-lives for investigative monoclonal antibodies, whichever is longer, and an interval of less than 30 days or <5 PK half-lives, whichever is longer, for investigative small molecules.

18. Having used any of the following treatments within 4 weeks before the screening visit

    a. Systemic immunosuppressive/immunomodulating drugs (eg, systemic corticosteroids, cyclosporine, mycophenolate-mofetil, interferon gamma, Janus kinase inhibitors, azathioprine, methotrexate, hydroxychloroquine, dapsone, sulfasalazine, colchine, etc).

    b. Intralesional corticosteroid injections and cryotherapy.

    c. Phototherapy, including tanning beds.

    d. Naltrexone or other opioid antagonist.

    e. Gabapentin, pregabalin, and thalidomide.

Or starting to use the following treatments or changed the dose of the following treatments in 3 months before the screening visit or expected the dose of the following treatments will be changed throughout the study:

f. Paroxetine, fluvoxamine, or other selective serotonin reuptake inhibitors (SSRIs).

g. Serotonin and norepinephrine reuptake inhibitors (SNRIs)

h. Amitriptyline or other tricyclic or tetracyclic antidepressants.

19. Previous treatment with biologic medicines within the following timeframe:

    a. Any cell-depleting agents including but not limited to rituximab: within 6 months before the screening visit.

    b. Omalizumab: within 5 months before screening visit.

    c. Other immunomodulatory biologics: within 5 half-lives (if known) or 16 weeks before the screening visit, whichever is longer.

20. Initiation of treatment with prescription moisturizers or moisturizers containing additives such as ceramide, hyaluronic acid, urea, menthol, polidocanol, or filaggrin degradation products during the screening period (patients may continue using stable doses of such moisturizers if initiated before the Screening visit).

21. Initiation of treatment with TCS/TCI (any potency) during the screening period or treatment with high potency or superpotent TCS/TCI during the screening period.

22. For participants who were on a stable regimen of TCS/TCI (maintain same medicine, same dose from 2 weeks prior to screening visit) at the screening visit:

    a. Application of TCS/TCI on fewer than 6 days during the 7 days immediately preceding randomization.

    b. Application of TCS/TCI of incorrect potency within 7 days before Day 1, ie, low potency if on low potency at screening visit and medium potency if on medium or higher potency at screening visit.

23. Treatment with a live (attenuated) vaccine within 4 weeks before the screening visit.

    NOTE: For patients who have vaccination with live, attenuated vaccines planned during the course of the study (based on national vaccination schedule/local guidelines), it will be determined, after consultation with a physician, whether the administration of vaccine can be postponed until after the end of study, or preponed

to before the start of the study, without compromising the health of the patient:

a. Patient for whom administration of live (attenuated) vaccine can be safely postponed would be eligible to enroll into the study.

b. Patients who have their vaccination preponed can enroll in the study only after a gap of 4 weeks following administration of the vaccine.

24. Planned or anticipated use of any prohibited medications and procedures during screening and study treatment period.

Prior/concurrent clinical study experience

25. Participation in prior dupilumab clinical study; treated in the past with dupilumab; prior use of biologics for PN.

Diagnostic assessments

26. For participants without history of HIV infection before screening visit, positive HIV serology at screening.

    For participants with history of HIV infection with CD4+ counts ≤300 cells/µL and/or detectable HIV viral load at screening.

27. Participants with any of the following result at screening:

    a. Positive (or indeterminate) HBs Ag or,

    b. Positive total HBc Ab confirmed by positive HBV DNA or,

    c. Positive HCV Ab confirmed by positive HCV RNA.

Other exclusions

28. Individuals accommodated in an institution because of regulatory or legal order; prisoners or subjects who are legally institutionalized.

29. Any country-related specific regulation that would prevent the subject from entering the study

30. Participant not suitable for participation, whatever the reason, as judged by the Investigator, including medical or clinical conditions, or participants potentially at risk of noncompliance to study procedures.

31. Participants are dependent on the Sponsor or Investigator (in conjunction with Section 1.61 of the International Council for Harmonisation (ICH) good clinical practice (GCP) Ordinance E6).

32. Participants are employees of the clinical study site or other individuals directly involved in the conduct of the study, or immediate family members of such individuals.

Trial name: LIBERTY-PN PRIME		NCT number: NCT04183335
	33. Any specific situation during study implementation/course that may raise ethics considerations. 34. Sensitivity to any of the study interventions, or components thereof, or drug or other allergy that, in the opinion of the Investigator, contraindicates participation in the study.	
Intervention	Subcutaneous dupilumab 300 mg (loading dose of 600 mg on day 1) every 2 weeks for 24 weeks. 75 patients received the intervention (dupilumab).	
Comparator(s)	Subcutaneous matching placebo every 2 weeks for 24 weeks. 76 patients received the comparator (placebo).	
Follow-up time	Duration of study period (per participant): • Screening period (2-4 weeks) • Randomized investigational medicinal product (IMP) intervention period (24 weeks) • Follow-up period (12 weeks)	
Is the study used in the health economic model?	Yes.	
Primary, secondary and exploratory endpoints	The primary endpoint was the proportion of patients with a ≥4-point reduction in Worst Itch Numeric Rating Scale (WI-NRS) score (range 0 ('no itch') to 10 ('worst imaginable itch')) at week 24 (PRIME) (endpoint included in this application). WI-NRS is validated in PN, with research to date supporting a four-point reduction as clinically meaningful. Key secondary end points included proportion of patients with reduction in skin lesion number to an Investigator Global Assessment for PN-Stage (IGA PN-S) score of 0 or 1 at week 24 (endpoint included in this application). IGA PN-S is also validated in PN, with scores ranging from 0 to 4 (0, 'clear' (no nodules); 1, 'almost clear' (≤5 nodules); 2, 'mild' (6–19 nodules); 3, 'moderate' (20–99 nodules); 4, 'severe' (≥100 nodules)) (endpoint included in this application). Other pre-specified secondary and tertiary endpoints included assessment of QoL, skin pain, sleep and mental health.	
Method of analysis	The primary analysis population for the efficacy endpoints was the ITT population. The primary analysis was conducted by using Cochran–Mantel–Haenszel test (CMH) test adjusted by documented history of atopy (atopic or non-atopic), stable use of TCS/TCI (yes or no), region, and baseline anti-depressant use (yes or no). Comparisons of the response rates between dupilumab and placebo were derived. In addition, odds	

Trial name: LIBERTY-PN PRIME	NCT number: NCT04183335
	ratio and response rate difference as well as the corresponding 95% confidence intervals (CI) are provided along with the p-values.
Subgroup analyses	To assess the homogeneity of the treatment effect across various subgroups, analyses were performed on the primary endpoint across the following subgroups (categories with fewer than 5 participants may be combined with other categories): • Participants without a current diagnosis of AD • Age group (<65, ≥65 years) • Gender (Male, Female) • Region • Territory • Race (Caucasian/White, Black/of African descent, Asian/Oriental, Others) • Ethnicity (Hispanic or Latino, Not Hispanic or Latino) • Baseline weight (<60, ≥60- < 90, ≥ 90 kg) • Baseline BMI (<25, ≥25- <30, ≥30 kg/m^2) • History of atopy (atopic or non-atopic) • Stable use of TCS/TCI (yes or no) • Antidepressant use (yes or no) at baseline • HIV (positive vs. negative) • Baseline IGA PN-S moderate vs severe (3 vs. 4) To test the interaction between intervention and subgroup factor, a logistic regression model incorporating subgroup-by-treatment interaction was built for each subgroup factor except the subgroup of participants without a current diagnosis of AD (very few AD participants will be excluded). The model included all the covariates in the main statistical model plus the subgroup variable and the subgroup-by-treatment interaction. A p-value for the test of interaction was provided. In each subgroup, the treatment effects for the primary endpoint were provided, as well as the corresponding 95% CI, using the same method as applied to the primary analysis. Forest plots were provided.
Other relevant information	

Table 73 Main characteristics of studies included (PRIME2)

Trial name: PRIME2	NCT number: NCT04202679
Objective	To evaluate the use of dupilumab in patients with PN inadequately controlled on topical prescription therapies or when those therapies are not advisable.
Publications – title, author, journal, year	Full paper – Yosipovitch G, Mollanazar N, Ständer S, Kwatra SG, Kim BS, Laws E, Mannent LP, Amin N, Akinlade B, Staudinger HW, Patel N, Yancopoulos GD, Weinreich DM, Wang S, Shi G, Bansal A, O'Malley JT. Dupilumab in patients with prurigo nodularis: two randomized, double-blind, placebo-controlled phase 3 trials. Nat Med. 2023 May;29(5):1180-1190. [44] Full paper – Yosipovitch G, Kim BS, Kwatra SG, Mollanazar NK, Ständer S, Satoh T, Mendes-Bastos P, Tsai TF, Laws E, Nivens MC, Maloney J, Shi G, Bansal A, Dubost-Brama A. Dupilumab improves pruritus and skin lesions in patients with prurigo nodularis: Pooled results from 2 phase 3 trials (LIBERTY-PN PRIME and PRIME2). JAAD Int. 2024 Apr 10;16:163-174. [45]
Study type and design	This study is a Phase 3, multi-center, 24-week treatment, parallel, double-blind, randomized, placebo controlled study to evaluate the use of dupilumab in patients with PN inadequately controlled on topical prescription therapies or when those therapies are not advisable. All participants will be centrally assigned to randomized study intervention using an Interactive Response Technology (IRT). Patients were randomized 1:1 to receive subcutaneous dupilumab 300 mg or matching placebo every 2 weeks for 24 weeks. Randomization will be stratified by the following factors: • documented history of atopy (atopic or non-atopic) • stable use of TCS/TCI (yes or no) • country/territory code
Sample size (n)	A total of 221 patients were screened and 160 were randomized (78 dupilumab and 82 placebo) at 55 study sites in 11 countries/regions.
Main inclusion criteria	Participants are eligible to be included in the study only if all of the following criteria apply: **Age** 1. Participants must be 18 to 80 years of age, at the time of signing the informed consent. **Type of participant and disease characteristics** Patients with a clinical diagnosis of PN, as defined by all of the following:

2. Diagnosed by a dermatologist for at least 3 months before the Screening visit.

3. On the WI-NRS ranging from 0 to 10, patients must have an average worst itch score of ≥7 in the 7 days prior to Day 1.

   NOTE: Baseline pruritus NRS average score for maximum itch intensity will be determined based on the average of daily NRS scores for maximum intensity (the daily score ranges from 0 to 10) during the 7 days immediately preceding randomization. A minimum of 4 daily scores out of the 7 days is required to calculate the baseline average score. For patients who do not have at least 4 daily scores reported during the 7 days immediately preceding the planned randomization date, randomization should be postponed until this requirement is met, but without exceeding the 28-day maximum duration of the screening period.

4. Patients must have a minimum of 20 PN lesions in total on both legs, and/or both arms and/or trunk, at Screening visit and on Day 1.

   NOTE: Patients need to have bilaterally symmetrical lesions on the extremities. The presence of lesions on at least 2 body surface areas is required.

5. History of failing a 2-week course of medium-to-superpotent TCS or when TCS are not medically advisable.

   NOTE: Failure is defined as patients who are unable to achieve and/or maintain remission and low disease activity (similar to IGA PN-S score of ≤2 [≤19 nodules]) despite treatment with a daily regimen of medium-to-superpotent TCS (±TCI as appropriate), applied for at least 14 days, or for the maximum duration recommended by the product prescribing information, whichever is shorter.

6. Have applied a stable dose of topical emollient (moisturizer) once or twice daily for at least 5 out of the 7 consecutive days immediately before Day 1 (NOTE: See exclusion criterion 20 for limitations regarding emollients).

7. Participants must be willing and able to complete a daily symptom eDiary for the duration of the study.

Sex

8. Male or Female

   Contraceptive use by women should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies.

   a) Female participants

   - A female participant is eligible to participate if she is not pregnant or breastfeeding, and at least one of the

	following conditions applies: Is not a WOCBP. - OR: - Is a WOCBP and agrees to use a contraceptive method during the study (at a minimum until 12 weeks after the last dose of study intervention). - A WOCBP must have a negative highly sensitive pregnancy test (urine or serum as required by local regulations) on Day 1 before the first dose of study intervention. - If a urine test cannot be confirmed as negative (eg, an ambiguous result), a serum pregnancy test is required. In such cases, the participant must be excluded from participation if the serum pregnancy result is positive. - The investigator is responsible for review of medical history, menstrual history, and recent sexual activity to decrease the risk for inclusion of a woman with an early undetected pregnancy. **Informed Consent** 9. Capable of giving signed informed consent of the protocol which includes compliance with the requirements and restrictions listed in the informed consent form (ICF) and in this protocol. In countries where legal age of majority is above 18 years, a specific ICF must also be signed by the participant's legally authorized representative.
Main exclusion criteria	Participants are excluded from the study if any of the following criteria apply: **Medical conditions** 1. Presence of skin morbidities other than PN and mild AD that may interfere with the assessment of the study outcomes. Conditions such as, but not limited to, the following: scabies, insect bite, lichen simplex chronicus, psoriasis, acne, folliculitis, habitual picking, lymphomatoid papulosis, chronic actinic dermatitis, dermatitis herpetiformis, sporotrichosis, bullous disease. NOTE: patients with mild active AD will represent up to 10% of the atopic PN study population.

2. PN secondary to medications (eg, opioids, angiotensin converting enzyme [ACE] inhibitors).
3. PN secondary to medical conditions such as neuropathy or psychiatric disease (eg, notalgia paresthetica, brachioradial pruritus, neurotic excoriations, obsessive compulsive disorder, delusions of parasitosis, etc).
4. Patients with a documented AD severity moderate to severe within 6 months before the screening visit, or documented diagnosis of moderate to severe AD from screening visit to randomization visit (eg, IGA AD of 3 or 4, eczema area and severity index [EASI] ≥16, scoring atopic dermatitis [SCORAD] ≥25).
5. Severe concomitant illness(es) under poor control that, in the investigator's judgment, would adversely affect the patient's participation in the study. Examples include, but are not limited to patients with life expectancy shorter than 1 year, patients with uncontrolled diabetes (hemoglobin A1c ≥9% according to the laboratory results within 3 months before screening visit), patients with cardiovascular conditions (eg, Class III or IV heart failure according to the New York Heart Association classification), hepato-biliary conditions (eg, Child-Pugh Class B or C), neurological conditions (eg, demyelinating diseases), active major autoimmune diseases (eg, lupus, inflammatory bowel disease, rheumatoid arthritis, etc), other severe endocrinological, gastrointestinal, metabolic, pulmonary, or lymphatic diseases. The specific justification for patients excluded under this criterion will be noted in study documents (chart notes, eCRF, etc).
6. Severe renal conditions (eg, patients with uremia and/or on dialysis).
7. Participants with uncontrolled thyroid disease.
8. Active TB or non-tuberculous mycobacterial infection, or a history of incompletely treated TB will be excluded from the study unless it is well documented by a specialist that the participant has been adequately treated and can now start treatment with dupilumab in the medical judgment of the investigator and/or infectious disease specialist. Tuberculosis testing will be performed on a country-by-country basis, according to local guidelines if required by regulatory authorities or ethics boards.
9. Diagnosed active endoparasitic infections; suspected or high risk of endoparasitic infection, unless clinical and (if necessary) laboratory assessment have ruled out active infection before randomization.
10. Active chronic or acute infection (except HIV infection) requiring treatment with systemic antibiotics, antivirals, antiprotozoals, or antifungals within 2 weeks before screening visit or during the screening period.
11. Known or suspected immunodeficiency, including history of invasive opportunistic infections (eg, TB, histoplasmosis, listeriosis,

coccidioidomycosis, pneumocystosis, aspergillosis) despite infection resolution, or otherwise recurrent infections of abnormal frequency or prolonged duration suggesting an immune-compromised status, as judged by the investigator.

12. Active malignancy or history of malignancy within 5 years before the baseline visit, except completely treated in situ carcinoma of the cervix, completely treated and resolved non-metastatic squamous or basal cell carcinoma of the skin.

13. History of systemic hypersensitivity or anaphylaxis to any biologic therapy, including any excipients.

14. Any other medical or psychological condition including relevant laboratory abnormalities at screening that, in the opinion of the investigator, suggest a new and/or insufficiently understood disease, may present an unreasonable risk to the study patient as a result of his/her participation in this clinical trial, may make patient's participation unreliable, or may interfere with study assessments. The specific justification for patients excluded under this criterion will be noted in study documents (chart notes, eCRF, etc).

15. History of substance and/or alcohol abuse.

16. Planned major surgical procedure during the patient's participation in this study.

Prior/concomitant therapy

17. Exposure to another systemic or topical investigative drug (monoclonal antibodies as well as small molecules) within a certain time period prior to Visit 1 (screening), as follows: an interval of less than 6 months or <5 PK half-lives for investigative monoclonal antibodies, whichever is longer, and an interval of less than 30 days or <5 PK half-lives, whichever is longer, for investigative small molecules.

18. Having used any of the following treatments within 4 weeks before the screening visit

    a. Systemic immunosuppressive/immunomodulating drugs (eg, systemic corticosteroids, cyclosporine, mycophenolate-mofetil, interferon gamma, Janus kinase inhibitors, azathioprine, methotrexate, hydroxychloroquine, dapsone, sulfasalazine, colchine, etc).

    b. Intralesional corticosteroid injections and cryotherapy.

    c. Phototherapy, including tanning beds.

    d. Naltrexone or other opioid antagonist.

    e. Gabapentin, pregabalin, and thalidomide.

Or starting to use the following treatments or changed the dose of the following treatments in 3 months before the screening visit or expected the dose of the following treatments will be changed throughout the study:

f. Paroxetine, fluvoxamine, or other selective serotonin reuptake inhibitors (SSRIs).

g. Serotonin and norepinephrine reuptake inhibitors (SNRIs)

h. Amitriptyline or other tricyclic or tetracyclic antidepressants.

19. Previous treatment with biologic medicines within the following timeframe:

    a. Any cell-depleting agents including but not limited to rituximab: within 6 months before the screening visit.

    b. Omalizumab: within 5 months before screening visit.

    c. Other immunomodulatory biologics: within 5 half-lives (if known) or 16 weeks before the screening visit, whichever is longer.

20. Initiation of treatment with prescription moisturizers or moisturizers containing additives such as ceramide, hyaluronic acid, urea, menthol, polidocanol, or filaggrin degradation products during the screening period (patients may continue using stable doses of such moisturizers if initiated before the Screening visit).

21. Initiation of treatment with TCS/TCI (any potency) during the screening period or treatment with high potency or superpotent TCS/TCI during the screening period.

22. For participants who were on a stable regimen of TCS/TCI (maintain same medicine, same dose from 2 weeks prior to screening visit) at the screening visit:

    a. Application of TCS/TCI on fewer than 6 days during the 7 days immediately preceding randomization.

    b. Application of TCS/TCI of incorrect potency within 7 days before Day 1, ie, low potency if on low potency at screening visit and medium potency if on medium or higher potency at screening visit.

23. Treatment with a live (attenuated) vaccine within 4 weeks before the screening visit.

    NOTE: For patients who have vaccination with live, attenuated vaccines planned during the course of the study (based on national vaccination schedule/local guidelines), it will be determined, after consultation with a physician, whether the administration of vaccine can be postponed until after the end of study, or preponed

to before the start of the study, without compromising the health of the patient:

a. Patient for whom administration of live (attenuated) vaccine can be safely postponed would be eligible to enroll into the study.

b. Patients who have their vaccination preponed can enroll in the study only after a gap of 4 weeks following administration of the vaccine.

24. Planned or anticipated use of any prohibited medications and procedures during screening and study treatment period.

Prior/concurrent clinical study experience

25. Participation in prior dupilumab clinical study; treated in the past with dupilumab; prior use of biologics for PN.

Diagnostic assessments

26. For participants without history of HIV infection before screening visit, positive HIV serology at screening.

    For participants with history of HIV infection with CD4+ counts ≤300 cells/µL and/or detectable HIV viral load at screening.

27. Participants with any of the following result at screening:

    a. Positive (or indeterminate) HBs Ag or,

    b. Positive total HBc Ab confirmed by positive HBV DNA or,

    c. Positive HCV Ab confirmed by positive HCV RNA.

Other exclusions

28. Individuals accommodated in an institution because of regulatory or legal order; prisoners or subjects who are legally institutionalized.

29. Any country-related specific regulation that would prevent the subject from entering the study

30. Participant not suitable for participation, whatever the reason, as judged by the Investigator, including medical or clinical conditions, or participants potentially at risk of noncompliance to study procedures.

31. Participants are dependent on the Sponsor or Investigator (in conjunction with Section 1.61 of the International Council for Harmonisation (ICH) good clinical practice (GCP) Ordinance E6).

32. Participants are employees of the clinical study site or other individuals directly involved in the conduct of the study, or immediate family members of such individuals.

Trial name: PRIME2		NCT number: NCT04202679
	33. Any specific situation during study implementation/course that may raise ethics considerations. 34. Sensitivity to any of the study interventions, or components thereof, or drug or other allergy that, in the opinion of the Investigator, contraindicates participation in the study.	
Intervention	Subcutaneous dupilumab 300 mg (loading dose of 600 mg on day 1) every 2 weeks for 24 weeks. 78 patients received the intervention (dupilumab).	
Comparator(s)	Subcutaneous matching placebo every 2 weeks for 24 weeks. 82 patients received the comparator (placebo).	
Follow-up time	Duration of study period (per participant): • Screening period (2-4 weeks) • Randomized investigational medicinal product (IMP) intervention period (24 weeks) • Follow-up period (12 weeks)	
Is the study used in the health economic model?	Yes.	
Primary, secondary and exploratory endpoints	The primary endpoint was the proportion of patients with a ≥4-point reduction in Worst Itch Numeric Rating Scale (WI-NRS) score (range 0 ('no itch') to 10 ('worst imaginable itch')) at week 12 and 24 (endpoint at week 24 is included in this application). WI-NRS is validated in PN, with research to date supporting a four-point reduction as clinically meaningful. Key secondary end points included proportion of patients with reduction in skin lesion number to an Investigator Global Assessment for PN-Stage (IGA PN-S) score of 0 or 1 at week 24 (endpoint included in this application). IGA PN-S is also validated in PN, with scores ranging from 0 to 4 (0, 'clear' (no nodules); 1, 'almost clear' (≤5 nodules); 2, 'mild' (6–19 nodules); 3, 'moderate' (20–99 nodules); 4, 'severe' (≥100 nodules)). Other pre-specified secondary and tertiary endpoints included assessment of QoL, skin pain, sleep and mental health.	
Method of analysis	The analysis population for the efficacy endpoints was the intent-to-treat (ITT) population defined as all randomized participants analysed according to the treatment group allocated by randomization regardless if treatment kit was used or not. The primary analysis on WI-NRS reduction ≥4 at Week 12 was conducted by using Cochran-Mantel-Haenszel (CMH) test stratifying by stratification factors (documented history of atopy [atopic or non-atopic], stable use of TCS/TCI [yes or no], and region [countries combined]) and covariate of baseline anti-depressant use (yes or no).	

	For participants discontinuing the study treatment before Week 12, their off-study treatment values measured up to Week 12 were included in the analysis. Participants taking selected prohibited medications and/or rescue medications prior to Week 12 or have missing data at Week 12 were considered non-responders. Sensitivity analyses using alternative methods were performed to handle missing data and/or data collected after participants taking selected prohibited medications and/or rescue medications. A subgroup analysis was performed excluding participants with a current diagnosis of AD. Secondary efficacy endpoints that measure binary responses will be analysed in the same fashion as the primary endpoint.
Subgroup analyses	To assess the homogeneity of the treatment effect across various subgroups, analyses will be performed on the primary endpoint across the following subgroups (categories with fewer than 5 participants may be combined with other categories): • Age group (< 90, ≥ 90 kg) • Gender (Male, Female) • Region • Territory • Race (Caucasian/White, Black/of African descent, Asian/Oriental, Others) • Ethnicity (Hispanic or Latino, Not Hispanic or Latino) • Baseline weight (<60, ≥60- < 90, ≥ 90 kg) • Baseline BMI (<25, ≥25-<30, ≥30 kg/m2) • Participants without a current diagnosis of AD • History of atopy (atopic or non-atopic) • Stable use of TCS/TCI (yes or no) • Antidepressant use (yes or no) at baseline • Baseline IGA PN-S moderate versus severe (3 vs. 4) • Participants who have not been impacted by COVID-19 vs impacted by COVID-19 (for participants who have been impacted by the COVID-19, the efficacy data will be descriptive only if the number of participants is not enough to perform statistical tests. Participants impacted by the COVID-19 pandemic are defined as randomized participants with any critical or major deviation related to COVID-19 or who permanently discontinued study intervention or study due to COVID-19.) To test the interaction between intervention and subgroup factor, a logistic regression model incorporating subgroup-by-treatment

Trial name: PRIME2		NCT number: NCT04202679
	interaction will be built for each subgroup factor except the subgroup of participants without a current diagnosis of AD (very few AD participants will be excluded). The model will include all the covariates in the main statistical model plus the subgroup variable and the subgroup-by-treatment interaction. A p-value for the test of interaction will be provided. In each subgroup, the treatment effects for the primary endpoint will be provided, as well as the corresponding 95% CI, using the same method as applied to the primary analysis. Forest plots will be provided.	
Other relevant information		

Appendix B. Efficacy results per study

Results per study

The results per study for all trials included in the assessment are presented in the tables below. As mentioned in section 7, values obtained by using different imputation methods were used in the ITC for some of the binary endpoints (sensitivity analysis 1). Furthermore, data from a subgroup of patients without stable use of TCS or TCI in the dupilumab trials was evaluated (sensitivity analysis 2). Therefore, all those values are presented below. For binary endpoints, the OR and the 95% confidence interval were calculated.

B.1 NCT03181503

Table 74 Results per study (NCT03181503)

Results of [NCT03181503]											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	**Study arm**	**N**	**Result**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
PP-NRS absolute change from baseline at week 12 NRI	Nemolizumab	34	-5.10	−3.0	(−4.4 – (−1.7))	NA	NA	NA	NA	All the efficacy data collected after the use of rescue therapy were treated as missing data. Missing data were imputed post hoc with the use of multiple-imputation missing-at-non-random assumptions.	[35]
	Placebo	36	-2.10								[35]

Results of [NCT03181503]											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	Study arm	N	Result	Difference	95% CI	*P* value	Difference	95% CI	*P* value		
PP-NRS absolute change from baseline at week 16 NRI	Nemolizumab	34	-5.0	NA	NA	NA	NA	NA	NA	All the efficacy data collected after the use of rescue therapy were treated as missing data. Missing data were imputed post hoc with the use of multiple-imputation missing-at-non-random assumptions.	[35]
	Placebo	36	-2.3								[35]

B.2 OLYMPIA 1, ITT population

Table 75 Results per study (OLYMPIA 1), ITT population

Results of [OLYMPIA 1 (NCT04501666)]											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	Study arm	N	Result	Difference	95% CI	*P* value	Difference	95% CI	*P* value		
PP-NRS improvem	Nemolizumab	190	111 (58.4%)	41.8	(31.5–52.0)	<0.001	[redacted]	[redacted]	NA	Endpoints were analysed with the Cochran–Mantel–Haenszel	[38] [32]

Results of [OLYMPIA 1 (NCT04501666)]											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	Study arm	N	Result	Difference	95% CI	*P* value	Difference	95% CI	*P* value		
ent ≥4 points at week 16 NRI	Placebo	96	16 (16.7%)							test and adjusted for the stratification variables of analysis center and baseline weight (<90 kg or ≥90 kg) with patients with missing data considered as not having had a response.	[38] [32]
PP-NRS improvement ≥4 points at week 16 OC	Nemolizumab	[redacted]	[redacted]	NA	NA	NA	[redacted]	[redacted]	NA	Endpoints were analysed with the Cochran–Mantel–Haenszel test and adjusted for the stratification variables of analysis center and baseline weight (<90 kg or ≥90 kg) with no imputations for missing data.	[32]
	Placebo	[redacted]	[redacted]								[32]
PP-NRS improvement ≥4 points at week 24 NRI	Nemolizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	NA	Endpoints were analysed post hoc using multiple imputation–missing at random methods	[38] [32]
	Placebo	[redacted]	[redacted]								[38] [32]

Results of [OLYMPIA 1 (NCT04501666)]											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	Study arm	N	Result	Difference	95% CI	*P* value	Difference	95% CI	*P* value		
PP-NRS improvement ≥4 points at week 24 OC	Nemolizumab	[redacted]	[redacted]	NA	NA	NA	[redacted]	[redacted]	NA	All observed data even after use of rescue therapy are included; No imputations for missing data.	[32]
	Placebo	[redacted]	[redacted]								[32]
PP-NRS absolute change from baseline at week 16 OC	Nemolizumab	[redacted]	[redacted]	NA	NA	NA	NA	NA	NA	All observed data even after use of rescue therapy are included; No imputations for missing data.	[32]
	Placebo	[redacted]	[redacted]								[32]
PP-NRS absolute change from baseline at week 16 NRI	Nemolizumab	190	-4.7 (SE: 0.2)	-3.1	(−3.9−(−2.4)	[redacted]	NA	NA	NA	Endpoints were analysed with an analysis of covariance (ANCOVA) model using multiple imputation, assuming missing data to be missing at random, and a mixed effects model for repeated measures (MMRM), including the	[38] [32]
	Placebo	96	-1.6 (SE: 0.3)								[38] [32]

Results of [OLYMPIA 1 (NCT04501666)]											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	Study arm	N	Result	Difference	95% CI	*P* value	Difference	95% CI	*P* value		
										analysis center and the baseline body-weight cutoff as factors.	
PP-NRS absolute change from baseline at week 24 OC	Nemolizumab	[redacted]	[redacted]				NA	NA	NA	All observed data even after use of rescue therapy are included; No imputations for missing data.	[32]
	Placebo	[redacted]	[redacted]								[32]
PP-NRS absolute change from baseline at week 24 NRI	Nemolizumab	190	-4.9 (SE: 0.2)	-3.4	(−4.2−(−2.7)	[redacted]	NA	NA	NA	Endpoints were analysed with an analysis of covariance (ANCOVA) model using multiple imputation, assuming missing data to be missing at random, and a mixed effects model for repeated measures (MMRM), including the analysis center and the baseline body-weight cutoff as factors.	[38] [32]
	Placebo	96	-1.5 (SE: 0.3)								[38] [32]

Results of [OLYMPIA 1 (NCT04501666)]											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	**Study arm**	**N**	**Result**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
IGA success at week 16	Nemolizumab	190	50 (26.3%)	14.6	(6.7–22.6)	0.003	[redacted]	[redacted]	NA	Endpoints were analysed with the Cochran–Mantel–Haenszel test and adjusted for the stratification variables of analysis center and baseline weight (<90 kg or ≥90 kg) with patients with missing data considered as not having had a response.	[38]
NRI	Placebo	96	7 (7.3%)								[38]
IGA success at week 24	Nemolizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	NA	Endpoints were analysed with the Cochran–Mantel–Haenszel test and adjusted for the stratification variables of analysis center and baseline weight (<90 kg or ≥90 kg) with patients with missing data considered as not having had a response.	[32]
NRI	Placebo	[redacted]	[redacted]								[32]
IGA success at week 24	Nemolizumab	[redacted]	[redacted]				[redacted]	[redacted]	NA	All observed data even after use of rescue therapy are included; No imputations for missing data.	[32]
	Placebo	[redacted]	[redacted]								[32]

Results of [OLYMPIA 1 (NCT04501666)]											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	Study arm	N	Result	Difference	95% CI	*P* value	Difference	95% CI	*P* value		
OC											
PP-NRS improvement ≥4 points and IGA success at week 16 NRI	Nemolizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	NA	Endpoints were analysed with the Cochran–Mantel–Haenszel test and adjusted for the stratification variables of analysis center and baseline weight (<90 kg or ≥90 kg) with patients with missing data considered as not having had a response.	[38] [32]
	Placebo	[redacted]	[redacted]								[38] [32]
PP-NRS improvement ≥4 points and IGA success at week 16 OC	Nemolizumab	[redacted]	[redacted]				[redacted]	[redacted]	NA	All observed data even after use of rescue therapy are included; No imputations for missing data.	[32]
	Placebo	[redacted]	[redacted]								[32]
PP-NRS improvem	Nemolizumab	190	43 (22.6%)	16.6	(9.1–24.1)		[redacted]	[redacted]	NA	Endpoints were analysed with the Cochran–Mantel–Haenszel	[38] [32]

Results of [OLYMPIA 1 (NCT04501666)]											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	Study arm	N	Result	Difference	95% CI	*P* value	Difference	95% CI	*P* value		
ent ≥4 points and IGA success at week 24 NRI	Placebo	96	4 (4.2%)							test and adjusted for the stratification variables of analysis center and baseline weight (<90 kg or ≥90 kg) with patients with missing data considered as not having had a response.	[38] [32]
PP-NRS improvement ≥4 points at week 24 and IGA success at week 24 OC	[redacted]			NA	NA	NA	[redacted]		NA	All observed data even after use of rescue therapy are included; No imputations for missing data.	[32] [32]
DLQI absolute change from baseline at week 16	Nemolizumab	190	−8.6 (SE: 0.6)	−6.4	(−8.4–(−4.4)	[redacted]	NA	NA	NA	Endpoints were analysed with an analysis of covariance (ANCOVA) model using multiple imputation, assuming missing data to be missing at random, and a mixed effects model for repeated measures	[38] [32]
	Placebo	96	−2.2 (SE: 0.9)								[38] [32]

Results of [OLYMPIA 1 (NCT04501666)]											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	Study arm	N	Result	Difference	95% CI	*P* value	Difference	95% CI	*P* value		
NRI										(MMRM), including the analysis center and the baseline body-weight cutoff as factors.	
DLQI absolute change from baseline at week 16 OC	Nemolizumab	[redacted]	[redacted]	NA	NA	NA	NA	NA	NA	All observed data even after use of rescue therapy are included; No imputations for missing data.	[32]
	Placebo	[redacted]	[redacted]								[32]
DLQI absolute change from baseline at week 24 NRI	Nemolizumab	190	−9.0 (SE: 0.6)	−8.4	(−10.5−(−6.3)	[redacted]	NA	NA	NA	Endpoints were analysed with an analysis of covariance (ANCOVA) model using multiple imputation, assuming missing data to be missing at random, and a mixed effects model for repeated measures (MMRM), including the analysis center and the baseline body-weight cutoff as factors.	[38] [32]
	Placebo	96	−0.6 (SE: 0.9)								[38] [32]

Results of [OLYMPIA 1 (NCT04501666)]											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	Study arm	N	Result	Difference	95% CI	*P* value	Difference	95% CI	*P* value		
DLQI absolute change from baseline at week 24 OC	[redacted]	[redacted]	[redacted]				NA	NA	NA	All observed data even after use of rescue therapy are included; No imputations for missing data.	[32]
	[redacted]	[redacted]	[redacted]								[32]
HADS absolute change from baseline at week 16 Subscale Anxiety	Nemolizumab	190	-2.1 (0.3)	−1.2	(−2.1−(−0.3)	[redacted]	NA	NA	NA	Endpoints were analysed with the use of analysis of covariance based on the observed cases (where no imputation was done, and all data were used as observed).	[38] [32]
	Placebo	96	-1.0 (0.4)								[38] [32]
HADS absolute change from baseline at week 24	Nemolizumab	190	-2.4 (SE: 0.3)	-1.6	(−2.5−(−0.7)	[redacted]	NA	NA	NA	Endpoints were analysed with the use of analysis of covariance based on the observed cases (where no imputation was done, and all data were used as observed).	[38] [32]
	Placebo	96	-0.8 (SE: 0.4)								[38] [32]

Results of [OLYMPIA 1 (NCT04501666)]											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	**Study arm**	**N**	**Result**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
Subscale Anxiety											
HADS absolute change from baseline at week 16 Subscale depression	Nemolizumab	190	-2.0 (0.3)	−1.3	(−2.2–(−0.5)	[redacted]	NA	NA	NA	Endpoints were analysed with the use of analysis of covariance based on the observed cases (where no imputation was done, and all data were used as observed).	[38] [32]
	Placebo	96	-0.7 (0.4)								[38] [32]
HADS absolute change from baseline at week 24 Subscale depression	Nemolizumab	190	-2.2 (0.3	-1.9	(−2.8–(−1.0)	[redacted]	NA	NA	NA	Endpoints were analysed with the use of analysis of covariance based on the observed cases (where no imputation was done, and all data were used as observed).	[38] [32]
	Placebo	96	-0.4 (0.4)								[38] [32]
EQ-5D absolute	Nemolizumab	190	12.9 (1.5)	7.5	(2.7–12.3)	[redacted]	NA	NA	NA	Endpoints were analysed with the use of analysis of	[38] [32]

Results of [OLYMPIA 1 (NCT04501666)]											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	**Study arm**	**N**	**Result**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
change from baseline at week 16	Placebo	96	5.4 (2.0)							covariance based on the observed cases (where no imputation was done, and all data were used as observed).	[38] [32]
EQ-5D absolute change from baseline at week 24	Nemolizumab	190	13.0 (1.6)	9.7	(4.4−14.9)	[redacted]	NA	NA	NA	Endpoints were analysed with the use of analysis of covariance based on the observed cases (where no imputation was done, and all data were used as observed).	[38] [32]
	Placebo	96	3.3 (2.3)								[38] [32]

B.3 OLYMPIA 2, ITT population

Table 76 Results per study (OLYMPIA 2), ITT population

Results of [OLYMPIA 2 (NCT04501679)]											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	**Study arm**	**N**	**Result**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
PP-NRS improvement ≥4 points at week 16 NRI	Nemolizumab	183	103 (56.3%)	37.4	(26.3–48.5)	<0.001	[redacted]		NA	Endpoints were analysed with the Cochran–Mantel–Haenszel test and adjusted for the stratification variables of analysis center and baseline weight (<90 kg or ≥90 kg) with patients with missing data considered as not having had a response.	[42] [33]
	Placebo	91	19 (20.9%)								[42] [33]
PP-NRS improvement ≥4 points at week 16 OC	Nemolizumab	[redacted]					[redacted]		NA	All observed data even after use of rescue therapy are included; No imputations for missing data.	[33]
	Placebo	[redacted]									[33]
PP-NRS improvement ≥4 points and IGA	Nemolizumab	[redacted]		[redacted]			[redacted]		NA	Endpoints were analysed with the Cochran–Mantel–Haenszel test and adjusted for the stratification variables of analysis center and baseline	[33]
	Placebo	[redacted]									[33]

Results of [OLYMPIA 2 (NCT04501679)]											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	Study arm	N	Result	Difference	95% CI	*P* value	Difference	95% CI	*P* value		
success at week 16 NRI										weight (<90 kg or ≥90 kg) with patients with missing data considered as not having had a response.	
PP-NRS improvement ≥4 points and IGA success at week 16 OC	[redacted]	[redacted]	[redacted]				[redacted]	[redacted]	NA	All observed data even after use of rescue therapy are included; No imputations for missing data.	[33] [33]
PP-NRS absolute change from baseline at week 16 NRI	Nemolizumab	183	-4.8 (SE: 0.3)	-3.1	(−3.9−(−2.3)	NA	NA	NA	NA	Endpoints were analysed with an analysis of covariance (ANCOVA) model using multiple imputation, assuming missing data to be missing at random, and a mixed effects model for repeated measures (MMRM), including the analysis center and the	[42]
	Placebo	91	-1.7 (SE: 0.4)								[42]

Results of [OLYMPIA 2 (NCT04501679)]											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	Study arm	N	Result	Difference	95% CI	*P* value	Difference	95% CI	*P* value		
										baseline body-weight cutoff as factors	
PP-NRS absolute change from baseline at week 16 OC	[redacted]	[redacted]	[redacted]				NA	NA	NA	All observed data even after use of rescue therapy are included; No imputations for missing data.	[33] [33]
IGA success at week 16 NRI	Nemolizumab	183	69 (37.7%)	28.5	(18.8–28.2)	<0.001	[redacted]		NA	Endpoints were analysed with the Cochran–Mantel–Haenszel test and adjusted for the stratification variables of analysis center and baseline weight (<90 kg or ≥90 kg) with patients with missing data considered as not having had a response.	[42] [42]
	Placebo	91	10 (11.0%)								
DLQI absolute	Nemolizumab	183	−8.9 (SE: 0.7)	−8.1	(−10.2−(−6.1)	[redacted]	NA	NA	NA	Endpoints were analysed with an analysis of covariance	[42] [33]

Results of [OLYMPIA 2 (NCT04501679)]											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	**Study arm**	**N**	**Result**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
change from baseline at week 16 NRI	Placebo	91	−0.8 (SE: 0.9)							(ANCOVA) model using multiple imputation, assuming missing data to be missing at random, and a mixed effects model for repeated measures (MMRM), including the analysis center and the baseline body-weight cutoff as factors.	[42] [33]
DLQI absolute change from baseline at week 16 OC	Nemolizumab	[redacted]	[redacted]				NA	NA	NA	All observed data even after use of rescue therapy are included; No imputations for missing data.	[33]
	Placebo	[redacted]	[redacted]								[33]
HADS absolute change from baseline at week 16	Nemolizumab	183	−2.6 [redacted]	−1.2	(−2.0−(−0.4)	[redacted]	NA	NA	NA	Endpoints were analysed with the use of ANCOVA, including the analysis center and the baseline bodyweight cutoff as factors and the baseline score as a covariate.	[42] [33]
	Placebo	91	−1.4 [redacted]								[42] [33]

Results of [OLYMPIA 2 (NCT04501679)]											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	**Study arm**	**N**	**Result**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
Subscale Anxiety											
HADS absolute change from baseline at week 16	Nemolizumab	183	−2.3 [redacted]	−1.5	(−2.3–(−0.8)	[redacted]	NA	NA	NA	Endpoints were analysed with the use of ANCOVA, including the analysis center and the baseline bodyweight cutoff as factors and the baseline score as a covariate.	[42] [33]
	Placebo	91	−0.7 [redacted]								[42] [33]
Subscale depression											

B.4 LIBERTY-PN PRIME, ITT population

Table 77 Results per study LIBERTY-PN PRIME, ITT population

Results of [LIBERTY-PN PRIME (NCT04183335)], ITT population											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	**Study arm**	**N**	**Result**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
WI-NRS improvement ≥4 points at week 24 NRI	Dupilumab	75	45 (60.0%)	42.7	(27.8–57.7)	<0.001	[redacted]	[redacted]		Endpoints were analysed using a Cochran–Mantel–Haenszel test adjusted by stratification factors and baseline antidepressant use. Patients with missing data at the timepoint or who used rescue/prohibited medications/procedures before the timepoint were considered non-responders.	[44]
	Placebo	76	14 (18.4%)								[44]
WI-NRS improvement ≥4 points at week 24	Dupilumab	75	48 (64.0%)	41.0	(25.4–56.7)	<0.001	[redacted]	[redacted]		Endpoints were analysed using a Cochran–Mantel–Haenszel test adjusted by stratification factors and baseline antidepressant use. Data collected after study intervention discontinuation and/or after taking the selected prohibited	[44]
	Placebo	76	19 (25.0%)								[44]

Results of [LIBERTY-PN PRIME (NCT04183335)], ITT population											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	**Study arm**	**N**	**Result**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
"As-observed analysis"										medications/procedures and/or rescue medications were included, and missing data at week 24 were considered non-responders.	
WI-NRS improvement ≥4 points at week 16 NRI (assumed)	Dupilumab	75	38 (50.7%)	NA	NA	NA	[redacted]	[redacted]		Extracted from clinicaltrials.gov	[46]
	Placebo	76	13 (17.1%)								[46]
IGA success at week 24 NRI	Dupilumab	75	36 (48.0%)	28.3	(13.4–43.2)	<0.001	[redacted]	[redacted]		Endpoints were analysed using a Cochran–Mantel–Haenszel test adjusted by stratification factors and baseline antidepressant use. Patients with missing data at the timepoint or who used rescue/prohibited medications/procedures	[44]
	Placebo	76	14 (18.4%)								[44]

Results of [LIBERTY-PN PRIME (NCT04183335)], ITT population											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	**Study arm**	**N**	**Result**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
										before the timepoint were considered non-responders.	
IGA success at week 24 "As observed analysis"	Dupilumab	75	36 (48.0%)	27.2%	(12.1-42.2)	<0.001§	[redacted]	[redacted]		Endpoints were analysed using a Cochran–Mantel–Haenszel test adjusted by stratification factors and baseline antidepressant use. Data collected after study intervention discontinuation and/or after taking the selected prohibited medications/procedures and/or rescue medications were included, and missing data at week 24 were considered non-responders.	[44]
	Placebo	76	15 (19.7%)								[44]
WI-NRS improvement ≥4 points and IGA success at week 24	Dupilumab	75	29 (38.7%)	29.6%	(16.4–42.8)	<0.001	[redacted]	[redacted]		Endpoints were analysed using a Cochran–Mantel–Haenszel test adjusted by stratification factors and baseline antidepressant use. Patients with missing data at the timepoint or who used	[44]
	Placebo	76	7 (9.2%)								[44]

Results of [LIBERTY-PN PRIME (NCT04183335)], ITT population											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	**Study arm**	**N**	**Result**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
NRI										rescue/prohibited medications/procedures before the timepoint were considered non-responders.	
WI-NRS improvement ≥4 points and IGA success at week 24 "As observed analysis"	Dupilumab	75	29 (38.7%)	28.5	(15.1–42.0)	<0.001	[redacted]	[redacted]	NA	Endpoints were analysed using a Cochran–Mantel–Haenszel test adjusted by stratification factors and baseline antidepressant use. Data collected after study intervention discontinuation and/or after taking the selected prohibited medications/procedures and/or rescue medications were included, and missing data at week 24 were considered non-responders.	[44]
	Placebo	76	8 (10.5%)								[44]
WI-NRS percentage change from	Dupilumab	75	−48.9 (SE: 5.6)	−26.7	(−38.4–(−14.9)	<0.001	NA	NA	NA	Endpoints were analysed using an analysis of covariance (ANCOVA) model with intervention group, stratification factors, baseline	[44]
	Placebo	76	−22.2 (SE: 5.7)								[44]

Results of [LIBERTY-PN PRIME (NCT04183335)], ITT population											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	**Study arm**	**N**	**Result**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
baseline at week 24 WOCF										antidepressant use and relevant baseline measurement as covariates. Data from patients who used rescue/prohibited medications/procedures were set to 'missing' after medication use, and the endpoint value was imputed by the worst post-baseline value available before medication use.	
WI-NRS absolute change from baseline at week 24 WOCF (assumed)	Dupilumab	75	−4.56 (SE: 0.42)							Extracted from clinicaltrials.gov	[46]
	Placebo	66	−2.28 (SE: 0.43)								[46]
	Dupilumab	75	-43.29 (SE: 5.44)								[46]

Results of [LIBERTY-PN PRIME (NCT04183335)], ITT population											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	Study arm	N	Result	Difference	95% CI	*P* value	Difference	95% CI	*P* value		
WI-NRS percentage change from baseline at week 16 WOCF (assumed)	Placebo	71	-18.10 (SE: 5.54)							Extracted from clinicaltrials.gov For the ITC Back Calculated from %	[46]
WI-NRS absolute change from baseline at week 12 WOCF (assumed)	Dupilumab	75	-3.87 (SE: 0.38)	NA	NA	NA	NA	NA	NA	Extracted from clinicaltrials.gov	[46]
	Placebo	72	-1.84 (SE: 0.38)								[46]
DLQI absolute change from	Dupilumab	[redacted]	[redacted]	NA	NA	NA	NA	NA	NA	Digitized using WebPlotDigitizer from a figure in the publication	[44]
	Placebo	[redacted]	[redacted]								[44]

Results of [LIBERTY-PN PRIME (NCT04183335)], ITT population											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	Study arm	N	Result	Difference	95% CI	*P* value	Difference	95% CI	*P* value		
baseline at week 12 MI, WOCF											
DLQI absolute change from baseline at week 24 MI, WOCF	Dupilumab	75	−12.0 (SE: 1.0)	−6.1	(−8.3−(−4.0)	<0.001	NA	NA	NA	Endpoints were analysed using an analysis of covariance (ANCOVA) model with intervention group, stratification factors, baseline antidepressant use and relevant baseline measurement as covariates. Data from patients who used rescue/prohibited medications/procedures were set to 'missing' after medication use, and the endpoint value was imputed by the worst post-baseline value available before medication use.	[44]
	Placebo	76	−5.8 (SE: 1.0)								[44]
HADS absolute change	Dupilumab	75	−4.6 (SE: 0.9)	−2.6	(−4.5−(−0.7)	0.008	NA	NA	NA	Endpoints were analysed using an analysis of covariance (ANCOVA) model with	[44]

Results of [LIBERTY-PN PRIME (NCT04183335)], ITT population											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	**Study arm**	**N**	**Result**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
from baseline at week 24										intervention group, stratification factors, baseline antidepressant use and relevant baseline measurement as covariates. Data from patients who used rescue/prohibited medications/procedures were set to 'missing' after medication use, and the endpoint value was imputed by the worst post-baseline value available before medication use.	
	Placebo	76	−2.0 (SE: 0.9)								[44]
HADS-A absolute change from baseline at week 16 Subscale Anxiety	Dupilumab	75	−2.7 (SE: 0.6)	−1.5	(−2.7−(−0.4)	0.008	NA	NA	NA	Endpoints were analysed using an analysis of covariance (ANCOVA) model with intervention group, stratification factors, baseline antidepressant use and relevant baseline measurement as covariates. Data from patients who used rescue/prohibited	

Results of [LIBERTY-PN PRIME (NCT04183335)], ITT population											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	**Study arm**	**N**	**Result**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
										medications/procedures were set to 'missing' after medication use, and the endpoint value was imputed by the worst post-baseline value available before medication use.	
	Placebo	76	−1.2 (SE: 0.5)								
HADS -D absolute change from baseline at week 16 Subscale Depression	Dupilumab	75	−1.9 (SE: 0.5)	−1.1	(−2.0−(−0.1)	0.033	NA	NA	NA	Endpoints were analysed using an analysis of covariance (ANCOVA) model with intervention group, stratification factors, baseline antidepressant use and relevant baseline measurement as covariates. Data from patients who used rescue/prohibited medications/procedures were set to 'missing' after medication use, and the endpoint value was imputed by the worst post-baseline	

Results of [LIBERTY-PN PRIME (NCT04183335)], ITT population											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	Study arm	N	Result	Difference	95% CI	*P* value	Difference	95% CI	*P* value		
										value available before medication use.	
	Placebo	76	−0.9 (SE: 0.5)								

B.5 LIBERTY-PN PRIME, no TCS/TCI subpopulation

Table 78 Results per study LIBERTY-PN PRIME, no TCS/TCI subpopulation

Results of [LIBERTY-PN PRIME (NCT04183335)]											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	Study arm	N	Result	Difference	95% CI	*P* value	Difference	95% CI	*P* value		
WI-NRS improvement ≥4	Dupilumab	28	16 (57.1%)	RRD: 33.5	(5.71-61.4)	NA	3.30	(1.08–9.9)	NA	Endpoints were analysed using a Cochran–Mantel–Haenszel test adjusted by stratification factors and baseline	[44]
	Placebo	31	8 (25.8%)								[44]

Results of [LIBERTY-PN PRIME (NCT04183335)]											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	Study arm	N	Result	Difference	95% CI	*P* value	Difference	95% CI	*P* value		
points at week 24 NRI										antidepressant use. Patients with missing data at the timepoint or who used rescue/prohibited medications/procedures before the timepoint were considered non-responders.	
IGA success at week 24	Dupilumab	28	11 (39.3%)	RRD: 11.2	(-13.6-35.9)		OR: 1.7	0.5-5.8	NA	Endpoints were analysed using a Cochran–Mantel–Haenszel test adjusted by stratification factors and baseline antidepressant use. Patients with missing data at the timepoint or who used rescue/prohibited medications/procedures before the timepoint were considered non-responders.	[44]
	Placebo	31	9 (29%)								[44]
WI-NRS improvement ≥4 and IGA	Dupilumab	28	8 (28.6%)	RRD: 19.6	(-2.1-41.3)		OR: 3.6	0.8-15.1	NA	Endpoints were analysed using a Cochran–Mantel–Haenszel test adjusted by stratification factors and baseline antidepressant use. Patients	[44]
	Placebo	31	4 (12.9%)								[44]

Results of [LIBERTY-PN PRIME (NCT04183335)]											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	Study arm	N	Result	Difference	95% CI	*P* value	Difference	95% CI	*P* value		
success at week 24										with missing data at the timepoint or who used rescue/prohibited medications/procedures before the timepoint were considered non-responders.	

B.6 PRIME2, ITT population

Table 79 Results per study PRIME2, ITT population

Results of [PRIME2 (NCT04202679)]											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	Study arm	N	Result	Difference	95% CI	*P* value	Difference	95% CI	*P* value		
WI-NRS improvem	Nemolizumab	78	45 (57.7%)	42.6%	(29.1%–56.1%)	<0.001	[redacted]	[redacted]	NA	Endpoints were analysed using a Cochran–Mantel–Haenszel	[44]

Results of [PRIME2 (NCT04202679)]											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	**Study arm**	**N**	**Result**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
ent ≥4 points at week 24 NRI	Placebo	82	16 (19.5%)							test adjusted by stratification factors and baseline antidepressant use. Patients with missing data at the timepoint or who used rescue/prohibited medications/procedures before the timepoint were considered non-responders.	[44]
WI-NRS improvement ≥4 points at week 24 Observed cases	Nemolizumab	82	49 (62.8%)	45.6%	(32.1%–59.0%)	<0.001	[redacted]	[redacted]	NA	Endpoints were analysed using a Cochran–Mantel–Haenszel test adjusted by stratification factors and baseline antidepressant use. Data collected after study intervention discontinuation and/or after taking the selected prohibited medications/procedures and/or rescue medications were included, and missing data at week 24 were considered non-responders.	[44]
	Placebo	82	18 (22.0%)								[44]

Results of [PRIME2 (NCT04202679)]											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	**Study arm**	**N**	**Result**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
WI-NRS improvement ≥4 points at week 16 NRI (assumed)	Nemolizumab	78	44.9%						NA	Extracted from CT.gov	[47]
	Placebo	82	19.5%								[47]
IGA success at week 24 NRI	Nemolizumab	78	35 (44.9%)	30.8	(16.4–45.2)	<0.001	[redacted]	[redacted]	NA	Endpoints were analysed using a Cochran–Mantel–Haenszel test adjusted by stratification factors and baseline antidepressant use. Patients with missing data at the timepoint or who used rescue/prohibited medications/procedures before the timepoint were considered non-responders.	[44]
	Placebo	82	13 (15.9%)								[44]
	Nemolizumab	82	38 (48.7%)	32.9	(18.2–47.6)	<0.001	[redacted]	[redacted]	NA	Endpoints were analysed using a Cochran–Mantel–Haenszel	[44]

Results of [PRIME2 (NCT04202679)]											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	**Study arm**	**N**	**Result**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
IGA success at week 24 Observed cases	Placebo	82	14 (17.1%)							test adjusted by stratification factors and baseline antidepressant use. Data collected after study intervention discontinuation and/or after taking the selected prohibited medications/procedures and/or rescue medications were included, and missing data at week 24 were considered non-responders.	[44]
WI-NRS improvement ≥4 points and IGA success at week 24 NRI	Nemolizumab	78	25 (32.1)	25.5%	(13.1–37.9)	<0.001	[redacted]	[redacted]	NA	Endpoints were analysed using a Cochran–Mantel–Haenszel test adjusted by stratification factors and baseline antidepressant use. Patients with missing data at the timepoint or who used rescue/prohibited medications/procedures before the timepoint were considered non-responders.	[44]
	Placebo	82	7 (8.5)								[44]

Results of [PRIME2 (NCT04202679)]											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	**Study arm**	**N**	**Result**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
WI-NRS improvement ≥4 points and IGA success at week 24 Observed cases	Nemolizumab	82	27 (34.6)	27.9	(15.5–40.3)	<0.001	[redacted]	[redacted]	NA	Endpoints were analysed using a Cochran–Mantel–Haenszel test adjusted by stratification factors and baseline antidepressant use. Data collected after study intervention discontinuation and/or after taking the selected prohibited medications/procedures and/or rescue medications were included, and missing data at week 24 were considered non-responders.	[44]
	Placebo	82	7 (8.5)								[44]
WI-NRS percentage change from baseline at week 24 NRI	Nemolizumab	78	−59.3 (SE: 6.4)	−23.2	(−33.8–(−12.5)	<0.001	NA	NA	NA	Endpoints were analysed using an analysis of covariance (ANCOVA) model with intervention group, stratification factors, baseline antidepressant use and relevant baseline measurement as covariates. Data from patients who used	[44]
	Placebo	82	−36.2 (SE: 6.2)								[44]

Results of [PRIME2 (NCT04202679)]											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	Study arm	N	Result	Difference	95% CI	*P* value	Difference	95% CI	*P* value		
										rescue/prohibited medications/procedures were set to 'missing' after medication use, and the endpoint value was imputed by the worst post-baseline value available before medication use.	
WI-NRS percentage change from baseline at week 16	Nemolizumab	78	-54.36 (SE: 5.91)				NA	NA	NA	Extracted from CT.gov	[47]
	Placebo	82	-37.8 (SE: 5.74)								[47]
WOCF											
DLQI absolute change from baseline at week 12	Nemolizumab	78	−11.9 (SE: 1.2)	NA	NA	NA	NA	NA	NA	Digitized using WebPlotDigitizer from a figure	[44]
	Placebo	82	−6.8 (SE: 1.1)							Digitized using WebPlotDigitizer from a figure	[44]

Results of [PRIME2 (NCT04202679)]											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	Study arm	N	Result	Difference	95% CI	*P* value	Difference	95% CI	*P* value		
MI, WOCF											
DLQI absolute change from baseline at week 24 MI, WOCF	Nemolizumab	78	−13.2 (SE: 1.2)	−6.4	(−8.4−(−4.4)	<0.001	NA	NA	NA	Endpoints were analysed using an analysis of covariance (ANCOVA) model with intervention group, stratification factors, baseline antidepressant use and relevant baseline measurement as covariates. Data from patients who used rescue/prohibited medications/procedures were set to 'missing' after medication use, and the endpoint value was imputed by the worst post-baseline value available before medication use.	[44]
	Placebo	82	−6.8 (SE: 1.2)								[44]
HADS absolute change from	Nemolizumab	78	−5.6 (SE: 1.1)	−3.0	(−4.7−(−1.2)	0.001	NA	NA	NA	Endpoints were analysed using an analysis of covariance (ANCOVA) model with intervention group, stratification factors, baseline	[44]
	Placebo	82	−2.6 (SE: 1.0)								[44]

Results of [PRIME2 (NCT04202679)]											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	Study arm	N	Result	Difference	95% CI	*P* value	Difference	95% CI	*P* value		
baseline at week 24										antidepressant use and relevant baseline measurement as covariates. Data from patients who used rescue/prohibited medications/procedures were set to 'missing' after medication use, and the endpoint value was imputed by the worst post-baseline value available before medication use.	
HADS-A absolute change from baseline at week 24 Subscale Anxiety	Nemolizumab	78	-3.3 (SE: 0.7)	-1.4	(−2.5−(−0.3)	0.012	NA	NA	NA	Endpoints were analysed using an analysis of covariance (ANCOVA) model with intervention group, stratification factors, baseline antidepressant use and relevant baseline measurement as covariates. Data from patients who used rescue/prohibited medications/procedures were set to 'missing' after	[44]
	Placebo	82	-1.9 (SE: 0.9)								[44]

Results of [PRIME2 (NCT04202679)]											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	Study arm	N	Result	Difference	95% CI	*P* value	Difference	95% CI	*P* value		
										medication use, and the endpoint value was imputed by the worst post-baseline value available before medication use.	
HADS-A absolute change from baseline at week 24 Subscale Depression	Nemolizumab	78	-2.1 (SE: 0.5)	-1.6	(−2.5−(−0.7)	<0.001	NA	NA	NA	Endpoints were analysed using an analysis of covariance (ANCOVA) model with intervention group, stratification factors, baseline antidepressant use and relevant baseline measurement as covariates. Data from patients who used rescue/prohibited medications/procedures were set to 'missing' after medication use, and the endpoint value was imputed by the worst post-baseline value available before medication use.	[44]
	Placebo	82	-0.5 (SE: 0.5)								[44]

B.7 PRIME2, no TCS/TCI subpopulation

Table 80 Results per study PRIME2, no TCS/TCI subpopulation

Results of [PRIME2 (NCT04202679)]											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	**Study arm**	**N**	**Result**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
WI-NRS improvement ≥4 points at week 24	Dupilumab	34	20 (58.8%)	RRD: 42.0	21.1-62.9	NA	OR: 7.0	1.9-26.6	NA	Endpoints were analysed using a Cochran–Mantel–Haenszel test adjusted by stratification factors and baseline antidepressant use. Patients with missing data at the timepoint or who used rescue/prohibited medications/procedures before the timepoint were considered non-responders.	[44]
	Placebo	36	10 (27.8%)								[44]
WI-NRS improvement ≥4 points at week 12	Dupilumab	34	12 (35.3%)	RRD: 9.3	-14.5-33.1	NA	OR: 1.5	0.5-4.2	NA	Endpoints were analysed using a Cochran–Mantel–Haenszel test adjusted by stratification factors and baseline antidepressant use. Patients with missing data at the timepoint or who used rescue/prohibited medications/procedures	[44]
	Placebo	36	11 (30.6%)								[44]

Results of [PRIME2 (NCT04202679)]											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	Study arm	N	Result	Difference	95% CI	*P* value	Difference	95% CI	*P* value		
										before the timepoint were considered non-responders.	
IGA success at week 24	Dupilumab	34	16 (47.1%)	26.2	(2.64-49.66)	NA	OR: 3.0	1.0-8.7	NA	Endpoints were analysed using a Cochran–Mantel–Haenszel test adjusted by stratification factors and baseline antidepressant use. Patients with missing data at the timepoint or who used rescue/prohibited medications/procedures before the timepoint were considered non-responders.	[44]
	Placebo	36	8 (22.2%)								[44]
WI-NRS improvement ≥4 and IGA success at week 24 NRI	Dupilumab	34	11 (32.4%)	22.8	2.1-43.6	NA	OR: 3.5	0.9-13.1	NA	Endpoints were analysed using a Cochran–Mantel–Haenszel test adjusted by stratification factors and baseline antidepressant use. Patients with missing data at the timepoint or who used rescue/prohibited medications/procedures	[44]
	Placebo	36	5 (13.9%)								[44]

Results of [PRIME2 (NCT04202679)]											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	Study arm	N	Result	Difference	95% CI	*P* value	Difference	95% CI	*P* value		
										before the timepoint were considered non-responders.	

B.8 LIBERTY-PN PRIME and PRIME 2, pooled analysis, both ITT population and "no TCS/TCI" subpopulation

Table 81 Results per study – LIBERTY-PN PRIME (NCT04183335) and PRIME2 (NCT04202679), pooled

Results of [LIBERTY-PN PRIME (NCT04183335) and PRIME2 (NCT04202679), pooled]											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	Study arm	N	Result	Difference	95% CI	*P* value	Difference	95% CI	*P* value		
DLQI absolute change from baseline at week 24	Dupilumab	62	-11.9				NA	NA	NA	MI, WOCF	[49]
	Placebo	67	-7.1								[49]

Results of [LIBERTY-PN PRIME (NCT04183335) and PRIME2 (NCT04202679), pooled]											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	**Study arm**	**N**	**Result**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
no TCS population MI, WOCF											
IGA success at week 24 no TCS population NRI (assumed)	Dupilumab	62	27 (43.5%)				[redacted]	[redacted]	NA		[49]
	Placebo	67	17 (25.4%)								[49]
WI-NRS improvement ≥4 and IGA success at week 12 ITT population NRI (assumed)	Dupilumab	34	28 (18.3%)			0.0021	[redacted]	[redacted]	NA		[45]
	Placebo	36	11 (7%)								[45]

Results of [LIBERTY-PN PRIME (NCT04183335) and PRIME2 (NCT04202679), pooled]											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	**Study arm**	**N**	**Result**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
ITT population	Dupilumab	153	92 (59.9%)				[redacted]	[redacted]	NA		[48]
Total TEAEs	Placebo	158	81 (51.0%)								[48]

Appendix C. Comparative analysis of efficacy

For all included trials, if data are available in more than one analysis population, the intention to treat will be prioritized for the analysis; if ITT is not reported, then mITT will be used. For safety outcomes, data from the safety populations (i.e., including all randomized patients who received at least one dose of the study drug) will be prioritized if multiple denominators are reported. Trial publications reporting ITT denominators for safety outcomes will be considered if the safety population is not provided.

The arm-level aggregate data of number of subjects evaluated for an event and the number of subjects with the event will be used as input data for each binary outcome (i.e., response or safety event), as indicated in the table below. Also, number of subjects, mean and standard deviation (SD) in each treatment arm for each continuous outcome of change from baseline will be used (given that such data are available from all trials reporting the outcome data). In scenarios where the trial reports percent change from baseline in WI-NRS, the absolute change from baseline will be calculated using the mean baseline WI-NRS and the percent change from baseline.

For an outcome, if SD for an arm is not reported at a specific timepoint, it will be calculated from arm-level data of standard error (SE) or the confidence interval (CI), where available. If that is not possible, then SD will be computed from the SE or CI or the exact P-value of the contrast-level data of mean difference (MD), where possible. For this, first SE (MD) will be computed from the CI or P-value of MD, if necessary, and then SD in an arm will be computed as SE(MD)/sqrt(1/N1 + 1/N¬2) assuming equal SD for both arms, N¬1 and N¬2 being the arm-sizes, for a 2-arm trial, for instance. However, if P-value for the MD is reported in "<0.x" format, the minimum of the SD calculated from P-value assuming it is 'x' and the SD as the median of available SDs at different timepoints in the same trial (if available) else the median of available SDs at the same timepoint in different trials, will be used. pool. When SD is still missing, the median of available SDs at different timepoints in the same trial (if available) else the median of available SDs at the same timepoint in different trials will be used.

Fixed-effects (FE) and Random-effects (RE) Bayesian NMAs were conducted for the outcomes listed in Table 1 above in the planned NMA section, when appropriate. RE analyses are widely understood to be appropriate when there is heterogeneity in patient/trial characteristics. This analysis does not assume that all studies estimate the same underlying effect; rather, it assumes that the true effects are randomly distributed around some population mean effect. However, since there are only a maximum of two or three studies for only one or two comparators, RE model may not be appropriate. Choice of RE or FE model will also be assessed using deviance information criteria (DIC) – see Section 4.3.4 below. We also explore the pairwise heterogeneity to see if the pairwise estimates are heterogeneous beyond chance so that the RE model can be justified in the base case.

In some other networks, the ability to use the data to help estimate an RE variance will be limited or non-existent as there were only one study for all comparisons except in the nemolizumab trials. In those instances, the FE will be the base case.

Each NMA will provide a central estimate of the relative effect of interest (e.g., odds ratio for proportion of IGA (0/1) responders, mean difference for CFB in DLQI) along with its 95% credible interval (CrI) and the probability that the first treatment is "better" (more efficacious or safer)

than the second treatment. For each comparison, risk ratio will also be obtained and presented from the corresponding estimate of the odds ratio and anchor (ie, placebo) event rate.

Table 82 Comparative analysis of studies comparing nemolizumab to dupilumab for patients with moderate to severe prurigo nodularis

Outcome		Absolute difference in effect			Relative difference in effect			Method used for quantitative synthesis	Result used in the health economic analysis?
	Studies included in the analysis	Difference	CI	P value	Difference	95% CrI	P value		
PP-NRS / WI-NRS improvement of ≥ 4 from baseline at week 16 Base case	Week 16 data: OLYMPIA 1, OLYMPIA 2, LIBERTY-PN PRIME, PRIME 2	NA	NA	NA	[redacted]	[redacted]	N/A		Yes
PP-NRS / WI-NRS improvement of ≥ 4 from baseline at week 24 NRI	Week 24 data: OLYMPIA 1, LIBERTY-PN PRIME, PRIME 2	NA	NA	NA	[redacted]	[redacted]	N/A		Yes
PP-NRS / WI-NRS absolute change from baseline at week 16 Base case	Week 16 data: OLYMPIA 1, OLYMPIA 2, NCT03181503, LIBERTY-PN PRIME, PRIME 2	NA	NA	NA	[redacted]	[redacted]	N/A		Yes
PP-NRS / WI-NRS absolute change from baseline at week 24 Base case	Week 24 data: OLYMPIA 1, LIBERTY-PN PRIME, PRIME 2	NA	NA	NA	[redacted]	[redacted]	N/A		Yes

Outcome		Absolute difference in effect			Relative difference in effect			Method used for quantitative synthesis	Result used in the health economic analysis?
	Studies included in the analysis	Difference	CI	P value	Difference	95% CrI	P value		
IGA success at week 24 Base case	Week 24 data: OLYMPIA 1, LIBERTY-PN PRIME, PRIME 2	N/A	N/A	N/A	[redacted]	[redacted]	N/A	Fixed-effects Bayesian NMA	Yes
Composite PP-NRS improvement ≥4 points and IGA success at week 12/16 Base case	Week 12 data: LIBERTY-PN PRIME, PRIME 2 Week 16 data: OLYMPIA 1, OLYMPIA2	N/A	N/A	N/A	[redacted]	[redacted]	N/A	Fixed-effects Bayesian NMA	Yes
Composite PP-NRS improvement ≥4 points and IGA success at week 24 Base case	Week 24 data: OLYMPIA 1, LIBERTY-PN PRIME, PRIME 2	N/A	N/A	N/A	[redacted]	[redacted]	N/A	Fixed-effects Bayesian NMA	Yes
DLQI absolute change from baseline at Week 12-16 Base case	Week 12 data: LIBERTY-PN PRIME, PRIME 2 Week 16 data: OLYMPIA 1, OLYMPIA 2,	[redacted]	[redacted]	N/A	N/A	N/A	N/A	Random-effects Bayesian NMA	Yes

Outcome		Absolute difference in effect			Relative difference in effect			Method used for quantitative synthesis	Result used in the health economic analysis?
	Studies included in the analysis	Difference	CI	P value	Difference	95% CrI	P value		
DLQI absolute change from baseline at Week 24 Base case	Week 24 data: OLYMPIA 1, LIBERTY-PN PRIME, PRIME 2	[redacted]	[redacted]	N/A	N/A	N/A	N/A	Fixed-effects Bayesian NMA	Yes
TEAEs end of study Base case	Week 16 data: LIBERTY-PN PRIME, PRIME 2 Week 24 data: LIBERTY-PN PRIME, PRIME 2	[redacted]	[redacted]	N/A	N/A	N/A	N/A	Fixed-effects Bayesian NMA	Yes

Abbreviations: CrI: credible interval; DLQI: Dermatology Life Quality Index; IGA: Investigator's Global Assessment; NMA: network meta-analysis; OR: odds ratio; PP-NRS: Peak Pruritus Numerical Rating Scale; TEAE: treatment-emergent adverse event; WI-NRS: Worst Itch Numerical Rating Scale

Source: [52]

Appendix D. Extrapolation (N/A)

Not applicable.

D.1 Extrapolation of [effect measure 1]

D.1.1 Data input

D.1.2 Model

D.1.3 Proportional hazards

[If the extrapolation model relies on proportional hazards, provide a plot with Schoenfeld residuals and a log-cumulative hazard plot.]

D.1.4 Evaluation of statistical fit (AIC and BIC)

[Provide a table with the AIC and BIC and discuss the statistical fit.]

D.1.5 Evaluation of visual fit

D.1.6 Evaluation of hazard functions

[Provide a plot of the hazard function of the effect measure. The plots must be presented in separate figures for the intervention and comparator, respectively, and must include the estimated hazard for the observed data (if applicable). The plot must be discussed in the context of chosen the distribution for extrapolating the data of the effect measure.]

D.1.7 Validation and discussion of extrapolated curves

D.1.8 Adjustment of background mortality

D.1.9 Adjustment for treatment switching/cross-over

D.1.10 Waning effect

D.1.11 Cure-point

D.2 Extrapolation of [effect measure 2]

[For each effect measure please, fill in this section using the same template as stated in section D.1]

Appendix E. Serious adverse events

The serious adverse events reported for each included study in the application are presented in the tables below.

Table 83 Serious adverse events (time frame: up to 18 weeks) - NCT03181503 [37]

	Nemolizumab 0.5 mg/kg (N=34) Affected / at Risk (%)	Placebo (N=36) Affected / at Risk (%)
Total	4/34 (11.76%)	3/36 (8.33%)
Injury, poisoning and procedural complications		
Clavicle Fracture†1	1/34 (2.94%)	0/36 (0.00%)
Spinal Fracture†1	0/34 (0.00%)	1/36 (2.78%)
Musculoskeletal and connective tissue disorders		
Back Pain†1	0/34 (0.00%)	1/36 (2.78%)
Fibromyalgia†1	1/34 (2.94%)	0/36 (0.00%)
Renal and urinary disorders		
Calculus Bladder†1	1/34 (2.94%)	0/36 (0.00%)
Skin and subcutaneous tissue disorders		
Neurodermatitis/atopic dermatitis †1	0/34 (0.00%)	3/36 (8.33%)
Dermatitis Psoriasiform†1	1/34 (2.94%)	0/36 (0.00%)
Eczema Nummular†1	1/34 (2.94%)	0/36 (0.00%)

Note: †Indicates events were collected by systematic assessment. [1]Term from vocabulary, MedDRA 19.0.

Table 84 Serious treatment emergent adverse events during treatment period by system organ class and preferred term, all causalities (safety population) – OLYMPIA 1 [38]

System Organ Class	Nemolizumab (N=187)	Placebo (N=95)

Preferred Term	n (%)	n (%)
Any SAE	16 (8.6)	10 (10.5)
Cardiac disorders	2 (1.1)	2 (2.1)
Acute myocardial infarction	1 (0.5)	0
Coronary artery disease	1 (0.5)	0
Cardiac sarcoidosis	0	1 (1.1)
Cardiogenic shock	0	1 (1.1)
General disorders and administration site conditions	0	1 (1.1)
Oedema peripheral	0	1 (1.1)
Hepatobiliary disorders	1 (0.5)	0
Cholecystitis acute	1 (0.5)	0
Infections and infestations	4 (2.1)	2 (2.1)
Acarodermatitis	1 (0.5)	0
Campylobacter colitis	1 (0.5)	0
Cellulitis	1 (0.5)	1 (1.1)
Urinary tract infection	1 (0.5)	0
COVID-19 pneumonia	0	1 (1.1)
Injury, poisoning and procedural complications	1 (0.5)	1 (1.1)
Subdural hemorrhage	1 (0.5)	0
Fall	0	1 (1.1)
Metabolism and nutrition disorders	1 (0.5)	0
Type 2 diabetes mellitus	1 (0.5)	0
Musculoskeletal and connective tissue disorders	1 (0.5)	0
Osteoarthritis	1 (0.5)	0

Neoplasms benign, malignant and unspecified (incl. cysts and polyps)	1 (0.5)	0
Basal cell carcinoma	1 (0.5)	0
Squamous cell carcinoma of skin	1 (0.5)	0
Nervous system disorders	2 (1.1)	0
Arachnoid cyst	1 (0.5)	0
Tension headache	1 (0.5)	0
Psychiatric disorders	1 (0.5)	1 (1.1)
Depressed mood	1 (0.5)	0
Panic disorder	0	1 (1.1)
Respiratory, thoracic and mediastinal disorders	0	1 (1.1)
Vocal cord polyp	0	1 (1.1)
Skin and subcutaneous tissue disorders	4 (2.1)	2 (2.1)
Neurodermatitis	3 (1.6)	2 (2.1)
Pemphigoid	1 (0.5)	0

Abbreviations: COVID-19, coronavirus disease 2019; Incl., including; N, number of patients in the treatment group; n, number of patients experienced the events; SAE, serious adverse event.

Note: Percentages (%) are based on number of patients in each treatment group (N). Adverse events are coded using Medical Dictionary for Regulatory Activities version 25.0. TEAEs during treatment period are defined as adverse events with onset date on or after the first dose date until 4 weeks after the last treatment or early discontinuation date whichever is earlier.

Table 85 Serious treatment emergent adverse events during treatment period by system – OLYMPIA 2 [42]

System Organ Class Preferred Term	Nemolizumab (N=183) n (%)	Placebo (N=91) n (%)
Any serious TEAE	4 (2.2%)	5 (5.5%)
Cardiac disorders	1 (0.5%)	2 (2.2%)

Supraventricular tachycardia	1 (0.5%)	0
Atrial flutter	0	1 (1.1%)
Coronary artery occlusion	0	1 (1.1%)
Myocardial infarction	0	1 (1.1%)
Infections and infestations	1 (0.5%)	1 (1.1%)
Pneumococcal sepsis	1 (0.5%)	0
Pneumonia	1 (0.5%)	0
Appendicitis	0	1 (1.1%)
Postoperative wound infection	0	1 (1.1%)
Musculoskeletal and connective tissue	0	1 (1.1%)
Osteoarthritis	0	1 (1.1%)
Skin and subcutaneous tissue disorders	2 (1.1%)	1 (1.1%)
Dermatitis contact	1 (0.5%)	0
Pemphigoid	1 (0.5%)	0
Dermatitis exfoliative generalized	0	1 (1.1%)

Abbreviation: TEAE, treatment emergent adverse event.

Note: Adverse events were coded using MedDRA version 25.0. Treatment-emergent adverse events (TEAEs) during treatment period were defined as adverse events with onset date on or after the first dose date till 4 weeks after the last treatment or early discontinuation, whichever was earlier.

Table 86 Serious adverse events (MedDRA System Organ Class and Preferred Term) - LIBERTY PN-PRIME and PRIME2 [44]

	LIBERTY PN-PRIME		PRIME2	
Primary MedDRA System Organ Class **MedDRA Preferred Term n (%)***	**Nemolizumab 300 mg every 2 weeks (n=75)**	**Placebo (n=75)**	**Nemolizumab 300 mg every 2 weeks (n=77)**	**Placebo n=82**

Any event	5 (6.7)	6 (8.0)	2 (2.6)	2 (2.4)
Infections and infestations	1 (1.3)	2 (2.7)	1 (1.3)	0
COVID-19 pneumonia	1 (1.3)	0	0	0
COVID-19	0	1 (1.3)	0	0
Sepsis	0	1 (1.3)	0	0
Pelvic inflammatory disease	0	0	1 (1.3)	0
Pyelonephritis acute	0	0	1 (1.3)	0
Neoplasms benign, malignant and unspecified (including cysts and polyps)	1 (1.3)	1 (1.3)	2 (2.6)	1 (1.2)
Papillary thyroid cancer	1 (1.3)	0	0	0
Hodgkin's disease	0	1 (1.3)	0	0
Lipomat	0	0	1 (1.3)	0
Uterine leiomyoma	0	0	1 (1.3)	0
Cutaneous T-cell lymphoma	0	0	0	1 (1.2)
Cardiac disorders	0	1 (1.3)	0	0
Acute myocardial infarction	0	1 (1.3)	0	0
Respiratory, thoracic, and mediastinal disorders	2 (2.7)	0	0	0
Asthma	1 (1.3)	0	0	0
Interstitial lung disease	1 (1.3)	0	0	0
Gastrointestinal disorders	0	1 (1.3)	0	0
Mesenteritis	0	1 (1.3)	0	0
Skin and subcutaneous tissue disorders	0	1 (1.3)	0	0
Neurodermatitis	0	1 (1.3)	0	0

Musculoskeletal and connective tissue disorder	1 (1.3)	0	0	1 (1.2)
Musculoskeletal chest pain	1 (1.3)	0	0	0
Rotator cuff syndrome	0	0	0	1 (1.2)
Injury, poisoning, and procedural complications	0	1 (1.3)	0	0
Alcohol poisoning	0	1 (1.3)	0	0

Abbreviation: MedDRA, Medical Dictionary for Regulatory Affairs-

Note: *n (%) denotes the number and percentage of patients with ≥1 treatment-emergent serious adverse event during the 24-week treatment period. †Event led to patient hospitalization for removal.

Appendix F. Health-related quality of life (N/A)

Not applicable.

Appendix G. Probabilistic sensitivity analyses

Table 87 Overview of parameters in the PSA

Input parameter	Point estimate	Lower bound	Upper bound	Probability distribution
Patient weight	72.6	58.08	87.12	Normal
TCS/TCI use every 2 weeks	100	80	120	Gamma
Discontinuation rate_nemo	0.42	0.336	0.504	Beta
Discontinuation rate_dupi	0.42	0.336	0.504	Beta
Week at discontinuation_nemo	16	12.8	19.2	Lognormal
Week at discontinuation_dupi	24	19.2	28.8	Lognormal
Nemo_price	14,995.00 kr	11,996.00 kr	17,994.00 kr	Gamma
Dupi_Price	8,274.34 kr	6,619.47 kr	9,929.21 kr	Gamma
Betamethason_Price	66.07 kr	52.86 kr	79.28 kr	Gamma
Mometason_Price	60.00 kr	48.00 kr	72.00 kr	Gamma
Clobetasol_Price	57.00 kr	45.60 kr	68.40 kr	Gamma
Tacrolimus_Price	284.12 kr	227.30 kr	340.94 kr	Gamma
Pimecrolimus_Price	224.00 kr	179.20 kr	268.80 kr	Gamma

Appendix H. Literature searches for the clinical assessment

H.1 Efficacy and safety of the intervention and comparator(s)

A systematic literature review (SLR) was performed to address the following question: What is the clinical efficacy and safety of treatments for PN, based on interventional trials (randomised controlled trials [RCTs], single-arm trials, and nonrandomised controlled trials)?

The SLR was conducted according to the standards of established guidelines (i.e., Preferred Reporting Items for Systematic Reviews and Meta-analyses [PRISMA] [58] and the Cochrane Handbook for Systematic Reviews of Interventions [59]) as well as the high quality standards required by the National Institute for Health and Care Excellence [60], the Canadian Drug and Health Technology Agency, and other health technology agencies.

Systematic literature searches were conducted in OvidSP (http://ovidsp.ovid.com/) on 25 September to identify peer-reviewed studies of interest in the electronic literature databases. One global search strategy was developed to identify clinical efficacy and safety evidence.

The searches were run in the following databases:

1. MEDLINE and MEDLINE In-Process
2. Embase
3. Cochrane Database of Systematic Reviews
4. Cochrane Central Register of Controlled Trials
5. PsycINFO
6. EconLit

The search strategies for each database are detailed in section H.1.1. Searches were conducted using a combination of free-text search terms and controlled vocabulary terms specific to each database, as recommended by the Cochrane Collaboration [59, 61].

No restrictions to publication date and geographical regions were applied. Only relevant publications published in English were included.

The literature searches were validated via manual review of the bibliographies of up to five of the most comprehensive, recently published, relevant systematic reviews identified from the database searches. The SLRs themselves were not included in the review to avoid double-counting of relevant studies. These additional steps were taken to ensure that the SLR provides complete and comprehensive coverage of all relevant literature.

The bibliographic databases included in the literature search are presented in Table 88. Searches were performed on the 25th of September 2023 and were updated on the 17th of May 2024. In the updated search, no new trials were identified, more details about the updated search are presented in section H.1.6.

Table 88 Bibliographic databases included in the literature search

Database	Platform/source	Relevant period for the search	Date of search completion
Embase	Ovid	1974 to September 22, 2023	25.09.2023
MEDLINE-ALL	Ovid	1946 to September 22, 2023	25.09.2023
Cochrane Central Register of Controlled Trials (EBM Reviews)	Ovid	August 2023	25.09.2023
Cochrane Database of Systematic Reviews (EBM Reviews)	Ovid	2005 to September 20, 2023	25.09.2023
EconLit	Ovid	1886 to September 14, 2023	25.09.2023
APA-PsycInfo	Ovid	1806 to September Week 2 2023	25.09.2023

Grey literature searches were conducted as outlined in Table 89 and Table 90 to identify recent, relevant research from the past two years that may not have been published in peer-reviewed journals and is therefore not captured by the database searches. Although many conference abstracts are published in supplements of peer-reviewed journals and indexed in electronic literature databases such as Embase, they are still considered grey literature. Separate searches were conducted via OvidSP for conferences indexed in Embase.com. For conferences not available in Embase, online conference websites or another relevant medium were searched.

In addition, searches of selected HTA body websites and clinical trial registries were conducted, as outlined in Table 89.

All identified grey literature was assessed by a single reviewer, and validation of relevant materials was performed by a second reviewer.

Table 89 Other sources included in the literature search

Source name	Location/source	Search strategy	Date of search
National Institute for Health and Care Excellence (NICE)	Published guidance, NICE advice and quality standards | Guidance | NICE	Manual search	2021 to 2023
Canadian Drug and Health Technology Agency (CADTH)	Search | CADTH	Manual search	2021 to 2023
Pharmaceutical Benefits Advisory Committee (PBAC)	Pharmaceutical Benefits Scheme (PBS) | Public Summary Documents by Product	Manual search	2021 to 2023
Institute for Clinical and Economic Review (ICER)	Assessments | Explore Our Research | ICER	Manual search	2021 to 2023
Institute for Quality and Efficiency in Health Care (IQWiG)	Projects & results | IQWiG.de	Manual search	2021 to 2023
Clinicaltrials.gov	https://clinicaltrials.gov/	Manual search	2021 to 2023
ISRCTN	ISRCTN - Advanced search	Manual search	2021 to 2023
EU Clinical Trials Register	Clinical Trials Register	Manual search	2021 to 2023
Tufts Medical Center Cost-Effectiveness Analysis Registry	Tufts CEA - Tufts CEA (tuftsmedicalcenter.org)	Manual search	2021 to 2023

Abbreviations: CADTH, Canadian Drug and Health Technology Agency; CEA, cost-effectiveness analysis; ICER, Institute for Clinical and Economic Review; IQWiG, Institute for Quality and Efficiency in Health Care; NICE, National Institute for Health and Care Excellence; PBAC, Pharmaceutical Benefits Advisory Committee

Table 90 Conference material included in the literature search

Conference	Source of abstracts	Search strategy	Words/terms searched	Date of search
American Academy of Dermatology	2021: Embase (via OvidSP) 2022: Embase (via OvidSP) 2023: AAD ePosters	Manual search	2021-2022: See Table 91 for Embase search 2023 abstract book: "prurigo nodularis"	2021 to 2023
World Congress of Dermatology	2021: not available 2022: not available 2023: Held every 4 years, with the next one planned for July 3–8, 2023	Manual search	2023: conference abstracts will be captured if the abstract book is available at that time	2021 to 2023
Congress of the European Academy of Dermatology and Venereology	2021: not available 2022: Abstract Books | EADV 2023: October 11–14, 2023	Manual search	2022 abstract book: "prurigo nodularis"	2021 to 2023
Professional Society for Health Economics and Outcomes Research	2021: Embase (via OvidSP) 2022: Embase (via OvidSP) 2023: November 12-15, 2023 (Europe); May 7-10, 2023 (US)	Manual search	2023: conference abstracts will be captured if the abstract book is available at that time	2021 to 2023

H.1.1 Search strategies

The search strategy for each database is detailed in the tables below. Searches were conducted using a combination of free-text search terms and controlled vocabulary terms specific to each database, as recommended by the Cochrane Collaboration [59, 61].

No restrictions to publication date and geographical regions were applied. Only relevant publications published in English were included.

Table 91 Search strategy table for Embase (Ovid): 1974 to 2023 September 22. Date searched: 25 September 2023

No.	Query	Results
#1	prurigo nodularis/	773
#2	(prurigo nodularis or nodular prurigo$).ti,ab,kw.	1,165
#3	#1 or #2	1,381
#4	#3 not (animals/ not humans/)	1,381
#5	(case report or case series or woman or man or child or adolescent or female or male or boy or girl or infant).ti.	1,073,682
#6	case reports/ or case study/ or case report$.jx. or case report$.jw.	369,632
#7	(Ephemera or "Introductory Journal Article" or News or "Newspaper Article" or Editorial or Comment or Overall).pt. or in vitro Techniques/ or in vitro study/ or (commentary or editorial or comment or letter or mice or rat or mouse or animal or murine).ti.	3,722,254
#8	review.pt. not (systematic or (meta and analy*) or ((indirect or mixed) and 'treatment comparison')).ti,ab.	2,876,762
#9	or/#5-8	7,716,889
#10	#4 not #9	1,074
#11	conference abstract.pt.	4,890,983
#12	#10 not #11	811
#13	limit #10 to (conference abstract and yr="2020-current")	141
#14	#12 or #13	952

Table 92 Search strategy table for MEDLINE-ALL (Ovid): 1946 to September 22, 2023. Date searched: 25 September 2023

No.	Query	Results
#1	(prurigo nodularis or nodular prurigo$).ti,ab,kw.	810
#2	#1 not (animals/ not humans/)	809
#3	(case report or case series or woman or man or child or adolescent or female or male or boy or girl or infant).ti.	954,091

No.	Query	Results
#4	case reports/ or case study/ or case report$.jw.	2,390,858
#5	(Ephemera or "Introductory Journal Article" or News or "Newspaper Article" or Editorial or Comment or Overall).pt. or in vitro Techniques/ or in vitro study/ or (commentary or editorial or comment or letter or mice or rat or mouse or animal or murine).ti.	3,371,355
#6	review.pt. not (systematic or (meta and analy*) or ((indirect or mixed) and 'treatment comparison')).ti,ab.	2,979,680
#7	or/#3-6	8,970,838
#8	#2 not #7	426

Table 93 Search strategy table for Cochrane Central Register of Controlled Trials (EBM Reviews) (Ovid): August 2023. Date searched: 25 September 2023

No.	Query	Results
#1	(prurigo nodularis or nodular prurigo$).mp.	87

Table 94 Search strategy table for Cochrane Database of Systematic Reviews (EBM Reviews) (Ovid): 2005 to September 20, 2023. Date searched: 25 September 2023

No.	Query	Results
#1	(prurigo nodularis or nodular prurigo$).mp.	3

Table 95 Search strategy table for EconLit (Ovid): 1886 to September 14, 2023. Date searched: 25 September 2023

No.	Query	Results
#1	(prurigo nodularis or nodular prurigo$).ti,ab,kw.	0

Table 96 Search strategy table for APA-PsycInfo (Ovid): 1806 to September Week 2 2023. Date searched: 25 September 2023

No.	Query	Results
#1	(prurigo nodularis or nodular prurigo$).mp.	12

H.1.2 Systematic selection of studies

After searches were conducted, the resulting titles and abstracts were imported to EndNote X21. Duplicate references identified from more than one database were removed. Following deduplication, the search results were uploaded to Nested Knowledge software. Nested Knowledge is an internet-based program that facilitates collaboration among reviewers during the study-selection process.

The study-selection process involved evaluating publications retrieved by the searches against predetermined population, interventions and comparisons, outcomes, and study design (PICOS) criteria (Table 97) to establish which studies were eligible for inclusion in the SLRs. Ultimately, for a study to be eligible for inclusion in the reviews, it had to meet none of the exclusion criteria and all of the inclusion criteria.

To facilitate the assessment of eligibility, the project team developed and tested screening questions for both the abstract and full-text screening levels based on the inclusion and exclusion criteria of each review. Before the formal screening process, a calibration exercise was conducted to pilot and refine the screening questions, to ensure appropriateness for use and to align screening decisions across team members.

Table 97 Inclusion and exclusion criteria used for assessment of studies

Clinical effectiveness	Inclusion criteria	Exclusion criteria	Changes, local adaption
Population	Adults (aged 18+ years old) with prurigo nodularis	Population not of interest (Studies not evaluating adults with PN)	None

Intervention	• Dual opioid receptor μ-antagonist/κ-agonist (e.g., nalbuphine)
	  ○ μ-Opioid receptor antagonists (naloxone, nalmefene, naltrexone)
	• Calcineurin inhibitors (TCIs)
	  ○ Topical tacrolimus
	  ○ Topical pimecrolimus
	• Topical capsaicin
	• Immunosuppressants (cyclosporin, methotrexate, thalidomide)
	• NK1R antagonists
		Intervention not of interest (Studies not evaluating interventions listed in the intervention inclusion criteria column)	None

	○ Serlopitant ○ Aprepitant • Topical corticosteroids • Gabapentinoids (gabapentin, pregabalin) • Antihistamines • UV therapy • Antidepressants (mirtazapine) • Oral steroids • Monoclonal antibodies, including but not limited to: ○ Dupilumab ○ Nemolizumab		
Comparators	• Any of the interventions above (or none required) • Placebo		None
Outcomes	Efficacy outcomes of interest: • PP/WI-NRS response • IGA • Composite endpoint of PP/WI-NRS and IGA • Improvement in sleep disturbance and sleep onset latency • PAS • Improvement from baseline in AP • Change from baseline in WASO • Other sleep-improvement outcomes • Change from baseline in PN-associated pain frequency/intensity • DPS • PGAD • DLQI, HADS Safety outcomes of interest:	Outcomes not of interest (Relevant outcomes are not reported, or data are not extractable) Outcomes not separable for the population of interest (Studies evaluating a mixed population, but results are not reported for adults with PN)	None

	• Discontinuation due to AEs • Discontinuation for any reason • TEAEs • Total grade 3 and 4 AEs • Total SAEs • DAEs • AEs of special interest: • Asthma or worsening of asthma • Conjunctivitis • Infusion-related reactions • Peripheral edema • Skin or systemic infection • Headache • Elevated ALT or AST in combination with elevated bilirubin • Neurodermatitis • Atopic dermatitis • Eczema		
Study design/publication type	RCTs (phase 2 and III) Single-arm trials Nonrandomised trials	Publication type not of interest (Editorial, erratum, trial protocol, guideline, case report, narrative review, etc.) Study design not of interest (In vitro, ex vivo, animal, or pharmacokinetic studies, phase 1 trials, etc.)	None
Language restrictions	Only relevant publications published in English were included	Articles published in language other than English	None

In the first screening pass, each title and abstract was reviewed by two independent reviewers to determine its eligibility for inclusion in the SLRs. Disagreements were resolved by a third reviewer, as necessary. Studies were designated as excluded or included for full-text review according to the inclusion and exclusion criteria. No study was excluded at the title and abstract level solely because it provided insufficient information. For abstracts that were deemed relevant during title and abstract screening, the corresponding full-text articles were retrieved for further screening.

Although a single comprehensive search strategy was used, information captured during the screening process helped to determine whether a record was relevant to the SLR for clinical efficacy and safety. This approach allowed separate PRISMA flow diagrams to be created for each of the three SLRs.

In the second screening pass, each full-text paper was reviewed by two independent reviewers. Disagreements were resolved by a third reviewer, as necessary. Studies were designated as excluded or included for full-text review according to the inclusion and exclusion criteria. For each excluded study, a specific reason for the exclusion was selected. If more than one reason for exclusion applied to a study, one was selected.

For studies that passed full-text screening (i.e., met the PICOS criteria), key information was captured to inform the preliminary feasibility assessment and to facilitate identification of key comparator trials to be prioritised for data extraction. The characteristics that were captured during screening were: study name/number, trial identifier, interventions and comparators, and study design (RCT, single-arm trial, nonrandomised trial).

After screening, the study listing was developed in Microsoft Excel®. The list included accepted primary studies (and their related publications); articles excluded at full-text screening, organised by reasons for exclusion; and the full list of studies reviewed at the abstract screening level. PRISMA flow diagrams (one diagram per SLR search topic) were also generated displaying the number of included and excluded publications at each stage (searches, deduplication, title and abstract screening, full-text screening), with the reasons for exclusion at the full-text screening level.

If relevant studies were identified through other sources or through search validation, these studies were included separately in the review and documented in the PRISMA diagram for transparency and replicability.

Data from the included studies for the SLR were extracted into data extraction templates (DETs) designed in Microsoft Excel. The final decision on the specific data elements to be extracted was made in conjunction with Galderma.

The data were extracted into the DETs by one reviewer; as a validation step, a second reviewer assessed the entries to ensure consistency and accuracy against the source article. A third reviewer was consulted to resolve disagreements, as necessary. Control measures were used to ensure the quality and consistency of data extraction throughout this project. These included pilot testing of the extraction form with two to three included studies, resolution of potential ambiguities and differences in the interpretation of findings, and written instructions on outcome measures to be extracted from the full

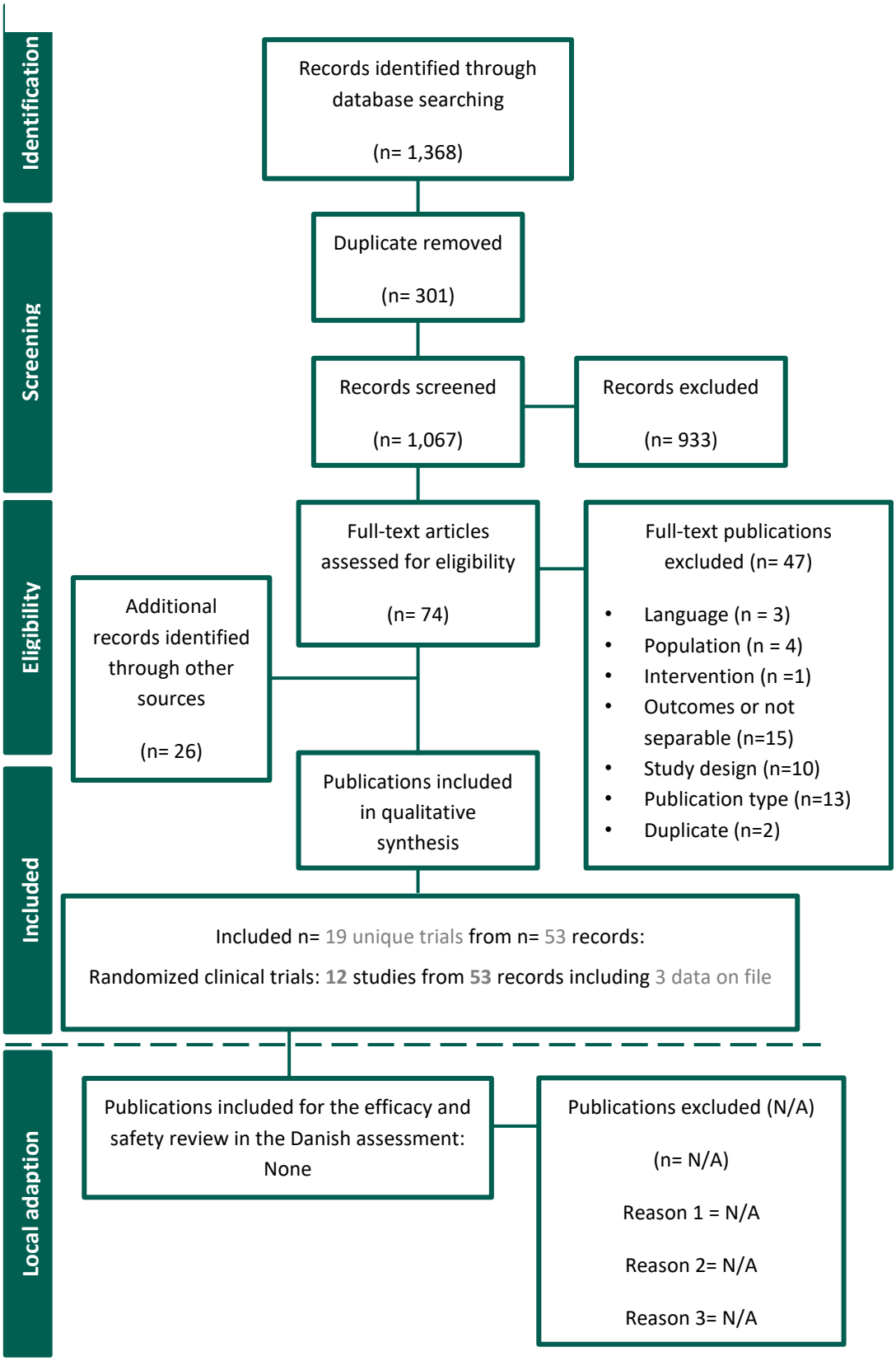
papers. Logic checks were performed on the validated data for additional quality assurance.

For studies from the same trial or database that were reported in multiple publications, a primary publication was identified, and its reference identification number (refID) was referred to as the primary refID. The related publications, referred to as kins, were grouped with their respective primary publication within the list of included full-text articles.

All data were extracted as reported, without calculation or digitisation, unless necessary for ITC purposes.

A total of 1,368 records were retrieved from the electronic literature databases; 301 records were removed during deduplication, and the 1,067 records remaining were screened at the title and abstract level. Of these, 74 records were sought for retrieval and screened at the full-text level. Following the full-text review, 26 records reporting on clinical outcomes from electronic databases were deemed eligible. Twenty-one records were included from grey literature searches. Data on file were available from Galderma as well (n=3). A total of 50 records reporting on 19 unique clinical trials met the eligibility criteria and were included in the SLR. The PRISMA diagram detailing the record identification process is presented in Figure 31.

Figure 31 PRISMA Flow Diagram. Search: 25 September 2023



Clinical burden was described across a total of 19 unique trials, as presented in Table 98. Study designs included 12 RCTs and seven single-arm trials (n=7). Among RCTs and single-arm trials, seven were phase III trials [44, 62-66], seven were phase II trials, [67-72] one was a phase IIb/II trial [73], and four studies did not report the study phase [74-77]. Total sample sizes across studies ranged from 10 patients [68, 77] to 558 patients [66] with PN. The study durations ranged from 8 weeks [78] to 24 months [74], and the treatment duration ranged from 4 weeks [71] to 24 weeks [44, 62, 74]. In two long-term studies, the study durations were 52 weeks [66] and 116 weeks [63]. Most studies recruited patients across multiple continents (nine studies), and the geographic locations for the remaining studies were primarily in Europe (seven studies), North America (two studies), and Asia (one study). The study periods spanned from 2003[76] to 2023 [62].

Serlopitant trials [65, 66, 70] are not considered in the further qualitative synthesis because they are no longer in development for the treatment of PN.

Table 98 Overview of study design for studies included in the analyses

Study/ID	Aim	Study design	Patient population	Intervention and comparator (sample size (n))	Primary outcome and follow-up period	Secondary outcome and follow-up period
APREPRU [71] EudraCT 2013-001601-85	To determine the antipruritic effect of aprepitant vs placebo in 58 patients with anti-histamine-refractory chronic pruritus in chronic nodular prurigo.	RCT, DB	Patients with antihistamine refractory PN	Aprepitant; placebo (n=58)	Intra-individual difference in mean itch intensity (VAS) in the last 24 before and after each treatment period 10 weeks	Patient global assessment worst itch (VAS); baseline adjusted itch, burning, and stinging (VRS); global/dynamic score according to PGA; DLQI, ItchyQoL, HADS, PAS; 10 weeks
NCT0050783 [72]	To investigate the efficacy of 1% pimecrolimus cream in comparison to 1% hydrocortisone cream in non-atopic prurigo nodularis (PN)	RCT, DB	Patients with non-atopic PN	Pimecrolimus; hydrocortisone (n=30)	Change in the mean itch VAS between day 1 and day 11	Change from baseline of skin neuropeptides, which are increased in PN skin 85 days
NCT02174419 [67]	To evaluate the efficacy and safety of two oral doses of the kappa opioid agonist and mu opioid antagonist nalbuphine extended release (NAL-ER) tablets in a phase 2, multicentre, randomized, double-blind,	RCT, DB	Patients with moderate-to-severe PN	Nalbuphine extended release 81 mg; Nalbuphine extended release 162 mg;	Proportion of subjects with a ≥30% reduction in 7-day mean WI-NRS from baseline to Week 10 for subjects who completed double-blind treatment, and from	Proportion of subjects with ≥50% reduction from baseline to Week 10 in 7-day mean WI-NRS and average daily itch intensities, Subjective Opiate Withdrawal Scale (SOWS), impact of itch on QoL (ItchyQoLTM), Hospital Anxiety and Depression Scale (HADS), sleep quality and quantity (12-item revised Medical

Study/ID	Aim	Study design	Patient population	Intervention and comparator (sample size (n))	Primary outcome and follow-up period	Secondary outcome and follow-up period
	placebo-controlled trial with an open-label, 50-week extension phase.			and placebo (n=63)	baseline to the last recorded week of daily itch scores for subjects who discontinued prior to Week 10 (last observed value; LOV).	Outcomes Sleep Scale [MOSR]) and PN lesions (Prurigo Activity Score [PAS]).
NCT03181503 [69]	To assess the efficacy and safety of nemolizumab as compared with placebo in the treatment of prurigo nodularis	RCT, DB	Patients with moderate-to-severe PN and severe pruritus	Nemolizumab; placebo (n=70)	The percent change from baseline in the peak pruritus score on the numerical rating scale at week 4	The changes from baseline in the peak and mean pruritus scores on the numerical rating scale at week 12, in the verbal rating scale score for itch (on a scale from 0 [no pruritus] to 4 [very severe pruritus]) at week 12, in the dynamic pruritus score for the change in itch (on a scale from 0 [strongly worsened pruritus] to 8 [almost no pruritus or no pruritus], with a score of 4 indicating no change) at week 4, in the investigator's global assessment of disease severity on the basis of the appearance of lesions (on a scale from 0 [clear] to 4 [severe]), and in a multidimensional, 7-item prurigo activity score10 to monitor the stage of disease (number, distribution, and activity of prurigo lesions) at week 12

Study/ID	Aim	Study design	Patient population	Intervention and comparator (sample size (n))	Primary outcome and follow-up period	Secondary outcome and follow-up period
TCP-102 [70] NCT02196324	To assess safety and efficacy of the neurokinin 1 receptor antagonist serlopitant for treatment of pruritus in PN.	RCT, DB	Patients with chronic, treatment-refractory PN	Serlopitant; placebo (n=128)	Average itch VAS pruritus intensity over the previous 24 hours	Global Assessment (IGA) score; and use of rescue medication. Pruritus intensity was rated at study visits on the VAS and once daily with the NRS, VRS, and IGA in a patient diary (ItchApp eDiary)
NCT03816891 [78]	To investigate vixarelimab efficacy and safety in patients with moderate-to-severe prurigo nodularis who were experiencing moderate-to-severe pruritus	RCT, DB	Patients with moderate-to-severe PN	Vixarelimab; placebo (n=50)	To evaluate the efficacy of subcutaneous (SC) KPL-716 vs. placebo in reducing pruritus in subjects with moderate to severe prurigo nodularis experiencing moderate to severe pruritus	To evaluate the effect of SC KPL-716 vs. placebo in improving sleep in subjects with moderate to severe prurigo nodularis experiencing moderate to severe pruritus; To evaluate the effect of SC KPL-716 vs. placebo in improving quality of life in subjects with moderate to severe prurigo nodularis experiencing moderate to severe pruritus; To evaluate the effect of SC KPL-716 vs. placebo in reducing disease severity in subjects with moderate to severe prurigo nodularis experiencing moderate to severe pruritus; To evaluate the safety and tolerability of SC KPL-716 vs. placebo in subjects with moderate to severe prurigo nodularis experiencing moderate to severe pruritus; To evaluate the pharmacokinetics (PK) of SC KPL-716 in subjects with moderate to severe prurigo

Study/ID	Aim	Study design	Patient population	Intervention and comparator (sample size (n))	Primary outcome and follow-up period	Secondary outcome and follow-up period
						nodularis experiencing moderate to severe pruritus; To evaluate the immunogenicity of SC KPL-716 in subjects with moderate to severe prurigo nodularis experiencing moderate to severe pruritus
PRISM [73] NCT03497975	To investigate vixarelimab efficacy and safety in patients with moderate-to-severe prurigo nodularis who were experiencing moderate-to-severe pruritus	RCT, DB	Patients with PN	Nalbuphine extended release; placebo (n=344)	Comparison of percentage of responders by arm	Change from baseline for itch-related quality of life: ItchyQoL total score, change from baseline for prurigo nodularis skin lesions , change from baseline for sleep disturbance
LIBERTY-PN PRIME [44] NCT04183335	To evaluate efficacy and safety of dupilumab in adults with PN inadequately controlled with topical prescription therapies	RCT, DB	Patients with PN inadequately controlled with topical prescription therapies	Dupilumab; placebo (n=151)	Proportion of patients with improvement (reduction) in WI-NRS by ≥4 points from baseline to week 24	Proportion of patients with reduction in skin lesion number to an IGA PN-S score of 0 or 1 at week 2; Proportion of patients concomitantly achieving a ≥4-point reduction in WI-NRS with an IGA PN-S of 0 or 1 at week 24 (United States and United States-reference countries only)
PRIME2 [44] NCT04202679	To evaluate efficacy and safety of dupilumab in adults with PN inadequately controlled with topical prescription therapies	RCT, DB	Patients with PN inadequately controlled with topical	Dupilumab; placebo (n=160)	Proportion of patients with improvement (reduction) in WI-NRS	Proportion of patients with improvement (reduction) in WI-NRS by ≥4 points from baseline to week 24; Proportion of patients with reduction in skin lesion number to an

Study/ID	Aim	Study design	Patient population	Intervention and comparator (sample size (n))	Primary outcome and follow-up period	Secondary outcome and follow-up period
			prescription therapies		by ≥4 points from baseline to week 12	IGA PN-S score of 0 or 1 at week 24; Proportion of patients concomitantly achieving a ≥4-point reduction in WI-NRS with an IGA PN-S of 0 or 1 at week 24 (United States and United States-reference countries only)
NCT03677401 [65]	To study of the efficacy, safety, and tolerability of serlopitant for the treatment of pruritus in adults with prurigo nodularis	RCT, DB	Patients with PN	Serlopitant; placebo (n=295)	Percent of Participants With Worst Itch Numeric Rating Scale (WI-NRS) 4-point Responder Rate at Week 10	Percent of Participants With WI-NRS 4-point Responder Rate at Week 4 [Time Frame: At Week 4] During the study, WI-NRS assessments were reported by the participant via eDiary once daily from screening/mid-screening visit through the follow-up visit. The Itch NRS is a validated, self reported, instrument for measurement of itch intensity and participants were asked to rate the intensity of their itch on an 11-point scale ranging from 0 (no itch) to 10 (worst itch imaginable); higher scores indicated greater itch intensity. A participant was a 4-point responder if their change from baseline is ≤ -4 (i.e. a decrease of at least 4). Percent of Participants With WI-NRS 4-point Responder Rate at Week 2 [Time Frame: At Week 2] During the study, WI-NRS

Study/ID	Aim	Study design	Patient population	Intervention and comparator (sample size (n))	Primary outcome and follow-up period	Secondary outcome and follow-up period
						assessments were reported by the participant via eDiary once daily from screening/mid-screening visit through the follow-up visit. The Itch NRS is a validated, self reported, instrument for measurement of itch intensity and participants were asked to rate the intensity of their itch on an 11-point scale ranging from 0 (no itch) to 10 (worst itch imaginable); higher scores indicated greater itch intensity. A participant was a 4-point responder if their change from baseline is ≤ -4 (i.e. a decrease of at least 4). Change From Baseline in WI-NRS at Weeks 2, 4, 6, and 10 [Time Frame: At Weeks 2, 4, 6, and 10] During the study, WI-NRS assessments were reported by the participant via eDiary once daily from screening/mid-screening visit through the follow-up visit. The Itch NRS is a validated, self reported, instrument for measurement of itch intensity and participants were asked to rate the intensity of their itch on an 11-point scale ranging from 0 (no itch) to 10 (worst itch imaginable); higher scores indicated greater itch intensity. Percent of

Study/ID	Aim	Study design	Patient population	Intervention and comparator (sample size (n))	Primary outcome and follow-up period	Secondary outcome and follow-up period
						Participants With WI-NRS 3-point Responder at Weeks 2, 4, and 10 [Time Frame: At Weeks 2, 4, and 10] During the study, WI-NRS assessments were reported by the participant via eDiary once daily from screening/mid-screening visit through the follow-up visit. The Itch NRS is a validated, self reported, instrument for measurement of itch intensity and participants were asked to rate the intensity of their itch on an 11-point scale ranging from 0 (no itch) to 10 (worst itch imaginable); higher scores indicated greater itch intensity. A participant was a 3-point responder if their change from baseline is ≤ -3 (i.e. a decrease of at least 3). Change From Baseline in Dermatology Life Quality Index (DLQI) to Week 10 [Time Frame: At Week 10] Dermatology Life Quality Index (DLQI) is a dermatology specific quality of life (QoL) instrument designed to assess the impact of the skin disease on a participant's QoL over the prior week. It is a ten item questionnaire that assesses overall QoL and six aspects that may affect QoL (symptoms and feelings, daily activities,

Study/ID	Aim	Study design	Patient population	Intervention and comparator (sample size (n))	Primary outcome and follow-up period	Secondary outcome and follow-up period
						leisure, work or school performance, personal relationships, and treatment). The DLQI questions are rated by the participant as 0 (not at all) to 3 (very much). Scores range from 0 to 30 with higher scores indicating poor QoL.). Change From Baseline in DLQI Question 1 to Week 10 [Time Frame: At Week 10] Dermatology Life Quality Index (DLQI) is a dermatology specific quality of life (QoL) instrument designed to assess the impact of the skin disease on a participant's QoL over the prior week. It is a ten item questionnaire that assesses overall QoL and six aspects that may affect QoL (symptoms and feelings, daily activities, leisure, work or school performance, personal relationships, and treatment). The DLQI questions are rated by the participant as 0 (not at all) to 3 (very much). Scores range from 0 to 30 with higher scores indicating poor QoL.). Change From Baseline in Investigator's Global Assessment of Prurigo Nodularis Stage (IGA PN-S) to Weeks 2, 4, and 10 [Time Frame: At Weeks 2, 4 and 10] The IGA PN-S is an instrument used to assess the overall number and

Study/ID	Aim	Study design	Patient population	Intervention and comparator (sample size (n))	Primary outcome and follow-up period	Secondary outcome and follow-up period
						thickness of PN lesions at a given time point, as determined by the investigator. It consists of a 5-point scale ranging from 0 (clear) to 4 (severe). Higher scores indicate severe prurigo nodularis. Change From Baseline in Investigator's Global Assessment of Prurigo Nodularis Activity (IGA PN-A) to Weeks 2, 4, and 10 [Time Frame: At Weeks 2, 4, and 10] The IGA PN-A is an instrument used to assess the overall activity of PN lesions at a given time point, as determined by the investigator. It consists of a 5-point scale ranging from 0 (clear) to 4 (severe). Higher scores indicate severe prurigo nodularis. Number of Participants With Treatment-emergent Adverse Events and Serious Adverse Events (SAEs) [Time Frame: From screening until the Follow-up (F/U) visit which occurred 35 days (+ 7 days) after the Week 10 visit or the last dose of study drug for participants who discontinued study drug early] Adverse events (AEs) and serious adverse events (SAEs) were recorded from the first study drug administration through the follow-up visit. Severity of all AEs were

Study/ID	Aim	Study design	Patient population	Intervention and comparator (sample size (n))	Primary outcome and follow-up period	Secondary outcome and follow-up period
						graded using the National Cancer Institute Common Terminology Criteria for Adverse Events v4.03. During the period between informed consent and first study drug dose, only SAEs caused by a protocol-mandated intervention were collected.
OLYMPIA 1[62] NCT04501666	To assess the efficacy and safety of nemolizumab§ compared with placebo in patients aged ≥18 years with moderate-to-severe prurigo nodularis	RCT, DB	Patients with moderate-to-severe PN	Nemolizumab; placebo (n=286)	Proportion of patients with: Itch response: ≥4-point improvement in PP NRS score from baseline at W16; IGA success at W16.	Proportion of patients with: ≥4-point improvement in PP NRS score from baseline through W24; ≥4-point improvement in SD NRS score from baseline through W24; IGA success at each visit through W24; >75% healed prurigo lesions (PAS item 5b) at each visit through W24
OLYMPIA 2 [64] NCT04501679	To assess the efficacy and safety of nemolizumab vs placebo in ≥18-year-old patients with moderate-to-severe PN after a 16-week treatment period	RCT, DB	Patients with moderate-to-severe PN	Nemolizumab; placebo (n=274)	Itch response, IGA response at W16	Reduction from baseline of 4 points or more on the PP-NRS score at week 4, a weekly average PP-NRS score of less than 2 at weeks 4 and 16, and a reduction from baseline of 4 or more points on the sleep disturbance numerical rating scale (SD-NRS; range, 0 [no sleep loss] to 10 [unable to sleep at all]) at weeks 4 and 16. A reduction from baseline of 4 points or more on the PP-NRS and on the

Study/ID	Aim	Study design	Patient population	Intervention and comparator (sample size (n))	Primary outcome and follow-up period	Secondary outcome and follow-up period
						SD-NRS represents a clinically meaningful improvement. Other secondary end points included additional aspects of skin lesions, patient-reported pruritus, sleep disturbance, pain frequency and intensity, global assessment of disease and treatment, health-related quality of life (assessed by the Dermatology Life Quality Index and EuroQoL Group 5-Dimensions [EQ-5D] questionnaire), and symptoms of anxiety and depression (assessed by the Hospital Anxiety and Depression Scale [HADS]). HADS measures 14 items, 7 for depression and 7 for anxiety, with higher scores indicating worse symptoms.
NCT03576287 [68]	To evaluate the efficacy of apremilast in patients with PN	Single-arm trial	Patients with clinically verified moderate-to-severe PN	Apremilast (n=10)	The primary objective of this 16-week phase II study was to evaluate the efficacy of 12 weeks' treatment of apremilast in patients with PN using the visual analogue scale (VAS)	Secondary endpoints were to evaluate the efficacy of apremilast using Physician Global Assessment (PGA, range 0–4), Patient Assessed Global Assessment (PaGA, range 0–5), QoL using Dermatology Life Quality Index (DLQI, range 0–30), and Pittsburgh Sleep Quality Index (PSQI, range 0–21)

Study/ID	Aim	Study design	Patient population	Intervention and comparator (sample size (n))	Primary outcome and follow-up period	Secondary outcome and follow-up period
					pruritus score (range 0–10).	
OLYMPIA LTE NCT03540160 [66]	To study of the long term safety of serlopitant for the treatment of pruritus in adults.	Single-arm trial, OL	Patients with pruritus associated with PN	Serlopitant (n=558)	Number of Subjects With Treatment-emergent Adverse Events 52 weeks	NA
NCT04204616[63]	To assess the long-term safety of nemolizumab (CD14152) in participants with prurigo nodularis (PN)	Single-arm trial	Patients with PN	Nemolizumab (n=450)	Incidence of Adverse Events (AEs) by Severity [Time Frame: Up to 192 weeks	1Percentage of Participants with an Investigator Global Assessment (IGA) Success up to Week 184 [Time Frame: Up to Week 184] Percentage of Participants with an Improvement of >=4 from Baseline in Peak Pruritus (PP) Numeric Rating Scale (NRS) up to Week 184 [Time Frame: Baseline Up to Week 184] 3. Percentage of Participants with Low Disease Activity State up to Week 184 [Time Frame: Up to Week 184]

Study/ID	Aim	Study design	Patient population	Intervention and comparator (sample size (n))	Primary outcome and follow-up period	Secondary outcome and follow-up period
						4. Percentage of Pruriginous Lesions with Excoriations/Crusts up (PAS item 5a) up to Week 184 [Time Frame: Up to Week 184] 5. Percentage of Healed Prurigo Lesions (PAS item 5b) up to Week 184 [Time Frame: Up to Week 184] 6. Change from Baseline in Number of Lesions in Representative Area (PAS item 4) up to Week 184 [Time Frame: Baseline Up to Week 184] 7. Percentage of Participants with PP NRS <2 up to Week 184 [Time Frame: Up to Week 184] 8. Percent Change from Baseline in PP NRS up to Week 184 [Time Frame: Baseline Up to Week 184] 9. Absolute Change from Baseline in PP NRS up to Week 184 [Time Frame: Baseline Up to Week 184]

Study/ID	Aim	Study design	Patient population	Intervention and comparator (sample size (n))	Primary outcome and follow-up period	Secondary outcome and follow-up period
						10. Percentage of Participants with Average Pruritus (AP) NRS <2 up to Week 52 [Time Frame: Up to Week 52] 11. Percentage of Participants with an Improvement of >=4 from Baseline in AP NRS up to Week 52 [Time Frame: Up to Week 52] 12. Percent Change from Baseline in AP NRS up to Week 52 [Time Frame: Up to Week 52] 13. Absolute Change from Baseline in AP NRS up to Week 52 [Time Frame: Up to Week 52] 14. Percentage of Participants with an Improvement of >=4 from Baseline in Sleep Disturbance (SD) NRS up to Week 184 [Time Frame: Up to Week 184] 15. Percent Change from Baseline in SD NRS up to Week 184 [Time Frame: Up to Week 184]

Study/ID	Aim	Study design	Patient population	Intervention and comparator (sample size (n))	Primary outcome and follow-up period	Secondary outcome and follow-up period
						Absolute Change from Baseline in SD NRS up to Week 184 [Time Frame: Up to Week 184] Change from Baseline in Prurigo Nodularis (PN)-associated Pain Frequency up to Week 184 [Time Frame: Baseline Up to Week 184] Change from Baseline in PN-associated Pain Intensity up to Week 184 [Time Frame: Baseline Up to Week 184] Percentage of Participants Reporting low Disease Activity Based on Patient Global Assessment of Disease (PGAD) up to Week 52 [Time Frame: Up to Week 52] Percentage of Participants Satisfied with Study Treatment Based on Patient Global Assessment of Treatment (PGAT) up to Week 52 [Time Frame: Up to Week 52]. Percentage of Participants with a Change of >=4 from Baseline in Dermatology Life Quality Index (DLQI) up to Week 184 [Time Frame: Baseline Up to Week 184]

Study/ID	Aim	Study design	Patient population	Intervention and comparator (sample size (n))	Primary outcome and follow-up period	Secondary outcome and follow-up period
						Change from Baseline in EuroQoL 5-Dimension (EQ-5D) up to Week 184 [Time Frame: Baseline Up to Week 184] Time to Permanent Study Drug Discontinuation [Time Frame: Baseline to 184 weeks] Time to Rescue Therapy [Time Frame: Baseline to 184 weeks] Percentage of Participants Receiving Any Rescue Treatment by Rescue Treatment [Time Frame: Baseline up to 184 weeks]
Ahsan, 2018 [75] NR	To determine the efficacy and safety of thalidomide in treatment of idiopathic prurigo nodularis.	Single-arm trial	Patients with idiopathic PN	Thalidomide (n=12)	NA	NA
Kwatra S, 2023[77] NR	To assess the efficacy, safety, and transcriptomic effects of abrocitinib in the treatment of PN and CPUO.	Single-arm trial	Patients with moderate-to-severe PN	Abrocitinib (n=10)	The primary efficacy endpoint was percent change in PP-NRS score from baseline to week 12	Percentage of patients achieving a ≥4-point reduction on the PP-NRS; percent change in Dermatology Life Quality Index (DLQI) score; and, for PN, percent change in IGA score.

Study/ID	Aim	Study design	Patient population	Intervention and comparator (sample size (n))	Primary outcome and follow-up period	Secondary outcome and follow-up period
						Cutaneous transcriptome analysis was performed at baseline and week 12.
Mazza M, 2013[74] NR	To investigate the efficacy of pregabalin in patients with PN	Single-arm trial	Patients with PN	Pregabalin (n=30)	NA	NA
Zalaudek, 2006 [76] NR	To investigate whether amitriptyline, a well investigated tricyclic antidepressant with a strong antipruritic effect based on a high binding affinity for the histamine H1 receptor, could represent a novel therapeutic approach.	Single-arm trial	Patients with PN, not treated previously	Amitriptyline (n=17)	NA	NA

Abbreviations: DB, Double-blind; DLQI, Dermatology Life Quality Index; EQ-5D, EuroQoL 5-Dimension; HADS, Hospital Anxiety and Depression Scale; IGA, Investigator's Global Assessment; PAS, Prurigo Activity Score; PN, prurigo nodularis; PGAD, Patient Global Assessment of Disease; PP-NRS, Peak Pruritus Numerical Rating Scale; RCT, Randomized controlled trial; SC, subcutaneous; TCI, topical calcineurin inhibitor; TCS, topical corticosteroid; TEAE, treatment-emergent adverse event; VAS, Visual Analogue Scale; WI-NRS, Worst Itch Numerical Rating Scale;.

H.1.3 Excluded fulltext references

A list of the excluded fulltext references together with a short reason for the exclusion is presented in Table 99.

Table 99 Excluded fulltext references

Author	Publication year	Title	Status
Kwatra, Shawn G	2023	Validation of the Peak Pruritus Numerical Rating Scale as a Patient-Reported Outcome Measure in Prurigo Nodularis.	Excluded: Outcomes not separable for the population of interest (FT only)
Agrawal, Diksha	2021	A Prospective Study Examining the Effect of Selected Topical and Systemic Drugs on Pruritus Grading System Score and STAT 6 Expression in Patients of Prurigo Nodularis.	Excluded: Study design not of interest
Liu, Taoming	2023	Successful treatment of prurigo nodularis with tofacitinib: The experience from a single center.	Excluded: Publication type not of interest
Sutaria, Nishadh	2022	Cluster Analysis of Circulating Plasma Biomarkers in Prurigo Nodularis Reveals a Distinct Systemic Inflammatory Signature in African Americans.	Excluded: Outcomes not of interest
Chu, L	2022	Plasma Steroids and Endocannabinoids Used as Biomarkers to Assess the Pruritus Severity of Patients With Prurigo Nodularis.	Excluded: Publication type not of interest
Stander, S	2022	Worst itch numerical rating scale for prurigo nodularis: a psychometric evaluation.	Excluded: Outcomes not of interest
Kimel, Miriam	2020	Validation of Psychometric Properties of the Itch Numeric Rating Scale for Pruritus Associated With Prurigo Nodularis: A Secondary Analysis of a Randomized Clinical Trial.	Excluded: Outcomes not of interest
Calugareanu, A	2020	Effectiveness and safety of dupilumab for the treatment of prurigo nodularis in a French multicenter adult cohort of 16 patients.	Excluded: Study design not of interest
Agelopoulos, K	2019	Neurokinin 1 receptor antagonists exhibit peripheral effects in prurigo nodularis including reduced ERK1/2 activation.	Excluded: Study design not of interest
Stander, Sonja	2006	Treatment of pruritic diseases with topical calcineurin inhibitors.	Excluded: Study design

			not of interest
Saraceno, Rosita	2010	An occlusive dressing containing betamethasone valerate 0.1% for the treatment of prurigo nodularis.	Excluded: Intervention not of interest (CLINICAL ONLY)
Stander, Sonja	2010	Targeting the neurokinin receptor 1 with aprepitant: a novel antipruritic strategy.	Excluded: Population not of interest
Lan, Cheng-Che E	2007	Treatment of idiopathic prurigo nodularis in Taiwanese patients with low-dose thalidomide.	Excluded: Study design not of interest
Maurer, Toby	2004	Thalidomide treatment for prurigo nodularis in human immunodeficiency virus-infected subjects: efficacy and risk of neuropathy.	Excluded: Outcomes not of interest
Stander, S	2001	Treatment of prurigo nodularis with topical capsaicin.	Excluded: Study design not of interest
Metze, D	1999	Efficacy and safety of naltrexone, an oral opiate receptor antagonist, in the treatment of pruritus in internal and dermatological diseases.	Excluded: Population not of interest
Ferrandiz, C	1997	Sequential combined therapy with thalidomide and narrow-band (TL01) UVB in the treatment of prurigo nodularis.	Excluded: Outcomes not of interest
Clemmensen, O J	1984	Thalidomide neurotoxicity.	Excluded: Study design not of interest
Bahloul D.	2023	42910 Validation of the Sleep Numeric Rating Scale (Sleep-NRS) for measuring sleep quality in adults with Prurigo Nodularis (PN): Results from dupilumab clinical studies	Excluded: Outcomes not of interest
Bahloul D.	2023	43531 Validation of the Dermatology Life Quality Index (DLQI) in prurigo nodularis (PN) based on clinical studies of dupilumab in adults with PN	Excluded: Outcomes not of interest
Bahloul D.	2023	42895 Validation of the skin pain numeric rating scale (NRS) in prurigo nodularis (PN) based on clinical studies of dupilumab in adults with PN	Excluded: Study design not of interest
Gao Z.	2022	Efficacy and safety of dupilumab in the treatment of adult prurigo nodularis	Excluded: Non-English Language
Xin H.	2022	Efficacy and safety of dupilumab in the treatment of 123 cases of atopic dermatitis	Excluded: Non-English Language

Hitosugi N.	2021	27284 The effect of combined therapy of topical anesthesia and capsaicin ointment in prurigo nodularis management	Excluded: Outcomes not of interest
Yosipovitch G.	2021	434 The study design of two trials of dupilumab in patients with prurigo nodularis inadequately controlled with topical therapies: LIBERTY PN PRIME and PRIME 2	Excluded: Publication type not of interest
Ardigo M.	2020	Efficacy of a topical product containing purified omental lipids and three anti-itching compounds in the treatment of chronic pruritus/ prurigo nodularis in elderly subjects: A prospective, assessor-blinded, 4-week trial with transepidermal water loss and optical coherence tomography assessments	Excluded: Population not of interest
Stander S.	2020	Treatment of prurigo nodularis with serlopitant: Impact on itch and pain	Excluded: Outcomes not of interest
Sonja S.	2020	Opioid receptor modulation as novel therapy target in chronic pruritus	Excluded: Study design not of interest
Stander S.	2020	Treatment of prurigo nodularis with serlopitant: Impact on prurigo activity score	Excluded: Outcomes not of interest
Hitosugi N.	2020	12928 The effect of combined therapy of topical anesthesia and capsaicin ointment in prurigo nodularis management	Excluded: Outcomes not of interest
Mcguire N.	2020	Real world experience of using dupilumab to treat eczema endotypes	Excluded: Outcomes not separable for the population of interest (FT only)
Ugajin T.	2019	Efficacy of anti-immunoglobulin E therapy in patients with prurigo: A pilot study	Excluded: Outcomes not of interest
Tanis R.	2019	Dupilumab Treatment for Prurigo Nodularis and Pruritis	Excluded: Publication type not of interest
Stander S.	2009	Treatment of chronic pruritus with the selective serotonin re-uptake inhibitors paroxetine and fluvoxamine: Results of an open-labelled, two-arm proof-of-concept study	Excluded: Population not of interest
Hershko K.	1999	Successful treatment of prurigo nodularis with cyclosporin A	Excluded: Publication

			type not of interest
Veraldi S.	1999	Treatment of nodular prurigo with cyclosporin in microemulsion	Excluded: Publication type not of interest
Johnke H.	1993	Thalidomide treatment of prurigo nodularis	Excluded: Non-English Language
Eudy-Byrne R	2023	A population pharmacokinetic–pharmacodynamic model evaluating efficacy of nalbuphine extended-release in patients with prurigo nodularis	Excluded: Study design not of interest
Stander S	2019	Improvement of itch and pain in patients with prurigo nodularis treated with serlopitant: secondary analysis of phase 2 clinical trial	Excluded: Outcomes not of interest
	2021	A Study to Evaluate the Durability of Response and Safety of Nemolizumab for 24 Weeks in Participants With Prurigo Nodularis	Excluded: Publication type not of interest
	2020	A Study of Nemolizumab (CD14152) in Participants With Prurigo Nodularis	Excluded: Publication type not of interest
	2020	A Study to Assess the Efficacy and Safety of Nemolizumab (CD14152) in Participants With Prurigo Nodularis (PN)	Excluded: Publication type not of interest
	2017	Safety and Efficacy of Nemolizumab in PN	Excluded: Publication type not of interest
	2018	Study of the Efficacy, Safety and Tolerability of Serlopitant for the Treatment of Pruritus (Itch) With Prurigo Nodularis	Excluded: Publication type not of interest
	2020	A Phase II/III, Randomized, Double-blind, Placebo-controlled, Parallel-group, Multi-Center Study to Evaluate the Efficacy and Safety of nemolizumab in Japanese Prurigo nodularis Patients with moderate to severe pruritus	Excluded: Publication type not of interest
	2014	Study of Nalbuphine HCl ER Tablets in Patients With Prurigo Nodularis	Excluded: Publication type not of interest
Sofen H	2023	Efficacy and safety of vixarelimab, a human monoclonal oncostatin M receptor &bgr; antibody, in moderate-to-severe prurigo nodularis: a randomised, double-blind, placebo-controlled, phase 2a study	Excluded: Duplicate

[Please provide in a list or table the references that were excluded during fulltext screening along with a short reason. If using an existing, locally adapted SLR, please fill in the references originally included in the SLR but excluded in the current application.]

H.1.4 Quality assessment

Quality assessment of the RCTs included in the SLR was conducted using the Cochrane Risk of Bias Assessment Tool 2.0 [79]. This assessment will summarise the risk of bias in the findings of randomised trials by considering five domains of potential bias: (1) bias arising from the randomisation process, (2) bias due to deviations from intended interventions, (3) bias due to missing outcome data, (4) bias in measurement of the outcome, and (5) bias in selection of the reported result. This version of the tool also considers outcome-specific bias—given that some outcomes have no or little room for judgement (e.g., all-cause mortality) and others have considerable room for judgement (e.g., assessment of depression scores)—and assesses different outcomes separately. An overall risk of bias judgement was assigned to each outcome assessed in each trial, using the following categories: Low risk of bias, Some concerns, or High risk of bias.

Only studies available in full text underwent a quality assessment, because of the lack of details available for assessment from abstracts and posters.

H.1.5 Unpublished data

Three documents corresponded to Galderma data on file, and therefore to unpublished data.

H.1.6 Updated SLR

The SLR included in this application was used to inform the ITC presented. However, in order to examine if new records were available, the searches performed on the SLR presented in this application were updated by re-running them on the 17th of May 2024. The updated SLR was conducted for the research area “Efficacy and safety from randomised controlled trials (RCTs) examining nemolizumab and relevant comparators in the management of PN”. The same comprehensive multi-string search strategies used in the previous SLR were utilised in the updated searches, as well as the same sources. No language restrictions were applied, and a date restriction of studies published from the 1st of September 2023 until the search date was applied.

From the original SLR, 53 publications of 19 studies were included. In the updated database searches. 238 records were returned, 126 records were removed through deduplication, pre-screening or cross-checking with the original SLR, thus 112 records were screened at the title and abstract stage. 90 records were excluded, and 22 records were sought for retrieval. All records were retrieved, 18 were excluded based on predetermined eligibility criteria. Thus, four publications were included in the review. An additional 18 records were identified through grey literature searching, 16 records were excluded leaving two records eligible for included in the review. In total, 59 records of 19 studies were included in the updated SLR.

Therefore, both in the originally performed SLR and in the updated one, nineteen unique trials met the selection criteria of the clinical SLR and reported on the clinical burden on PN. Of these, the majority (12 of 19) were randomized control trials, with the remaining seven being single-armed trials.

Appendix I. Literature searches for health-related quality of life (N/A)

I.1 Health-related quality-of-life search

Not applicable.

Table 100 Bibliographic databases included in the literature search

Database	Platform	Relevant period for the search	Date of search completion
Embase	Embase.com		dd.mm.yyyy
Medline	Ovid		dd.mm.yyyy
Specific health economics databases[1]			dd.mm.yyyy

Abbreviations:

Table 101 Other sources included in the literature search

Source name	Location/source	Search strategy	Date of search
e.g. NICE	www.nice.org.uk		dd.mm.yyyy
CEA Registry	Tufts CEA - Tufts CEA		dd.mm.yyyy

Table 102 Conference material included in the literature search

Conference	Source of abstracts	Search strategy	Words/terms searched	Date of search
Conference name	e.g. conference website	Electronic search	List individual terms used to search in the	dd.mm.yyyy

[1] Papaioannou D, Brazier J, Paisley S. Systematic searching and selection of health state utility values from the literature. Value Health. 2013;16(4):686-95.

Conference	Source of abstracts	Search strategy	Words/terms searched	Date of search
			congress material:	
	Journal supplement [insert reference]	Skimming through abstract collection		dd.mm.yyyy

I.1.1 Search strategies

Table 103 Search strategy for [name of database]

No.	Query	Results
#1		88244
#2		85778
#3		115048
#4		7011
#5		10053
#6		12332
#7		206348
#8		211070
#9	#7 OR #8	272517
#10	#3 AND #6 AND #9	37

Literature search results included in the model/analysis:

I.1.2 Quality assessment and generalizability of estimates

I.1.3 Unpublished data

Appendix J. Literature searches for input to the health economic model (N/A)

J.1 External literature for input to the health economic model

Not applicable.

J.1.1 Example: Systematic search for […]

Table 51 Sources included in the search

Database	Platform/source	Relevant period for the search	Date of search completion
Embase	e.g. Embase.com	e.g. 1970 until today	dd.mm.yyyy
Medline			dd.mm. yyyy
CENTRAL	Wiley platform		dd.mm. yyyy

Abbreviations:

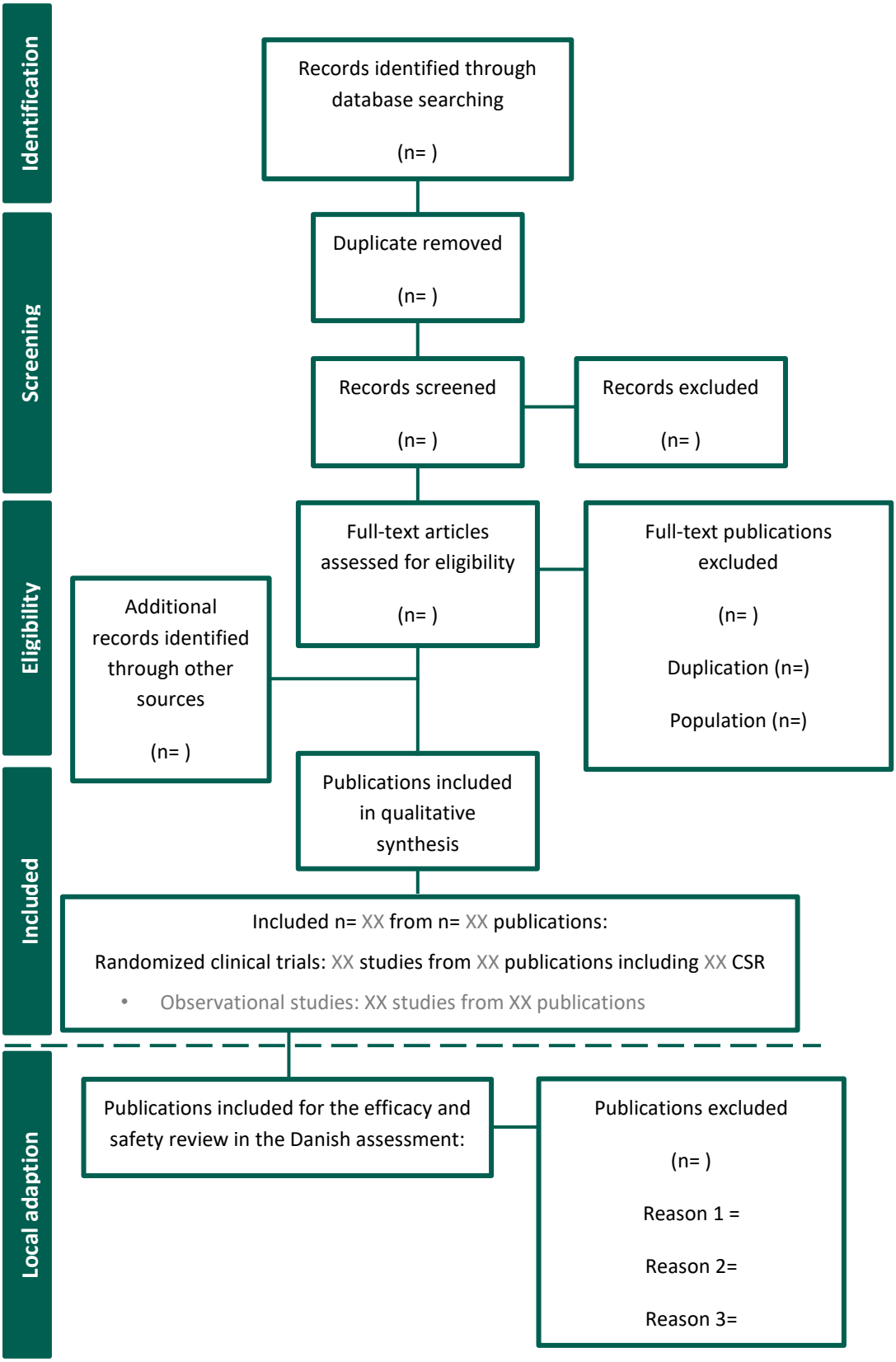
J.1.2 Example: Targeted literature search for [estimates]

Table 52 Sources included in the targeted literature search

Source name/ database	Location/source	Search strategy	Date of search
e.g. NICE	www.nice.org.uk		dd.mm.yyyy
			dd.mm.yyyy

Abbreviations:

Example of PRISMA diagram. The diagram is editable and may be used for recording the records flow for the literature searches and for the adaptation of existing SLRs.



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