Medicinrådet

Bilag til Medicinrådets anbefaling vedr. dupilumab til moderat til svær prurigo nodularis

Vers. 1.0

Bilagsoversigt

1. Ansøgers notat til Rådet vedr. dupilumab
2. Forhandlingsnotat fra Amgros vedr. dupilumab
3. Ansøgers endelige ansøgning vedr. dupilumab

Fra:	Jain, Pavika /DK
Til:	Louise Klokker Madsen
Cc:	Fyhn, Birgitte /DK; Pernille Winther Johansen
Emne:	RE: Udkast til anbefalingsrapport vedr. dupilumab til voksne med moderat til svær prurigo nodularis
Dato:	25. oktober 2023 11:33:53

Kære Louise,

Tak for tilsendte dokument. Vi har ingen kommentarer.

Vh.
Pavika

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24.10.2023

DBS/INK

Prisnotat

Dato for behandling i Medicinrådet	22. november 2023
Leverandør	Sanofi-Aventis
Lægemiddel	Dupixent (dupilumab)
Ansøgt indikation	Dupilumab til behandling af voksne med moderat til svær prurigo nodularis (PN)
Nyt lægemiddel / indikationsudvidelse	Indikationsudvidelse

Prisinformation

Amgros har følgende pris på Dupixent:

Tabel 1: Aftalepris

Lægemiddel	Styrke	Pakningsstørrelse	AIP (DKK)	Nuværende SAIP, (DKK)	Rabatprocent ift. AIP
Dupixent	200 mg	2 stk.	7.989,84	[redacted]	[redacted]
Dupixent	300 mg	2 stk.	8.460,47	[redacted]	[redacted]

Aftaleforhold

[redacted]

Dupixent indgår i behandlingsvejledninger vedrørende lægemidler til behandling af svær astma, atopisk eksem og svær rhinosinuitis med næsepolypper.

[redacted]

Konkurrencesituationen

Dupixent er den eneste lægemiddel til systemiske behandling af voksne med moderat til svær prurigo nodularis (PN).

Tabel 2: Lægemiddeludgift

Lægemiddel	Styrke	Pakningsstørrelse	Dosering	Pris pr. pakning (SAIP, DKK)	Lægemiddeludgift 24 md (SAIP, DKK)
Dupixent	300 mg	2 stk.	Startdosis på 600 mg og herefter 300 mg hver 2. uge	[redacted]	[redacted]

Status fra andre lande

Tabel 3: status fra andre lande

Land	Status	Link
Norge	Under vurdering	Link til vurdering
England	Under vurdering	Link til vurdering

Konklusion

Prurigo nodalaris er en indikation til en lille patientgruppe[redacted]

Medicinrådet

Application for the assessment of dupilumab for the treatment of prurigo nodularis

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Color scheme for text highlighting	
Color of highlighted text	**Definition of highlighted text**
	Confidential information
[other]	[definition of color-code]

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Medicinrådet

1. Basic information

Contact information	
Name	**Pavika Jain Lyngsie**
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Overview of the pharmaceutical	
Proprietary name	Dupixent®
Generic name	Dupilumab
Marketing authorization holder in Denmark	Sanofi
ATC code	D11AH05
Pharmacotherapeutic group	Recombinant monoclonal antibody
Active substance(s)	Dupilumab
Pharmaceutical form(s)	Solution administered as subcutaneous injection
Mechanism of action	Dupilumab is an interleukin-4 (IL-4) receptor alpha antagonist. It is a human monoclonal antibody of the immunoglobulin G4 subclass that inhibits IL-4 and interleukin-13 (IL-13) signalling by specifically binding to the IL-4 receptor alpha subunit, which is shared by the two IL-4 and IL-13 receptor complexes; type 1: γc & IL-4Rα, type 2: IL-4Rα/IL-13Rα1 (1). Dupilumab inhibits IL-4 signalling via the type 1 receptor and both IL-4 and IL-13 signalling via the type 2 receptor. By blocking the IL-4R alpha subunit, dupilumab inhibits signalling through itch sensory neurons as well as IL-4 and IL-13 cytokine-induced responses, including the release of proinflammatory cytokines, chemokines, and immunoglobulin E.

Overview of the pharmaceutical	
Dosage regimen	**Adult patients (18+ years)** 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 administered as subcutaneous injection.
Therapeutic indication relevant for assessment (as defined by the European Medicines Agency, EMA)	Dupilumab is indicated as treatment of adults with moderate-to-severe prurigo nodularis who are candidates for systemic therapy.
Other approved therapeutic indications	**Atopic dermatitis** Adults and adolescents Dupixent® is indicated for the treatment of moderate-to-severe atopic dermatitis in adults and adolescents 12 years and older who are candidates for systemic therapy. Children 6 months to 11 years of age Dupixent® is indicated for the treatment of severe atopic dermatitis in children 6 months to 11 years old who are candidates for systemic therapy. **Asthma** Adults and adolescents Dupixent® is indicated in adults and adolescents 12 years and older as add-on maintenance treatment for severe asthma with type 2 inflammation characterised by raised blood eosinophils and/or raised fraction of exhaled nitric oxide (FeNO) who are inadequately controlled with high dose inhaled corticosteroids plus another medicinal product for maintenance treatment. Children 6 to 11 years of age Dupixent® is indicated in children 6 to 11 years old as add-on maintenance treatment for severe asthma with type 2 inflammation characterised by raised blood eosinophils and/or raised fraction of exhaled nitric oxide (FeNO) who are inadequately controlled with medium to high dose inhaled corticosteroids plus another medicinal product for maintenance treatment. **Chronic rhinosinusitis with nasal polyposis** Dupixent® is indicated as an add-on therapy with intranasal corticosteroids for the treatment of adults with severe chronic rhinosinusitis with nasal polyposis for whom therapy with systemic corticosteroids and/or surgery do not provide adequate disease control. **Eosinophilic esophagitis (EoE)** Dupixent is indicated for the treatment of eosinophilic esophagitis in adults and adolescents 12 years and older, weighing at least 40 kg, who are inadequately controlled by, are intolerant to, or who are not candidates for conventional medicinal therapy
Will dispensing be restricted to hospitals?	Yes

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Overview of the pharmaceutical	
Combination therapy and/or co-medication	Dupilumab is indicated in combination with or without emollients and topical prescription therapy (e.g., low to medium potent topical corticosteroids. and/or topical calcineurin inhibitors)
Packaging – types, sizes/number of units, and concentrations	200 mg dupilumab (Dupixent®) injection fluid in pen (2 per pack) 300 mg dupilumab (Dupixent®) injection fluid in pen (2 per pack) 200 mg dupilumab (Dupixent®) injection fluid in cannula (2 per pack) 300 mg dupilumab (Dupixent®) injection fluid in cannula (2 per pack)
Orphan drug designation	No

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2. Abbreviations

ANCOVA	analysis of covariance
BSC	best supportive care
CHM	Cochran–Mantel–Haenszel
DLQI	Dermatology Life Quality Index
DMC	Danish Medicines Council
EMA	European Medical Agency
EOS	end of study
EOT	end of treatment
EQ-5D-5L	European Quality of Life 5 Dimensions 5 Level Version
GRA	glucocorticoid response elements
HIV	human immunodeficiency virus
HRQoL	health related quality of life
HSUV	health state utility values
HUI3	Health Utilities Index Mark 3
ICER	incremental cost per QALY
IFSI	International Forum for the Study of Itch
IGA	Investigator Global Assessment scale
IL-4	interleukin-4
ITT	intention to treat
LYs	life-years
OR	odds ratio
PRO	patient-reported outcome
Q2W	every 2 weeks
QALY	quality-adjusted life-year
QoL	quality of life
RCT	randomised clinical trial
SD	standard deviation
SLR	systematic literature search
SoC	standard of care
TCI	topical calcineurin inhibitors
TCS	topical corticosteroids
TEAE	Treatment-emergent serious adverse event
UV	Ultraviolet
WI-NRS	Worst Itching Intensity Numerical Rating Scale
WOCF	worst-observation carried forward

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3. Table of Content

3.1 Table of Tables

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4. Summary

Prurigo nodularis (PN) is a chronic, neural and immune-mediated disease, characterized by intense pruritus and nodular skin lesions. PN is driven by neuronal sensitisation to itch and development of an itch-scratch cycle (2). The intense continued itching and scratching results in the formation of nodular lesions (2). Itching and scratching are the most commonly reported symptoms and can be continuous or sporadic (3). Other common symptoms include burning, stinging and tingling sensations, sleep disturbances and psychological distress (4),(3).

The intensity of itch in PN is reported to be higher than in other skin diseases, including atopic dermatitis (AD) and urticaria (11). Compared to other dermatological diseases there is a larger impact on patients' quality of life (QoL) (5, 6). A study of 533 patients diagnosed with chronic prurigo (number of PN patients = 69) showed that nearly half (42%) of all patients indicate that QoL is often or always impacted by their disease and that PN has the highest impact on QoL (5). In addition, patients with PN have an increased likelihood of phycological co-morbidities (6).

There is limited epidemiological information on PN, but existing estimates indicate that PN affects a small population of patients with a prevalence of approx. 900 patients and an incidence of 60 patients in Denmark. Of these approx. 12% are estimated to be moderate-to-severe PN patients and 50% are estimated eligible for systemic therapy (approx. 55-60 patients per year). However, there is currently no other European Medical Agency (EMA) approved systemic therapy for moderate-to-severe PN patients. In addition, there are currently no Danish Medicines Council (DMC) or Danish-specific treatment guidelines for PN. In addition, there is a lack of randomised clinical trial (RCT) evidence to support currently used off-label treatment regimens (7, 8, 9). Therefore, in this application, the safety and efficacy of dupilumab in combination with standard of care (SoC) (moisturizers, low to medium-potent topical corticosteroids, topical calcineurin inhibitors, light therapy and zinc bandages) will be compared to SoC alone.

Dupilumab is a recombinant human IgG4 monoclonal antibody that inhibits IL-4 and IL-13 signalling by specifically binding to the IL-4Rα subunit shared by the IL-4 and IL-13 receptor complexes. IL-4 and IL-13 are key type 2 cytokines involved in atopic disease (10). Type 2 inflammation plays an important role in the pathogenesis of multiple atopic conditions. IL-4 and IL-13 act as major drivers of type 2 inflammation by activating multiple cell types (e.g., mast cells, lymphocytes, eosinophils, neutrophils, and macrophages) and inducing multiple mediators involved in type 2 inflammation.

The efficacy of dupilumab was evaluated in two pivotal, randomised, placebo-controlled, phase 3 studies, LIBERTY-PN PRIME and PRIME2(11). The efficacy can be evaluated via several different criteria, as several outcomes can be used to measure the severity of PN, but Worst Itching Intensity Numerical Rating Scale (WI-NRS) is commonly used to describe the severity of the disease. WI-NRS is a single-item patient-reported outcome measure in which patients indicate the intensity of the worst itching they experienced over the past 24 hours.

In LIBERTY-PN PRIME, statistically significant and clinically meaningful between-group differences were reached for the primary and key secondary endpoints. Dupilumab + SoC demonstrated a statistically significant and clinically meaningful improvement in itch control, as measured by the proportion of participants with an improvement (reduction) in WI-NRS by ≥4 points from baseline to Week 24 compared to placebo + SoC (60.0% versus 18.4%; p<0.0001). Also, the treatment with dupilumab + SoC statistically significantly reduced the number of PN lesions, as measured by the proportion of participants with an IGA PN-S 0 ("clear") or 1 ("almost clear") score at Week 24 compared to placebo + SoC (48.0% versus 18.4%; p=0.0004). Dupilumab treatment also statistically significantly increased the proportion of participants achieving both an improvement (reduction) in WI-NRS by ≥4 points from baseline to Week 24 and an IGA PN-S 0 or 1 score at Week 24 compared to placebo + SoC (38.7% versus 9.2%;

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p<0.0001).(11) Dupilumab was well tolerated in the LIBERTY PN PRIME study with 53 (70.7%) participants in the dupilumab + SoC group and 47 (62.7%) participants in the placebo + SoC group experienced at least 1 TEAE[1]. Treatment-emergent SAEs[2] were reported in 5 (6.7%) participants in the dupilumab + SoC group and 8 (10.7%) participants in the placebo + SoC group. Only 1 of these events in the placebo + SoC group was considered related to treatment by the Investigator (sepsis and mesenteritis)(12).

In PRIME2, statistically significant and clinically meaningful between-group differences were reached for the primary and key secondary efficacy endpoints. Dupilumab demonstrated a statistically significant and clinically meaningful improvement in itch control, as measured by the proportion of participants with an improvement in WI-NRS by ≥4 points from baseline to Week 12 compared to placebo (37.2% versus 22.0%; p=0.0216) and to Week 24 (57.7% versus 19.5%; p<0.0001). In addition, dupilumab treatment statistically significantly reduced the number of PN lesions, as measured by the proportion of participants with an IGA PN-S 0 ("clear") or 1 ("almost clear") score at Week 24 compared to placebo (44.9% versus 15.9%; p<0.0001). Dupilumab treatment also statistically significantly increased the proportion of participants achieving both an improvement in WI-NRS by ≥4 points from baseline to Week 24 and an IGA PN-S 0 or 1 score at Week 24 compared to placebo (32.1% versus 8.5%; p=0.0001).(11) Dupilumab was tolerated with 44 (57.1%) participants in the dupilumab group and 42 (51.2%) participants in the placebo + SoC group experienced at least 1 TEAE. Treatment-emergent SAEs were reported in 2 (2.6%) participants in the dupilumab group and 4 (4.9%) participants in the placebo + SoC group. None of these events was considered related to treatment by the Investigator(13).

The treatment efficacy and safety was confirmed in the pooled intention to treat (ITT) analysis, as the results demonstrated significant improvement in both primary endpoints of dupilumab + SoC versus placebo + SoC in improving the signs and symptoms of PN. Dupilumab was well tolerated and had a favourable safety profile in both studies and the pooled ITT safety analysis of participants with PN (14).

In order to evaluate the cost-effectiveness of implementing dupilumab as a standard treatment in Denmark for PN patients that are candidates for systemic treatment, a health economic model was developed with the objective of presenting the costs and outcomes associated with dupilumab as an add-on treatment and best supportive care (BSC). The excel model includes a decision tree for the 24 weeks of trial data followed by a Markov model with a cycle length of 12 weeks. In the initial decision tree patients with moderate to severe PN can be treated with either dupilumab plus BSC (dupilumab + BSC) or BSC alone. At the first assessment point at week 24, a clinical check is performed to determine response in both arms. Responders move to the "Response" branch of the decision tree and continue the current treatment while non-responders move to the "No response" branch and switch to BSC. Patients receiving BSC alone upon entering the model stay on BSC treatment regardless of response status. The patient population for the model was based on the cohorts included in the clinical trials: patients with PN who are inadequately controlled on topical prescription therapies or when those therapies are not advisable. The model considers a Danish restrictive societal perspective, consistent with the guidelines presented by the DMC (15). A lifetime horizon was selected to ensure the full impact of treatment in terms of cost and health outcomes are captured. A lifetime horizon of 50 years (i.e., up until patients reached the age of 100 years old) was applied in the base case. The treatment effectiveness was based on the pooled PRIME and PRIME2 data (14).

[redacted]

[1] TEAE: an adverse event which occurred during the treatment emergent period, defined as the period from the first IMP administration to the last IMP administration + 98 days.

[2] SAE: a serious adverse event, defined as any untoward medical occurrence that, at any dose: results in death, is life-threatening, requires inpatient hospitalisation or prolongation of existing hospitalisation, results in persistent disability/incapacity or is a congenital anomaly/birth defect.

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[redacted]

5. The patient population, the intervention and choice of comparator(s)

5.1 The medical condition and patient population

5.1.1 Prurigo nodularis – Definition and symptoms

PN is the most well-known subtype of chronic prurigo[3] and can persist for many years (2). PN is driven by neuronal sensitisation to itch and the development of an itch-scratch cycle (16). Continued itching and scratching result in the formation of nodular lesions (4). A hyperpigmented border is frequently observed around the outside of whitish or pink lesions (17). The occurrence and intensity of itch in PN are reported to be higher than in other skin diseases, including atopic dermatitis (AD) and urticaria (18).

Reported age of onset is highly variable, ranging from 3 years to 81 years with a mean of 45 years (18). Similarly, multiple studies have reported a wide range of duration of disease. The mean duration of disease has been reported in studies ranging from 3.8 ((standard deviation (SD) = 0.9) years while others have reported as high as 13.7 (SD = 13.6) years (5, 16, 19, 20).

Patients mostly present with one or more localised groups of lesions at disease onset, but over half of the cases will progress to generalised PN (3, 21). In some individuals, symptoms may be localised due to local underlying diseases, such as leg venous insufficiency or brachioradial pruritus (8). PN lesions are usually distributed symmetrically across areas that are easily scratched, such as the arms and legs, and 49% of patients have three to four affected areas (4, 18, 21).

Itching and scratching are the most commonly reported symptoms and can be continuous or sporadic (3). Other common symptoms include burning, stinging and tingling sensations, sleep disturbances and psychological distress (4) (3). Less commonly reported symptoms include changes in temperature (hot and cold) and prickling, sharp, stroking and electrical sensations. Compared to other dermatological diseases there is a larger impact on patients' quality of life (QoL) (5, 6). A study of 533 patients diagnosed with chronic prurigo (number of PN patients = 69) showed that nearly half (42%) of all patients indicate that QoL is often or always impacted by their disease and that PN has the highest impact on QoL (5). In addition, patients with PN have an increased likelihood of a large array of psychological co-morbidities such as anxiety (odds ratio (OR) = 1.93), schizophrenia (OR = 2.26), substance use (OR = 1.62) and self-harm (OR = 3.17) (6). A study reported the impact on PN patients´ QoL to be similar in severity to that of patients with other debilitating chronic conditions, such as stroke and chronic bronchitis(22).

[3] Chronic prurigo is a 'distinct disease' characterised by the key symptoms of 'chronic pruritus (≥6 weeks), history and/or signs of repeated scratching (e.g., excoriations and scars) and the localised or generalised presence of multiple pruriginous lesions (75%)'.

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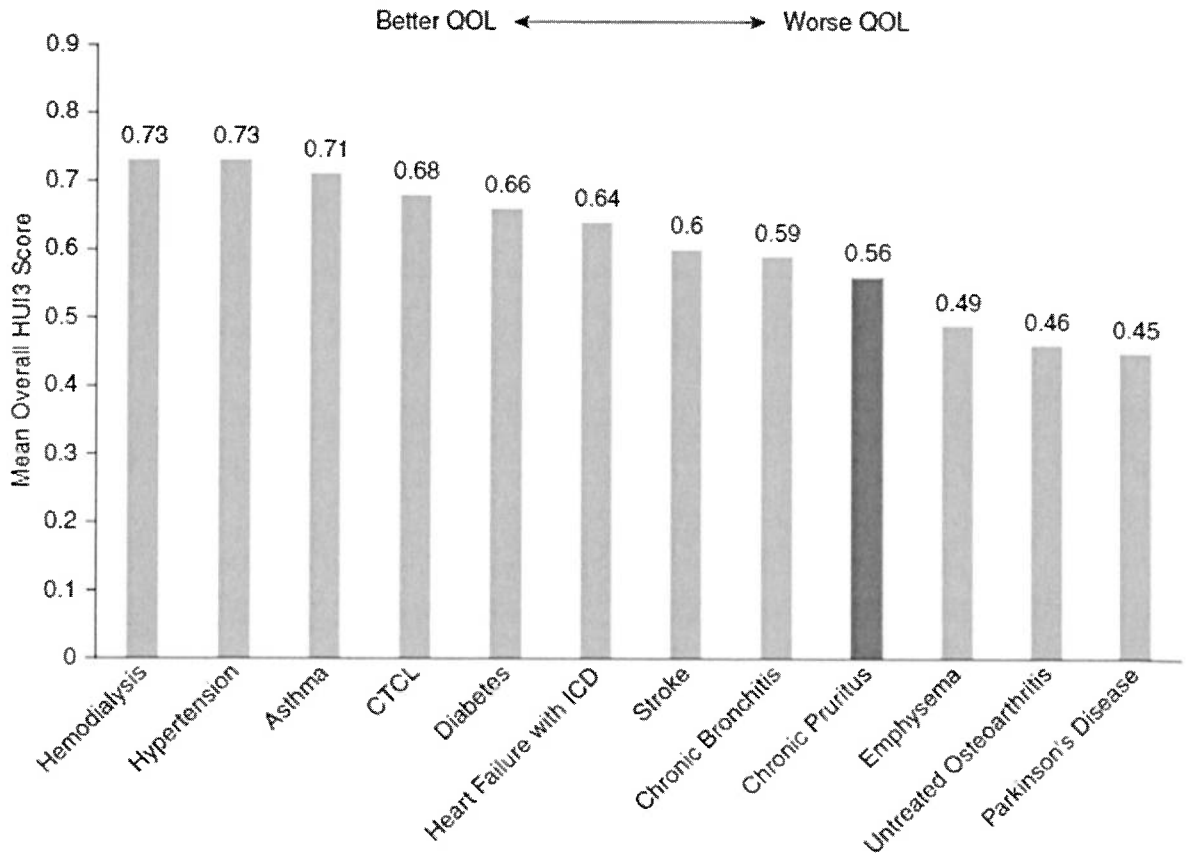
Figure 1 Mean overall HUI3 score (Whang et al. 2021(22))



5.1.2 Prurigo nodularis – Pathophysiology

While the pathophysiology of PN remains incompletely understood, several investigations have indicated that a combination of pro-inflammatory and pruritogenic molecules results in the release of neuropeptides, which contribute to inflammation and sensory dysfunction by activating immune cells (7, 23). PN is associated with an increase in the levels of T cells, mast cells, granulocytes, dendritic cells and eosinophils in the dermis. These cell types are also involved in the regulation of type 2 inflammation through release of tryptase, histamines, interleukins (IL) (including IL-31, IL-4 and IL-13) and prostaglandins (8, 9, 23).

Additionally, damage to the skin causes production of more cytokines from epithelial cells, including IL-25, IL-33 and thymic stromal lymphopoietin. These are key activators of type 2 inflammation and result in stimulation of the itch-sensory neurons that innervate the epidermis and are responsible for inducing a chronic itching sensation (23, 24). Inhibition of itch-sensory neurons through scratching, which activates pain-sensory fibres, can temporarily relieve itchy skin. However, persistent and repeated scratching in response to chronic itching results in development of an itch-scratch cycle (Figure 2) (25) where continued itching and scratching results in further production of cytokines and the formation of nodular lesions (23). A study by Oetjen et al. 2017 demonstrated that type 2 cytokines directly activate sensory neurons in both mice and humans, and that chronic itch is dependent on neuronal IL-4Rα and JAK1 signalling.(26)

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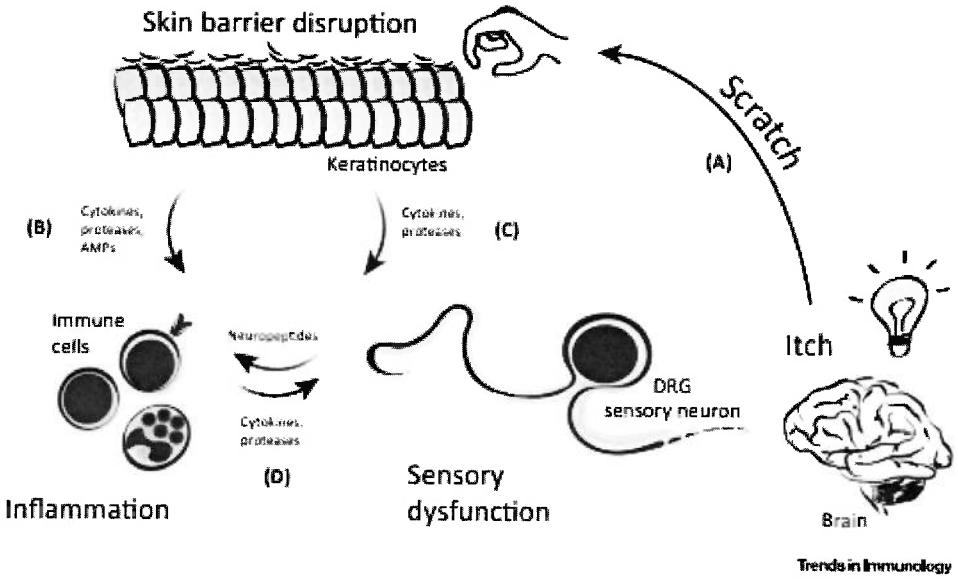
Figure 2: The Itch-Scratch Cycle



The majority of PN cases have mixed-origin underlying disease comprised of dermatologic, systemic and neurologic factors, and globally it is assumed approximately 50% of patients have an atopic disposition (2, 8, 27, 28). Up to 82% of all PN patients harbour other diseases, primarily dermatological conditions, such as AD, T cell lymphoma, lichen planus, xerosis cutis, keratoacanthomas and bullous pemphigoid (29). Systemic and metabolic aetiologies such as chronic kidney disease, liver disease, human immunodeficiency virus (HIV), thyroid disease, diabetes and malignancies are estimated to contribute to between 38% and 50% (29). Moreover, PN can arise from depression and anxiety as well as to neurological abnormalities, as an adverse effects of cancer therapies (specifically chemotherapy, carboplatin, paclitaxel and pembrolizumab) and following skin infections such as herpes zoster and tuberculosis (7, 29).

5.1.2.1 Grading

The number and size of lesions, which can range from a few to hundreds and from a few millimetres to 3 cm, respectively, are used to assess the extent of PN (8). One of several grading systems, based on an Investigator Global Assessment (IGA) scale[4], scores the extent of symptoms from 0 to 4 using a system depending on the number of present lesions (21):

Grade 0 (clear): no nodules (zero nodules)

Grade 1 (almost clear): rare, flattened lesions, with no more than five dome-shaped palpable nodules (one to five nodules)

Grade 2 (mild): few, mostly flattened lesions, with small number of dome-shaped palpable nodules (six to 19 nodules)

Grade 3 (moderate): many lesions, partially flattened and dome-shaped palpable nodules (20 to 100 nodules)

Grade 4 (severe): abundant lesions, majority are dome-shaped palpable nodules (>100 nodules)

[4] The IGA is a clinical reported outcome in which investigators assess disease severity and classify patients on a five-point scale ranging from 0 (clear) to 4 (severe). IGAs are also used to assess patients with AD and psoriasis. Criteria for each grade vary depending on the indication.

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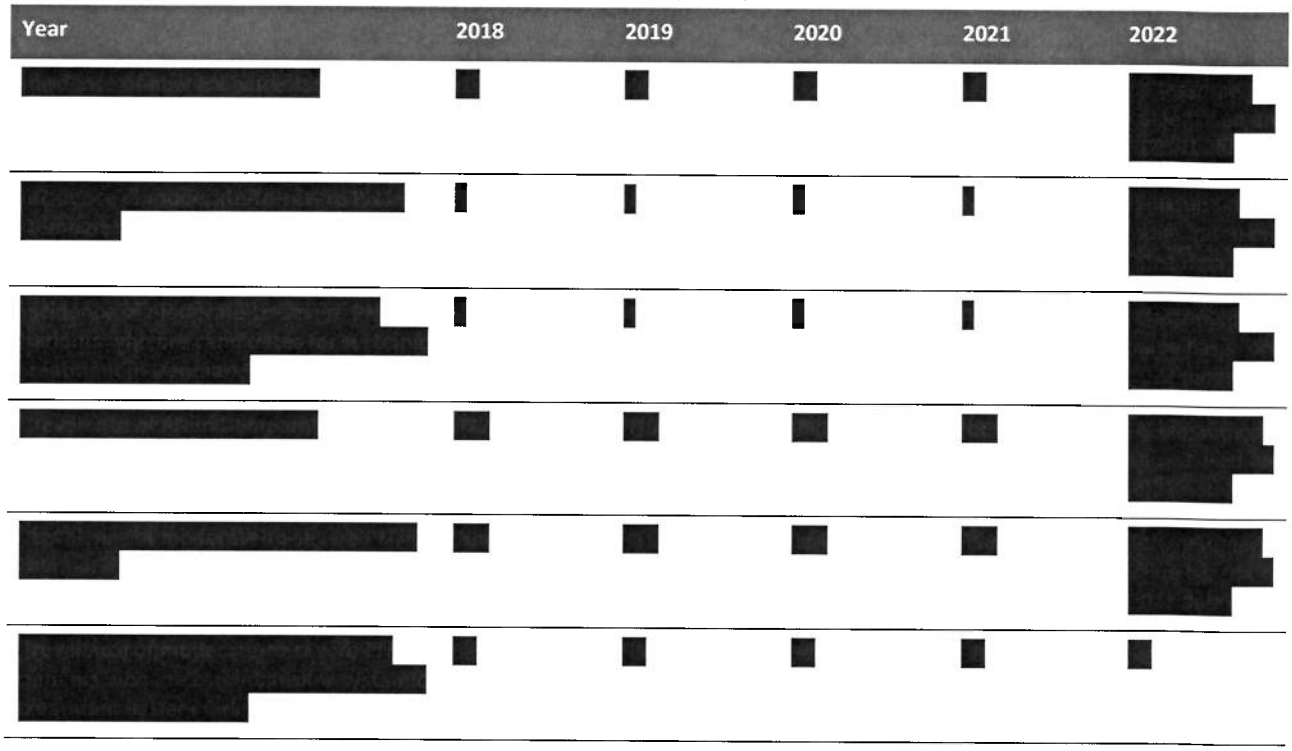
5.1.3 Prurigo nodularis – Incidence and prevalence in Denmark

There is limited epidemiological information on PN, but existing estimates suggest that PN affects a small population of patients (7, 8, 9). The incidence and prevalence of moderate to severe PN in Denmark are uncertain and therefore Sanofi Denmark has undertaken a retrospective database analysis of the national registries to identify patients in Denmark diagnosed with diagnosis code: DL281 (Prurigo Nodularis). The table below shows the results of this retrospective database analysis. Due to the rarity of the disease, it is the opinion of a Danish clinical expert that these patients are expected to include mild, moderate and severe grades of PN, and the Danish clinical expert estimated that 12% of the patients are in the moderate-to-severe group, while 50% of the moderate-to-severe patients are expected to be eligible for systemic therapy (30). The estimated patient numbers in Denmark are presented in Table 1.

Table 1: Incidence and prevalence of moderate to severe PN in the past 5 years



Abbreviations: KOL, key opinion leader; PN, prurigo nodularis
Footnote: [a] Incidence and prevalence of the Danish adult population diagnosed with PN are extracted from the Landspatientregisteret (LPR) database based on the diagnosis code DL281 (Prurigo Nodularis) based on guidance from a Danish clinical expert. Given feedback from the Danish clinical expert, this number includes PN patients regardless of their severity. However, there are potentially some PN patients who are not referred to the hospital. In addition, there are also some patients who have Chronic Prurigo and have been incorrectly coded. Due to lack of better available data, in this application we assume the vast majority of PN patients, regardless of their severity are referred to the hospital and thus the data represents the total incidence and prevalence of PN patients in Denmark. Despite the limitations and uncertainty of this data, the Danish clinical expert agrees this is the most appropriate data to include in this application
[b] Percentage of PN patients that are graded as moderate-to-severe is 12% based on feedback from a Sanofi Advisory board with Danish Clinical experts
[c] Percentage of moderate-to-severe PN patients eligible for systemic therapy is 50% % based on feedback from a Sanofi Advisory board with Danish Clinical experts and supported by a smaller Danish study (33)
Source: Danish clinical expert (31)

5.1.4 Patient populations relevant for this application

The Danish PN patient population expected to be candidates for treatment with dupilumab in combination with topical prescription therapy (e.g., low to medium potent topical corticosteroids and/or topical calcineurin inhibitors) are adult patients with moderate-to-severe PN who are candidates for systemic therapy.

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A large pan-European study shows that a proportion of patients diagnosed with PN present other atopic co-morbidities (32). Specifically, in Northern Europe (Sweden, Norway) 50% of patients in the cohort (45/90) had atopic eczema co-morbidity, as well as 22% of patients (20/91) were also diagnosed with asthma. Given these, the estimates in the table above are assumed to be a maximum number of patients, as some of these patients are potentially already treated or eligible for treatment with dupilumab.

In this application, it is estimated that 63 patients will be eligible for treatment with dupilumab for the indication in 2023, which is equal to the eligible prevalence from 2021 plus the eligible incidence from 2021 (Table 2).

Table 2: Estimated number of patients eligible for treatment

Year	2023	2024	2025	2026	2027
Number of patients in Denmark who are expected to use the pharmaceutical in the coming years	63	67	71	74	78

Footnote: The number of patients was calculated based on the eligible prevalence from 2021 plus 3.84 (rounded to 4 patients) incident patients based on 2021 eligible incident patients. Additional 3.84 incident patients were assumed per year. Total numbers were rounded to whole numbers.

Source: (33)

5.2 Current treatment options and choice of comparator(s)

5.2.1 Current treatment options

The multi-factorial aetiology of PN requires multi-modal treatment and long-term management, including both topical and systematic therapies, to achieve pruritic relief and healing of PN lesions (7, 34). However, no approved treatments for PN exist and there is a lack of evidence to support currently used off-label treatment regimens (7, 8, 9). The absence of approved, systematic therapies for PN, combined with a lack of evidence from RCTs and real-world data (RWD) to support decision-making, make successful treatment of PN challenging (7, 8, 9, 21, 27). In a large European study, 57% of physicians reported that they believe there is a need for new therapies to successfully treat patients with PN (25). In addition, another large European study found that 56.8% of patients were not satisfied with their existing treatment and 28.7% of patients did not consider any treatments to be effective (35).

There are currently no DMC or Danish-specific treatment guidelines or approved therapies specifically for PN. However, a proposed treatment algorithm for chronic prurigo, which includes PN, has been composed by an international expert group (21), including a Danish Clinical Expert. These guidelines recommend a patient-centred approach allowing the treating physician to identify the best treatment option from all levels of treatments to obtain optimal disease management, as illustrated in Figure 3. These recommendations are based on expert opinion and available RCT data.

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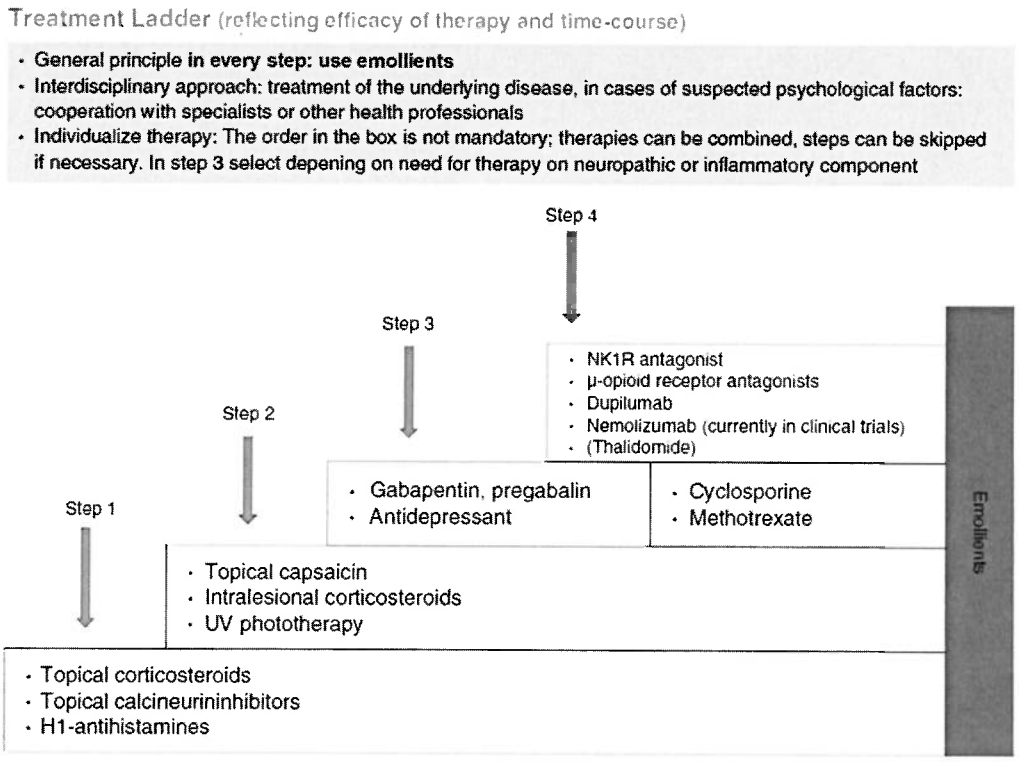
Figure 3 IFSI-guideline on chronic prurigo including prurigo nodularis treatment ladder (strong consensus).



A multi-modal treatment approach is recommended to control pruritus, treating the potential cause of pruritus and healing the pruriginous lesions (21). The use of emollients as supportive care is advised throughout the treatment course (34). The main therapeutic modalities recommended across the severity steps are (21):

- Topical therapies, including topical corticosteroids and calcineurin inhibitors
- Intralesional corticosteroids
- Ultraviolet (UV) phototherapy
- Systemic therapies, including immunosuppressants and antidepressant treatments

However, a combination of treatments across steps can be used and personalised therapeutic plans should be tailored to the patient's age, comorbidities, PN severity, quality-of-Life, treatment history and associated adverse events (7, 8, 9, 21, 34).

In some cases, the prescribed treatments are not effective, and patients, therefore, receive multiple therapies over the course of their disease (35). A smaller Danish study enrolled 52 adult PN patients with a mean disease duration of 11.6 (standard deviation (SD): 8.2) years. Over the course of disease, topical corticosteroids (94.2%), corticosteroids under occlusion (76.9%), intradermal corticosteroids (26.9%), zinc dressing (71.2%) and phototherapy (88.4%) were the most commonly used therapies (36). Under half of patients used systemic treatments (46.2%), with the most common being methotrexate (30.8%) and thalidomide (23.1%) (36).

5.2.2 Choice of comparator(s)

There is currently no EMA approved systemic therapy for moderate-to-severe PN patients. In addition, there is limited data on the safety and efficacy of the currently used off-labelled systematic therapies for PN patients. In Denmark a

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range of treatments are included within current SoC, such topical corticosteroids (94.2%), corticosteroids under occlusion (76.9%), intradermal corticosteroids (26.9%), zinc dressing (71.2%) and phototherapy (88.4%).

Given this, in this application the safety and efficacy of dupilumab in combination with SoC (moisturizers, low to medium potent topical corticosteroids and topical calcineurin inhibitors) will be compared to SoC.

5.2.3 Description of the comparator(s)

See below a description of relevant SoC treatments offered to patients. SoC treatment was recommended by a Danish clinical expert (30)

Table 3: Description of hydrocortisone

Subject	Description
Generic name (ATC-code)	Hydrocortisone (H02AB09)
Mode of action	The short-term effects of corticosteroids are decreased vasodilation and permeability of capillaries, as well as decreased leukocyte migration to sites of inflammation. Corticosteroids binding to the glucocorticoid receptor mediates changes in gene expression that lead to multiple downstream effects over hours to days. Glucocorticoids inhibit neutrophil apoptosis and demarginating; they inhibit phospholipase A2, which decreases the formation of arachidonic acid derivatives; they inhibit NF-Kappa B and other inflammatory transcription factors; they promote anti-inflammatory genes like interleukin-10. Lower doses of corticosteroids provide an anti-inflammatory effect, while higher doses are immunosuppressive. High doses of glucocorticoids for an extended period bind to the mineralocorticoid receptor, raising sodium levels and decreasing potassium levels.
Pharmaceutical form	Cream, ointment
Posology	Use sparingly over a small area twice daily. If the condition has not improved, or worsens, consult your doctor. Treatment should not be recommended for use on children under 10 years of age without medical advice.
Method of administration	For cutaneous use
Necessary monitoring, both during administration and during the treatment period	Efficacy should be evaluated by trained professional. If condition has not improved, or worsened, discontinuation should be considered
Should the pharmaceutical be administered with other medicines	Moisturizer
Treatment duration / Criteria for end of treatment:	To be applied twice daily Treatment should not be longer than 6 weeks. Contraindications: Rosacea Acne vulgaris Perioral dermatitis Bacterial (e.g., impetigo), viral (e.g., Herpes simplex) or fungal (e.g., candidal or dermatophyte) infections of the skin.
Need for diagnostic or other test	No additional diagnostics needed

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Subject	Description
Packaging	Cream: 10mg/g hydrocortisone (packs of 15g, 30g, 100g) Ointment: 10mg/g hydrocortisone (pack of 15g)

Source: (37, 38, 39)

Table 4: Description of hydrocortison-17-butyrat

Subject	Description
Generic name (ATC-code)	Hydrocortison-17-butyrat (D07AB02)
Mode of action	Hydrocortisone binds to the cytosolic glucocorticoid receptor. After binding the receptor, the newly formed receptor-ligand complex translocates itself into the cell nucleus, where it binds to many glucocorticoid response elements (GRE) in the promoter region of the target genes. The DNA bound receptor then interacts with basic transcription factors, causing the increase in expression of specific target genes. The anti-inflammatory actions of corticosteroids are thought to involve lipocortins, phospholipase A2 inhibitory proteins which, through inhibition arachidonic acid, control the biosynthesis of prostaglandins and leukotrienes. Specifically, glucocorticoids induce lipocortin-1 (annexin-1) synthesis, which then binds to cell membranes preventing the phospholipase A2 from coming into contact with its substrate arachidonic acid. This leads to diminished eicosanoid production. The cyclooxygenase (both COX-1 and COX-2) expression is also suppressed, potentiating the effect. In other words, the two main products in inflammation Prostaglandins and Leukotrienes are inhibited by the action of Glucocorticoids. Glucocorticoids also stimulate the lipocortin-1 escaping to the extracellular space, where it binds to the leukocyte membrane receptors and inhibits various inflammatory events: epithelial adhesion, emigration, chemotaxis, phagocytosis, respiratory burst and the release of various inflammatory mediators (lysosomal enzymes, cytokines, tissue plasminogen activator, chemokines etc.) from neutrophils, macrophages and mastocytes. Additionally, the immune system is suppressed by corticosteroids due to a decrease in the function of the lymphatic system, a reduction in immunoglobulin and complement concentrations, the precipitation of lymphocytopenia, and interference with antigen-antibody binding.
Pharmaceutical form	Cream, ointment
Posology	Adults and older people A thin and even layer should be applied to the affected area of the skin, 1 to 2 times daily. The same dose is used for adults and older people, as clinical evidence would indicate that no special dosage regimen is necessary in older people. Paediatric population Long term treatment, large amounts, and occlusion should be avoided. Infants Therapy should be limited to a maximum of seven days.
Method of administration	For cutaneous use
Necessary monitoring, both during administration and during the treatment period	Efficacy should be evaluated by trained professional. If condition has not improved, or worsened, discontinuation should be considered
Should the pharmaceutical be administered with other medicines	Moisturizer

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Subject	Description
Treatment duration / Criteria for end of treatment:	To be applied once-twice daily Treatment should not be longer than 6 weeks. For smaller kids and infants, treatment should be longer than 7 days. Contraindications: Rosacea Acne vulgaris Perioral dermatitis Bacterial (e.g., impetigo), viral (e.g., Herpes simplex) or fungal (e.g., candidal or dermatophyte) infections of the skin.
Need for diagnostic or other test	No additional diagnostics needed
Packaging	Cream: 0.1% hydrocortison-17-butyrat (packs of 30g, 90g, 100g, 120g) Ointment: 0.1% hydrocortison-17-butyrat (pack of 30g)

Source: (37, 38, 39)

Table 5: Description of betamethasone

Subject	Description
Generic name (ATC-code)	Betamethasone (D07XC01)
Mode of action	Glucocorticoids inhibit neutrophil apoptosis and demargination, and inhibit NF-Kappa B and other inflammatory transcription factors. They also inhibit phospholipase A2, leading to decreased formation of arachidonic acid derivatives.1 In addition, glucocorticoids promote anti-inflammatory genes like interleukin-10. Corticosteroids like betamethasone can act through nongenomic and genomic pathways. The genomic pathway is slower and occurs when glucocorticoids activate glucocorticoid receptors and initiate downstream effects that promote transcription of anti-inflammatory genes including phosphoenolpyruvate carboxykinase, IL-1-receptor antagonist, and tyrosine amino transferase On the other hand, the nongenomic pathway is able to elicit a quicker response by modulating T-cell, platelet and monocyte activity through the use of existing membrane-bound receptors and second messengers.
Pharmaceutical form	Cream
Posology	**Adults** • To be applied in a thin layer 1-2 times a day for no more than 4 weeks. • After each application, sufficient time should pass for the cream to be absorbed before application of other emollient. • In particularly resistant lesions, such as thickened plaque psoriasis on the elbows and knees, the effect of betamethasone can be increased, if necessary, by using an occlusive dressing.
Method of administration	For cutaneous use
Necessary monitoring, both during administration and	Efficacy should be evaluated by trained professional. If condition has not improved, or worsened, discontinuation should be considered.

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Subject	Description
during the treatment period	After improvement is established, the frequency of the treatment is reduced, or a less potent preparation is switched to. The treatment should not be extended for longer than absolutely necessary and should not be discontinued abruptly, as recurrence of the skin disorder may occur.
Should the pharmaceutical be administered with other medicines	Moisturizers.
Treatment duration / Criteria for end of treatment:	• 1-2 times a day for no more than 4 weeks. • If the condition worsens or does not improve within 2-4 weeks, the treatment and diagnosis must be reassessed.
Need for diagnostic or other test	No additional diagnostics needed
Packaging	Cream 1 mg/g (30g pack)

Source: (40, 41)

Table 6: Description of tacrolimus

Subject	Description
Generic name (ATC-code)	Tacrolimus (D11AH01)
Mode of action	The mechanism of action of tacrolimus in atopic dermatitis is not known. While the following have been observed, the clinical significance of these observations in atopic dermatitis is not known. It has been demonstrated that tacrolimus inhibits T-lymphocyte activation by first binding to an intracellular protein, FKBP-12. A complex of tacrolimus-FKBP-12, calcium, calmodulin, and calcineurin is then formed and the phosphatase activity of calcineurin is inhibited. This prevents the dephosphorylation and translocation of nuclear factor of activated T-cells (NF-AT), a nuclear component thought to initiate gene transcription for the formation of lymphokines. Tacrolimus also inhibits the transcription for genes which encode IL-3, IL-4, IL-5, GM-CSF, and TNF-, all of which are involved in the early stages of T-cell activation. Additionally, tacrolimus has been shown to inhibit the release of pre-formed mediators from skin mast cells and basophils, and to downregulate the expression of FceRI on Langerhans cells.
Pharmaceutical form	Ointment
Posology	Adults: Initially, ointment 0.1% is applied twice daily. If the clinical condition allows it, one should try to reduce the application frequency or use the strength 0.03%. Treatment should continue until the lesion is healed. Generally, improvement is seen within one week of starting treatment. Children over 2 years: Initially, ointment 0.03% is applied twice daily for 3 weeks, after which the frequency is reduced to once daily until the lesion is healed. Continued need is assessed by a doctor. Maintenance treatment: Ointment is applied once a day, twice a week. in case of eczema outbreaks, treatment should be reintroduced twice a day. After 12 months, the need for continued treatment is assessed by a doctor.
Method of administration	For cutaneous use

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Subject	Description
Necessary monitoring, both during administration and during the treatment period	Patients, particularly paediatric patients should be continuously evaluated during treatment with respect to the response to treatment and the continuing need for treatment
Should the pharmaceutical be administered with other medicines	Moisturizers
Treatment duration / Criteria for end of treatment:	Treatment should continue until the lesion is healed. Generally, improvement is seen within one week of starting treatment. If no signs of improvement are seen after two weeks of treatment, further or other treatment options should be considered.
Need for diagnostic or other test	No additional diagnostics needed
Packaging	Ointment 0.03% tacrolimus (pack of 30g) Ointment 0.1% tacrolimus (pack of 30g)

Source: (42, 43, 44)

Table 7: Description of zinc and light therapy (part of current SoC)

Subject	Description
Mode of action	Zinc bandages and light therapy are currently being used in clinical practice as SoC. Although not included in the clinical trial it is considered SoC in Denmark and Danish clinical expert maintained it was relevant to include in the economic analysis
Posology	Based on clinical expert input: Light treatment: 2-3 treatments/week, and 20-30 treatments/session. 1-2 sessions a year. Approx. 40-50% of patients receive light therapy. ZiNC bandages (Zipzoc or duoderm) - 1x week for 6-12 weeks – approx. 40% of patients. Average 1.5 session per year.

Source: (33)

5.3 The intervention

The characteristics of dupilumab are presented below in Table 8.

Table 8: Description of dupilumab

Subject	Description
Generic name (ATC-code)	Dupilumab (D11AH05)

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Subject	Description
Mode of action	Dupilumab is a recombinant human IgG4 monoclonal antibody that inhibits IL-4 and IL-13 signalling by specifically binding to the IL-4Rα subunit shared by the IL-4 and IL-13 receptor complexes. IL-4 and IL-13 are key type 2 cytokines involved in atopic disease (45, 46, 47). Type 2 inflammation plays an important role in the pathogenesis of multiple atopic conditions. IL-4 and IL-13 act as major drivers of type 2 inflammation by activating multiple cell types (e.g., mast cells, lymphocytes, eosinophils, neutrophils, macrophages) and inducing multiple mediators involved in type 2 inflammation. Blocking the IL-4/IL-13 pathway with dupilumab in patients decreases many of these markers of type 2 inflammation, including immunoglobulin E, periostin and multiple proinflammatory cytokines and chemokines. Blocking the IL-4/IL-13 pathway with dupilumab in humanised animal models has been shown to prevent the downstream actions of these cytokines and chemokines (45, 46, 47).
Pharmaceutical form	Injection solution in syringe/pen
Posology	Adult patients (18+ years) initial loading dose – 600mg Subsequent dose – 300mg every 2 weeks
Method of administration	Subcutaneous injection
Necessary monitoring, both during administration and during the treatment period	Dupilumab (Dupixent®) does not require additional monitoring.
Should the pharmaceutical be administered with other medicines	Dupilumab is indicated in combination with topical prescription therapy (e.g., moisturizers, low to medium potent topical corticosteroids and/or topical calcineurin inhibitors)
Treatment duration / Criteria for end of treatment:	Dupilumab is contraindicated in patients who have known hypersensitivity to dupilumab or any of its excipients [a] Consideration should be given to discontinuing treatment in patients who have shown no response after 16 weeks of treatment for atopic dermatitis. Some patients with initial partial response may subsequently improve with continued treatment beyond 16 weeks. If dupilumab treatment interruption becomes necessary, patients can still be successfully re-treated.
Need for diagnostic or other test	Dupilumab (Dupixent®) does not require initial lab testing or lab monitoring.
Packaging	200 mg dupilumab (Dupixent®) injection fluid in pen (2 per pack) 300 mg dupilumab (Dupixent®) injection fluid in pen (2 per pack) 200 mg dupilumab (Dupixent®) injection fluid in cannula (2 per pack) 300 mg dupilumab (Dupixent®) injection fluid in cannula (2 per pack)

Footnote: [a] arginine hydrochloride, histidine polysorbate 80 (E433), sodium acetate trihydrate, glacial acetic acid (E260), sucrose, water for injections.

Source: (10)

Dupilumab has received an EMA CHMP positive opinion recommending its use in treating adults with moderate-to-severe PN who are candidates for systemic therapy. With this approval, dupilumab is the first and only medicine specifically indicated to treat PN in the European Union (approved by the EMA). It is expected that dupilumab will enter the treatment algorithm as first systemic treatment of adults with moderate-to-severe PN who are candidates for systemic therapy.

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6. Literature search and identification of efficacy and safety studies

In accordance with the DMC guidance, if a head-to-head study with the relevant comparator for the indication in question for the application, the literature search can be omitted (48). There is currently no EMA approved systemic treatment for the indication. As such, SoC (moisturizers, low to medium potent topical corticosteroids, topical calcineurin inhibitors, light treatment and zinc bandages) is considered the relevant comparator in Danish clinical setting. Sanofi have conducted two similarly designed multicentre, randomised, double-blind, placebo-controlled, parallel group, 24-week-treatment phase 3 studies, LIBERTY-PN PRIME (49) and PRIME2 (50) (see 7.1.2.1 and 7.1.2.2).(11)

The evidence of the two studies (LIBERTY-PN PRIME and PRIME2) are considered to provide the best possible basis to inform the comparison of dupilumab + SoC with the relevant comparator in Danish clinical practice (SoC) for adults with moderate-to-severe PN who are candidates for systemic therapy.

Table 9: Relevant studies included in the assessment

Reference (title, author, journal, year)	Trial name	NCT number	Dates of study (start and expected completion date)	Used in comparison of
Dupilumab in patients with prurigo nodularis: two randomized, double-blind, placebo-controlled phase 3 trials, Yosipovitch, Nat Med, 2023(11, 49)	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	Start: December 12, 2019 End: November 12, 2021	Dupilumab + SoC vs. SoC for adults with moderate-to-severe prurigo nodularis who are candidates for systemic therapy.
Dupilumab in patients with prurigo nodularis: two randomized, double-blind, placebo-controlled phase 3 trials, Yosipovitch, Nat Med, 2023(11, 50)	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	Start: January 16, 2020 End: August 30, 2021	Dupilumab + SoC vs. SoC for adults with moderate-to-severe prurigo nodularis who are candidates for systemic therapy.

For detailed information about included studies, refer to appendix B.

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7. Efficacy and safety

7.1 Efficacy and safety of dupilumab + SoC compared to placebo + SoC for adults with moderate-to-severe prurigo nodularis who are candidates for systemic therapy

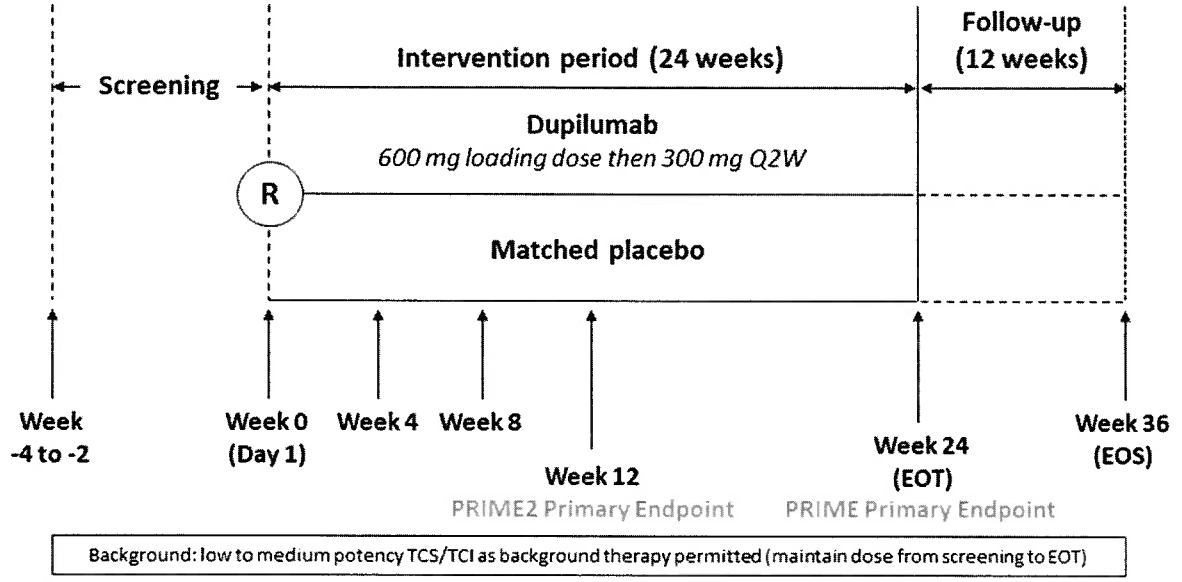
7.1.1 Relevant studies

The efficacy and safety of dupilumab in patients with PN who are inadequately controlled on topical therapies or when those therapies are not advised, have been evaluated in two similarly designed multicentre, randomised, double-blind, placebo-controlled, parallel group, 24-week-treatment phase 3 studies (N=311 overall) conducted in multiple locations in Europe, North and Latin America and Asia (49, 50).(11)

The two studies have similar designs, but the primary endpoint (proportion of patients with WI-NRS improvement (reduction) by ≥4 points from baseline) was measured at Week 24 in LIBERTY-PN PRIME and at Week 12 in PRIME2 (12, 13). During the course of the two studies, the results from PRIME2 became available while LIBERTY-PN PRIME was still blinded, indicating that the treatment effect of dupilumab increased beyond Week 12. Consequently, the LIBERTY-PN PRIME study protocol was updated to include assessment of WI-NRS improvement ≥4 from baseline at Week 24 as its primary endpoint.(11)

The LIBERTY-PN PRIME and PRIME2 studies included a screening period (2 to 4 weeks), a 24-week treatment period and a 12-week post-treatment follow-up period. Patients were randomised (1:1) to receive an initial loading dose of 600 mg of dupilumab subcutaneously at Day 1 or placebo followed by 300 mg of dupilumab subcutaneously once Q2W or placebo Q2W until Week 24 (Figure 1). The application of emollients once or twice daily were required for patients in both study groups for at least 5 days during the week before the start of the intervention period and continuously until the end of the study (Week 36). Patients on low- to medium- potency TCS or TCI were allowed to continue their stable regimen throughout the study treatment period, while those on high-potency or super-potent TCS were required to decrease their regimen to medium potency. Randomization was also done on stable use of TCS/TCI, to ensure same level of stable users in the two treatment arms.(11)

Figure 1 Study design for LIBERTY-PN PRIME and PRIME2



Note: Patients in both study groups were allowed to continue the use of low to medium potency TCS/TCI on stable regime without change from screening to EOT.

Abbreviations: EOT, end of treatment; EOS, end of study; TCI, topical calcineurin inhibitors; TCS, topical corticosteroids; Q2W, every 2 weeks.

Source: (12, 13)

7.1.2 Efficacy and safety – results per study

7.1.2.1 LIBERTY-PN PRIME

7.1.2.1.1 Efficacy

Statistically significant and clinically meaningful between-group differences were reached for the primary and key secondary endpoints in this study. Dupilumab + SoC treatment demonstrated a statistically significant and clinically meaningful improvement in itch control, as measured by the proportion of participants with an improvement (reduction) in WI-NRS by ≥4 points from baseline to Week 24 compared to placebo + SoC (60.0% versus 18.4%; p<0.0001). In addition, dupilumab + SoC treatment statistically significantly reduced the number of PN lesions, as measured by the proportion of participants with an IGA PN-S 0 ("clear") or 1 ("almost clear") score at Week 24 compared to placebo + SoC (48.0% versus 18.4%; p=0.0004). Dupilumab treatment also statistically significantly increased the proportion of participants achieving both an improvement (reduction) in WI-NRS by ≥4 points from baseline to Week 24 and an IGA PN-S 0 or 1 score at Week 24 compared to placebo + SoC (38.7% versus 9.2%; p<0.0001) (Table 10). Treatment with dupilumab significantly increased patient health related quality of life (HRQoL), DLQI decrease from baseline at Week 12 and Week 24 (Table 12).(11)

Table 10: Summary of the primary and key secondary endpoints – ITT population

Parameter	Dupilumab + SoC (N=75)	Placebo + SoC (N=76)	Difference (95% CI) Dupilumab vs. Placebo	Odds ratio (95% CI)	p-value
Primary endpoint					
Proportion of participants with WI-NRS improvement (reduction) by ≥4 points from baseline to Week 24	45 (60.0%)	14 (18.4%)	42.7% (27.76%: 57.72%)	6.5 (2.78: 15.41)	<0.0001
Key secondary endpoint					
Proportion of participants with IGA PN-S 0 or 1 score at Week 24	36 (48.0%)	14 (18.4%)	28.3% (13.41%: 43.16)	4.0 (1.81: 8.98)	0.0004
Proportion of participants with both an improvement (reduction) in WI-NRS by ≥4 points from baseline to Week 24 and an IGA PN-S 0 or 1 score at Week 24	29 (38.7%)	7 (9.2%)	29.6% (16.42%: 42.81%)	6.9 (2.49: 19.05)	<0.0001

The mean (SD) IGA PN-S scores at baseline were 3.28 (0.45) in the dupilumab group and 3.29 (0.46) in the placebo group. A greater decrease (improvement) in IGA PN-S score was observed in the dupilumab group as compared to the placebo group as early as Week 4. The LS mean (SE) change from baseline in IGA PN-S at Week 4 was -0.44 (0.10) in the dupilumab group versus -0.15 (0.10) in the placebo group (LS mean difference versus placebo: -0.29 [95% CI: -0.50, -0.08]; nominal p=0.0059). This difference between the 2 intervention groups progressively increased throughout the remainder of the 24-week intervention period (nominal p<0.05 at all subsequent measurements through Week 24).(11)

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Table 11 Change and percent change from baseline in IGA-PN from the PRIME study

				Change difference for dupilumab vs. placebo			% Change difference for dupilumab vs. placebo		
Timepoint and intervention	n	Baseline mean (SD)	Post-baseline mean (SD)	Change from baseline LS mean (SE)	LS mean (95% CI)	p-value	% Change from baseline LS mean (SE)	LS mean (95% CI)	p-value
Week 4									
Dupilumab 300 mg Q2W (N=75)	74	3.28 (0.45)	2.82 (0.80)	-0.44 (0.10)	-0.29 (-0.50, -0.08)	0.0059	-13.03 (3.11)	-8.97 (-15.34, -2.60)	0.0058
Placebo (N=76)	70	3.29 (0.46)	3.16 (0.61)	-0.15 (0.10)			-4.06 (3.13)		
Week 8									
Dupilumab 300 mg Q2W (N=75)	72	3.28 (0.45)	2.43 (1.02)	-0.79 (0.13)	-0.51 (-0.77, -0.24)	0.0002	-24.14 (3.97)	-15.83 (-24.12, -7.54)	0.0002
Placebo (N=76)	72	3.29 (0.46)	2.99 (0.76)	-0.29 (0.13)			-8.31 (4.01)		
Week 12									
Dupilumab 300 mg Q2W (N=75)	75	3.28 (0.45)	2.15 (1.15)	-1.13 (0.15)	-0.61 (-0.92, -0.30)	0.0001	-34.44 (4.53)	-18.40 (-27.82, -8.98)	0.0001
Placebo (N=76)	74	3.29 (0.46)	2.78 (0.93)	-0.52 (0.15)			-16.04 (4.57)		
Week 24									
Dupilumab 300 mg Q2W (N=75)	75	3.28 (0.45)	1.67 (1.22)	-1.59 (0.17)	-0.97 (-1.32, -0.62)	<.0001	-48.53 (5.21)	-28.68 (-39.44, -17.92)	<.0001
Placebo (N=76)	69	3.29 (0.46)	2.67 (1.11)	-0.62 (0.17)			-19.85 (5.33)		

LS: least squares; WOCF: worst observation carried forward; MI: multiple imputation. Each of the imputed complete data were analysed by fitting an ANCOVA model with the corresponding baseline value, intervention group, documented history of atopy (atopic or non-atopic), stable use of TCS/TCI (yes or no), region and baseline anti-depressant use (yes or no) as covariates. Note: Data collected after study intervention discontinuation were included. Data post the select prohibited medications/procedures and/or rescue medications that impacted efficacy were set to missing and imputed by WOCF. Missing data after study intervention discontinuation for lack of efficacy were imputed by WOCF, and other missing data were imputed by MI. Descriptive statistics at each visit include participants after WOCF at the visit, and participants whose values were imputed by MI at the visit were excluded from the descriptive analysis.

Table 12: Summary of the quality-of-life endpoints – ITT population (PRIME)

Parameter	Dupilumab + SoC (N=75)	Placebo + SoC (N=76)	Difference (95% CI) Dupilumab vs. Placebo	p-value
Quality-of-life endpoints				
Change in DLQI from baseline at Week 24	-11.97 (1.02)	-5.77 (1.05)	-6.19 (-8.34, -4.05)	<0.0001
Change in DLQI from baseline at Week 12	-10.95 (0.89)	-5.67 (0.90)	-5.27 (-7.13, -3.41)	0.0004

7.1.2.1.2 Safety

Dupilumab was well tolerated and had a favourable safety profile in this study of participants with PN. Overall, 53 (70.7%) participants in the dupilumab + SoC group and 47 (62.7%) participants in the placebo + SoC group experienced at least 1 TEAE[5].

Treatment-emergent SAEs[6] were reported in 5 (6.7%) participants in the dupilumab + SoC group and 8 (10.7%) participants in the placebo + SoC group. Only 1 of these events in the placebo + SoC group was considered related to treatment by the Investigator (sepsis and mesenteritis). No participant died during the study. The overall study intervention discontinuation rate due to TEAEs was low in both intervention groups (0 participants in the dupilumab + SoC group and 3 [4.0%] participants in the placebo + SoC group). (Table 13)

Table 13: Summary of safety – ITT population

	Dupilumab + SoC, N=75 n (%)	Placebo + SoC, N=75 n (%)
TEAEs	53 (70.7)	47 (62.7)
Treatment-related TEAEs	11 (14.7)	10 (13.3)
Serious TEAEs	5 (6.7)	8 (10.7)
Discontinuation	0 (0)	3 (4)
Treatment-related discontinuation	0 (0)	0 (0)

7.1.2.2 PRIME2

7.1.2.2.1 Efficacy

Statistically significant and clinically meaningful between-group differences were reached for the primary and key secondary efficacy endpoints in this study. Dupilumab treatment demonstrated a statistically significant and clinically

[5] TEAE: an adverse event which occurred during the treatment emergent period, defined as the period from the first IMP administration to the last IMP administration + 98 days.

[6] SAE: a serious adverse event, defined as any untoward medical occurrence that, at any dose: results in death, is life-threatening, requires inpatient hospitalisation or prolongation of existing hospitalisation, results in persistent disability/incapacity or is a congenital anomaly/birth defect.

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meaningful improvement in itch control, as measured by the proportion of participants with an improvement in WI-NRS by ≥4 points from baseline to Week 12 compared to placebo (37.2% versus 22.0%; p=0.0216) and to Week 24 (57.7% versus 19.5%; p<0.0001). In addition, dupilumab treatment statistically significantly reduced the number of PN lesions, as measured by the proportion of participants with an IGA PN-S 0 ("clear") or 1 ("almost clear") score at Week 24 compared to placebo (44.9% versus 15.9%; p<0.0001). Dupilumab treatment also statistically significantly increased the proportion of participants achieving both an improvement in WI-NRS by ≥4 points from baseline to Week 24 and an IGA PN-S 0 or 1 score at Week 24 compared to placebo (32.1% versus 8.5%; p=0.0001) (Table 14). Treatment with dupilumab significantly increased patient health related quality of life (HRQoL), DLQI decrease from baseline at Week 12 and Week 24 (Table 16).(11)

Table 14: Summary of the primary and key secondary endpoints – ITT population

Parameter	Dupilumab + SoC (N=78)	Placebo + SoC (N=82)	Difference (95% CI) Dupilumab + SoC vs. Placebo + SoC	Odds ratio (95% CI)	p-value
Primary endpoint					
Proportion of participants with WI-NRS improvement (reduction) by ≥4 points from baseline to Week 12	29 (37.2%)	18 (22.0%)	16.8% (2.34%, 31.16%)	2.3 (1.08, 5.00)	0.0216
Key secondary endpoints					
Proportion of participants with WI-NRS improvement (reduction) by ≥4 points from baseline to Week 24	45 (57.7%)	16 (19.5%)	42.6% (29.06%, 56.08%)	9.0 (3.56, 22.66)	<0.0001
Proportion of participants with IGA PN-S 0 or 1 score at Week 24	35 (44.9%)	13 (15.9%)	30.8% (16.37%, 45.22%)	4.4 (2.02, 9.55)	<0.0001
Proportion of participants with both an improvement (reduction) in WI-NRS by ≥4 points from baseline to Week 24 and an IGA PN-S 0 or 1 score at Week 24	25 (32.1%)	7 (8.5%)	25.5% (13.09%, 37.86%)	6.1 (2.03, 18.11)	0.0001

The mean (SD) IGA PN-S scores at baseline were 3.37 (0.49) in the dupilumab group and 3.40 (0.49) in the placebo group. A greater decrease (improvement) in IGA PN-S score was observed in the dupilumab group as compared to the placebo group as early as Week 8. The LS mean (SD) change from baseline in IGA PN-S at Week 8 was -1.19 (0.17) in the dupilumab group versus -0.79 (0.17) in the placebo group (LS mean difference versus placebo: -0.40 [95% CI: -0.69, -0.11]; nominal p=0.0073). This difference between the 2 intervention groups progressively increased throughout the remainder of the 24-week intervention period (nominal p<0.05 at all subsequent measurements through Week 24).(11)

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Table 15 Change and percent change from baseline in IGA-PN from the PRIME2 study

				Change difference for dupilumab vs. placebo			% Change difference for dupilumab vs. placebo		
Timepoint and intervention	n	Baseline mean (SD)	Post-baseline mean (SD)	Change from baseline LS mean (SE)	LS mean (95% CI)	p-value	% Change from baseline LS mean (SE)	LS mean (95% CI)	p-value
Week 4									
[redacted]									
Week 12									
Dupilumab 300 mg Q2W (N=78)	77	3.37 (0.49)	2.22 (1.05)	-1.47 (0.18)	-0.61 (-0.92, -0.30)	<.0001	-44.37 (5.54)	-18.81 (-28.06, -9.56)	<.0001
Placebo (N=82)	78	3.40 (0.49)	2.82 (1.03)	-0.86 (0.18)			-25.57 (5.35)		
Week 24									
Dupilumab 300 mg Q2W (N=78)	77	3.37 (0.49)	1.74 (1.12)	-2.03 (0.20)	-0.97 (-1.30, -0.63)	<.0001	-60.69 (6.02)	-28.42 (-38.57, -18.27)	<.0001
Placebo (N=82)	74	3.40 (0.49)	2.72 (1.12)	-1.07 (0.20)			-32.27 (5.94)		

LS: least squares; WOCF: worst observation carried forward; MI: multiple imputation. Each of the imputed complete data were analysed by fitting an ANCOVA model with the corresponding baseline value, intervention group, documented history of atopy (atopic or non-atopic), stable use of TCS/TCI (yes or no), region and baseline anti-depressant use (yes or no) as covariates. Note: Data collected after study intervention discontinuation were included. Data post the select prohibited medications/procedures and/or rescue medications that impacted efficacy were set to missing and imputed by WOCF. Missing data after study intervention discontinuation for lack of efficacy were imputed by WOCF, and other missing data were imputed by MI. Descriptive statistics at each visit include participants after WOCF at the visit, and participants whose values were imputed by MI at the visit were excluded from the descriptive analysis.

Table 16: Summary of the quality-of-life endpoints – ITT population (PRIME-2)

Parameter	Dupilumab + SoC (N=75)	Placebo + SoC (N=76)	Difference (95% CI) Dupilumab vs. Placebo	p-value
Quality-of-life endpoints				
Change in DLQI from baseline at Week 24	-13.16 (1.21)	-6.77 (1.18)	-6.39 (-8.42, -4.36)	<0.0001
Change in DLQI from baseline at Week 12	-12.07 (1.16)	-7.05 (1.12)	-5.02 (-6.96, -3.09)	<0.0001

7.1.2.2.2 Safety

Dupilumab was well tolerated and had a favourable safety profile in this study of participants with PN.

Overall, 44 (57.1%) participants in the dupilumab group and 42 (51.2%) participants in the placebo + SoC group experienced at least 1 TEAE. Treatment-emergent SAEs were reported in 2 (2.6%) participants in the dupilumab group and 4 (4.9%) participants in the placebo + SoC group. None of these events was considered related to treatment by the Investigator. No participants died during this study. (Table 17)

Table 17: Summary of safety – ITT population

	Dupilumab + SoC N=77 n (%)	Placebo + SoC N=82 n (%)
TEAEs	44 (57.1)	42 (51.2)
Treatment-related TEAEs	15 (19.5)	11 (13.4)
Serious TEAEs	2 (2.6)	4 (4.9)
Discontinuation	0 (0)	1 (1.2)
Treatment-related discontinuation	0 (0)	0 (0)

7.1.3 Comparative analyses of efficacy and safety

Efficacy and safety results from the individual pivotal LIBERTY-PN PRIME and PRIME2 studies were further evaluated in a combined prespecified analysis (pooled ITT analysis).

7.1.3.1 Method of synthesis

For the primary endpoint and binary secondary endpoints assessments, the Cochran–Mantel–Haenszel (CHM) test was used, adjusted for randomisation strata (documented history of atopy, stable use of TCS/TCI, and region) and baseline antidepressant use. Non-responders were considered patients receiving rescue treatment or with missing values. Time to first WI-NRS improvement was analysed using a Cox proportional hazards model, which included treatment, stratification factors, and baseline antidepressant use. Continuous secondary endpoints were analysed using an analysis of covariance (ANCOVA) model; efficacy data after rescue treatment were set to missing and imputed by worst-observation carried forward (WOCF). Missing data after treatment discontinuation for lack of efficacy were imputed by WOCF, and other missing data were imputed by multiple imputation.

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A hierarchical testing procedure was used to control the overall type-1 error rate at 0.05 for the primary, key secondary, and selected other endpoints for dupilumab versus placebo.

7.1.3.2 Results from the comparative analysis

7.1.3.2.1 Pooled ITT participants

7.1.3.2.1.1 Efficacy

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

The proportion of patients in the pooled ITT analysis with WI-NRS improvement by ≥4 points was significantly higher in the dupilumab + SoC group compared to the placebo + SoC group both from baseline at Week 12 (40.5% vs. 19%, p<0.0001) and from baseline at Week 24 (58.8% vs. 19%, p<0.0001; Table 18) (51).

Similarly, a significant reduction in PN lesions was reported in terms of proportion of patients with IGA PN-S score of 0 or 1 at Week 24 in the dupilumab + SoC group compared to the placebo + SoC group for the ITT pooled analysis (46.4% vs. 17.1%, p<0.0001) (Table 18) (12, 13, 51).

In addition, the proportion of patients with concurrent reduction in WI-NRS and skin lesions at Week 24 was statistically significant in the pooled dupilumab + SoC group compared to the pooled placebo + SoC group (35.3% vs. 8.9%, p<0.0001) (Table 18) (12, 13, 51).

Table 18: Primary and key secondary efficacy endpoints – ITT population from pooled ITT analysis

	Dupilumab + SoC (N=153)	Placebo + SoC (N=158)	OR, (95% CI) [a] Dupilumab + SoC vs. placebo SoC	p value[b] Dupilumab + SoC vs. placebo SoC	RRD (%), (95% CI) [a] Dupilumab + SoC vs. placebo SoC
Patients with WI-NRS improvement (reduction) by ≥4 points from baseline at Week 24 (Primary endpoint for LIBERTY-PN PRIME/ Key secondary endpoint for PRIME2)					
Responders, n (%)	90 (58.8)	30 (19.0)	7.6 (4.03, 14.24)	<0.0001	42.7 (32.60, 52.71)
Patients with WI-NRS improvement (reduction) by ≥4 points from baseline at Week 12 (Primary endpoint for PRIME2)					
Responders, n (%)	62 (40.5)	30 (19.0)	3.1 (1.77, 5.43)	<0.0001	22.7 (12.40, 33.08)
Patients with IGA PN-S 0 or 1 at Week 24 (Key secondary endpoint)					
Responders, n (%)	71 (46.4)	27 (17.1)	4.2 (2.42, 7.37)	<0.0001	29.6 (19.22, 39.94)
Patients with both an improvement (reduction) in WI-NRS by ≥4 points and IGA PN-S score of 0 or 1 at Week 24 (Key secondary endpoint)					
Responders, n (%)	54 (35.3)	14 (8.9)	6.5 (3.05, 13.67)	<0.0001	27.5 (18.43, 36.51)

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Note: A low score indicates good outcome for WI-NRS (range 0-10) and IGA PN-S (range 0-4).

Footnote: [a] Derived from the Mantel-Haenszel estimator.

[b] Cochran-Mantel Haenszel test was performed on the association between the responder status and intervention group, adjusted by documented history of atopy (atopic or non-atopic), stable use of TCS/TCI (yes or no), region and baseline anti-depressant use (yes or no). In addition, the pooled analysis was also adjusted by study indicator (LIBERTY-PN PRIME or PRIME2).

Abbreviations: CI, confidence interval; IGA PN-S, Investigator's Global Assessment 0 or 1 score for PN-Stage; ITT, intent-to-treat; OR, odds ratio; RRD, response rate difference; TCI, topical calcineurin inhibitors; TCS, topical corticosteroids; WI-NRS, worst-itch numeric rating scale.

Sources: (12, 13)

7.1.3.2.1.2 Safety

The pooled analysis of safety outcomes for dupilumab in patients with PN includes data from all treated patients in LIBERTY-PN PRIME and PRIME2 at the primary cut-off dates for these studies (12 November 2021 and 30 August 2021, respectively) (52). All safety analyses were descriptive and performed on the safety population, defined as all patients who received at least one dose of study intervention and analysed according to the intervention actually received (12, 13).

Dupilumab was well tolerated and had a favourable safety profile in patients with PN (Table 19) (52).
The safety of dupilumab observed in LIBERTY-PN PRIME and PRIME2 was consistent with the established safety profile of dupilumab in other indications (53).

In the pooled safety analysis, 97 (63.8%) patients in the dupilumab + SoC group and 89 (56.7%) patients in the placebo + SoC group experienced ≥1 TEAE (52). The majority of TEAEs were mild or moderate in intensity (46). Severe TEAEs[7] were reported in five (3.3%) patients in the dupilumab + SoC group and nine (5.7%) patients in the placebo + SoC group. Treatment-emergent SAEs were reported in seven (4.6%) patients in the dupilumab + SoC group and 12 (7.6%) patients in the placebo + SoC group (52). The proportion of patients reporting ≥1 TEAE, severe TEAEs and treatment-emergent SAEs in both treatment groups were numerically higher in LIBERTY-PN PRIME than in PRIME2 (12, 51).

The number of TEAEs considered by investigators to be treatment-related in the pooled safety analysis was 26 (17.1%) in the dupilumab + SoC group compared to 21 (13.4%) the placebo + SoC group (13). No patients in the dupilumab + SoC group and four (2.5%) patients in the placebo + SoC group discontinued treatment due to TEAEs (52). One (0.7%) patient in the dupilumab + SoC group and two (1.3%) patients in the placebo + SoC group experienced a treatment-related adverse event of special interest (AESI; systemic hypersensitivity reaction) (52). No patients in either treatment group died during the study (52).

While the exposure-adjusted rates of TEAEs were higher in the dupilumab + SoC group than in the placebo + SoC group in the pooled safety analysis and both individual studies, the exposure-adjusted rates of treatment-emergent SAEs were higher in the placebo + SoC group than in the dupilumab group (12, 13, 52). The exposure-adjusted rates of TEAEs and treatment-emergent SAEs were higher in LIBERTY-PN PRIME than in PRIME2 (12, 13).

Table 19: Safety summary – safety population pooled safety analysis

	Placebo + SoC (N=157)	Dupilumab + SoC (N=152)
Any TEAE, n (%)	89 (56.7)	97 (63.8)
Exposure-adjusted incidence rates of TEAEs, n with at least one event per 100 patient-years	172.9	183.9
Severe TEAE, n (%)	9 (5.7)	5 (3.3)

[7] Severe TEAE: a TEAE that prevents normal everyday activities ('severe' is used to rate the intensity of an event and should not be confused with 'serious').

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Treatment-emergent SAE, n (%)	12 (7.6)	7 (4.6)
Exposure-adjusted incidence rate of treatment-emergent SAEs, n with at least one event per 100 patient-years	13.8	7.2
TEAE leading to death, n (%)	0	0
TEAE leading to permanent treatment discontinuation, n (%)	4 (2.5)	0
Treatment-emergent AESI, n (%)	2 (1.3)	1 (0.7)
Treatment-emergent other selected AE, n (%)	18 (11.5)	16 (10.5)
Exposure-adjusted incidence rate treatment-emergent other selected AESIs, n with at least one event per 100 patient-years	NR	NR
Treatment-related TEAE, n (%)	21 (13.4)	26 (17.1)

Abbreviations: AE, adverse event; AESI, Adverse event of special interest; SAE, Serious adverse event; TEAE, Treatment emergent adverse event.

Sources: (12, 13)

Table 20: Safety summary – TEAEs reported in ≥2% in either treatment group – pooled safety analysis

Primary system organ class Preferred term, n (%)	Placebo (N=157)	Dupilumab (N=152)	Dupilumab vs. placebo RR (95% CI)
[redacted]			

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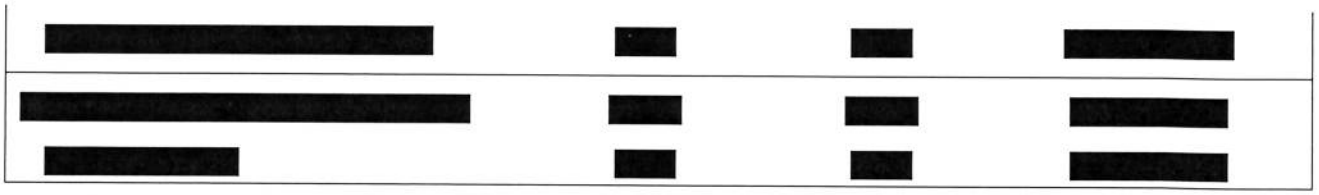

Sources: (52)

7.1.3.2.1.3 HRQoL

A post-hoc analysis of patient-reported outcome (PRO) pooled data from LIBERTY-PN PRIME and PRIME2 showed that the most impacted EQ-5D-5L dimensions at baseline were pain/discomfort and anxiety/depression. The percentage of patients reporting severe/extreme problems was 35% and 12%, respectively (Table 21).

At week 12 and week 24, a higher percentage of patients in the dupilumab + SoC group compared to the placebo + SoC group reported improvement for the EQ-5D-5L Pain/Discomfort dimension (59.9% vs. 44.4% and 60.5% vs. 36.8%, respectively) and for the EQ-5D-5L Anxiety/Depression dimension (32.9% vs. 20.9% and 38.2% vs. 19.4%; Table 21).

Table 21: Percentage improvement of all EQ-5D-5L dimensions assessed from baseline at Week 12 and Week 24 – Pooled ITT analysis

Most impacted dimensions at baseline (patients with severe/extreme problems)		% of patients reporting ≥1 category improvement			
		Week 12		Week 24	
Dimensions [a]	% patients overall	Dupilumab + SoC (%) (N=152)	Placebo + SoC (%) (N=153)	Dupilumab + SoC (%) (N=152)	Placebo + SoC (%) (N=144)
Pain/ Discomfort	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Anxiety/ Depression	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mobility	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Selfcare	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Usual activities	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Footnote: Data collected after study intervention discontinuation were included. Data post the select prohibited medications/procedures and/or rescue medications that impacted efficacy were set to missing and imputed by WOCF. Missing data after study intervention discontinuation for lack of efficacy were imputed by WOCF.

Abbreviations: EQ-5D-5L, EuroQoL 5 dimensions 5 levels; ITT, intent-to-treat.

Sources: (12, 13)

Changes in all EQ-5D-5L health state dimensions from baseline to Week 12 and Week 24 were summarised according to Paretian classification[8]. Improvement was assigned when outcomes were better on at least one dimension and not worse on any other dimension, worsening was assigned when outcomes were worse in at least one dimension and no improvement was reported in any other dimension, mixed change was assigned when outcomes were improved in at least one dimension while at the same time outcomes were worse in at least one other dimension, and finally no change was assigned when no improvement or worsening was reported in any dimension. Paretian classification of

[8] Method for summarizing changes in profile data 54. Devlin N, Parkin D, Janssen B. Analysis of EQ-5D Profiles. In: Devlin N, Parkin D, Janssen B, editors. Methods for Analysing and Reporting EQ-5D Data. Cham: Springer International Publishing; 2020. p. 23-49.

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health change for all EQ-5D-5L dimensions demonstrated that improvement in the dupilumab + SoC group was reported by [redacted] of patients at Week 12 and [redacted] of patients at Week 24 compared to [redacted] respectively, in the placebo + SoC group (Table 22). Worsening profile was reported by 16.4% of patients at Week 12 and 12.5% of patients at Week 24 in the dupilumab + SoC group compared to 12.4% and 9.7%, respectively, in the placebo + SoC group (Table 22)

Table 22: Summary of EQ-5D-5L health state according to Paretian classification from baseline at Week 12 and Week 24 – Pooled ITT analysis(55)

EQ-5D-5L health state comparison from baseline	Week 12		Week 24	
	Dupilumab + SoC (%) (N=152)	Placebo + SoC (%) (N=153)	Dupilumab + SoC (%) (N=152)	Placebo + SoC (%) (N=144)
Improvement [a]	[redacted]	[redacted]	[redacted]	[redacted]
No change [b]	[redacted]	[redacted]	[redacted]	[redacted]
Worsening [c]	[redacted]	[redacted]	[redacted]	[redacted]
Mixed change [d]	[redacted]	[redacted]	[redacted]	[redacted]

Footnote: [a] Better on at least one dimension and no worse on any other dimension. [b] No change in any dimension. [c] Worse in at least one dimension and no better in any other dimension. [d] Better in at least one dimension but worse in at least one other.

Data collected after study intervention discontinuation were included. Data post the select prohibited medications/procedures and/or rescue medications that impacted efficacy were set to missing and imputed by WOCF. Missing data after study intervention discontinuation for lack of efficacy were imputed by WOCF. Health state is assessed according to Paretian Classification of Health Change.

Abbreviations: EQ-5D-5L, EuroQoL 5 dimensions 5 levels; IT, intent-to-treat.

Sources: (12, 13)

7.1.3.2.2 Subgroup analysis - Pooled ITT participants by prior systemic use

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Table 23: Primary and key secondary efficacy endpoints – - Pooled ITT participants by prior systemic use

Weekly average WI-NRS improvement ≥ 4 points at Week 24 from baseline (primary method)	Dupilumab + SoC (N=153) n (%)	Placebo + SoC (N=158) n (%)	OR, (95% CI) [a] Dupilumab + SoC vs. Placebo + SoC	P-value [b] Dupilumab + SoC vs. Placebo + SoC	RRD (%), (95% CI) [a] Dupilumab + SoC vs. Placebo + SoC	Overall p-value for interaction [c]
Weekly average WI-NRS improvement ≥ 4 points at Week 24 from baseline (primary method)						
Patients with prior systemic immunosuppressants						
Responder						
Non-responder						
Imputed non-responder						
Patients without prior systemic immunosuppressants						
Responder						
Non-responder						
Imputed non-responder						
IGA PN-S 0 or 1 score at Week 24 (primary method)						
Patients with prior systemic immunosuppressants						
Responder						
Non-responder						
Imputed non-responder						
Patients without prior systemic immunosuppressants						
Responder						
Non-responder						
Imputed non-responder						
Both WI-NRS improvement (reduction) ≥ 4 points from baseline and IGA PN-S 0 or 1 score at Week 24 (primary method)						
Patients with prior systemic immunosuppressants						
Responder						
Non-responder						
Imputed non-responder						
Patients without prior systemic immunosuppressants						
Responder						
Non-responder						
Imputed non-responder						

Footnote: [a] derived from the Mantel-Haenszel estimator.

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

[c] Logistic regression model was used for the interaction test including intervention group, adjusted documented history of atopy (atopic or non-atopic), stable use of TCS/TCI (yes or no), region, baseline anti-depressant use (yes or no), study indicator (EFC16459 or EFC16460), plus the subgroup variable and the subgroup-by-intervention in the model.

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Note: Participants who received the prohibited medications/procedures and/or rescue medications that impacted efficacy before Week 24 were considered as non-responders, and missing data at Week 24 were considered as non-responders.
Abbreviations: CMH, Cochran-Mantel Haenszel; CI, confidence interval; OR: odds ratio; RRD: response rate difference WI-NRS, worst-itch numeric rating scale.
Source: (56)

7.2 Conclusion

Results from both the pooled ITT analysis, subgroup analyses, and individual pivotal phase 3 studies demonstrated consistent efficacy and safety of dupilumab versus placebo in improving the signs and symptoms of PN (51, 52). Statistical significance was achieved for the primary endpoint of both studies as measured by reduction in WI-NRS by ≥4 points (12, 13, 51). A greater proportion of patients in the dupilumab group compared to the placebo group achieved weekly average reduction of WI-NRS by ≥4 at Week 12 (<0.0001) and Week 24 (<0.0001) (13). Furthermore, the treatment benefit magnitude was greater at Week 24 than Week 12 within the dupilumab group (40.5% vs. 58.8%) (51) and safety of dupilumab versus placebo in improving the signs and symptoms of PN (51, 52). Statistical significance was achieved for the primary endpoint of both studies as measured by reduction in WI-NRS by ≥4 points (12, 13, 51). A greater proportion of patients in the dupilumab group compared to the placebo group achieved weekly average reduction of WI-NRS by ≥4 at Week 12 (<0.0001) and Week 24 (<0.0001) (13). Furthermore, the treatment benefit magnitude was greater at Week 24 than Week 12 within the dupilumab group (40.5% vs. 58.8%) (51).

Key secondary endpoints were also met across the studies (51).

- The proportion of patients with healing PN skin lesions (IGA PN-S score of 0 or 1) and concomitant itch and skin lesions improvement (WI-NRS reduction by ≥4 points and IGA PN-S score of 0 or 1) at Week 24 in the dupilumab group was significantly higher than in the placebo group (51).
- In terms of prurigo activity, the proportion of patients in the dupilumab group with an IGA PN-A score of 0 or 1 was significantly higher compared to the placebo group as early as Week 4, with the highest difference being reported at Week 24 (55.6% vs. 19%) (51).
- Treatment with dupilumab resulted in greater decrease in weekly average Skin Pain-NRS score as early as Week 2 and gradually decreased over time with the greatest difference observed at Week 24 (51).
- Nominally significant improvement in weekly average Sleep-NRS score from baseline at Week 24 was reported in the dupilumab group compared to the placebo group in the pooled ITT analysis and the LIBERTY-PN PRIME results (12, 51). The difference in treatment effect reported in the weekly average Sleep-NRS score in PRIME2 between the dupilumab and the placebo group, although trending towards improvement, was not statistically significant (13).

Moreover, Paretian classification of health change for all EQ-5D-5L dimensions demonstrated that improvement in the dupilumab group was numerically greater than the placebo group at both Week 12 and Week 24 (55). Consistent results were seen for DLQI with statistically significant improvements.

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8. Health economic analysis

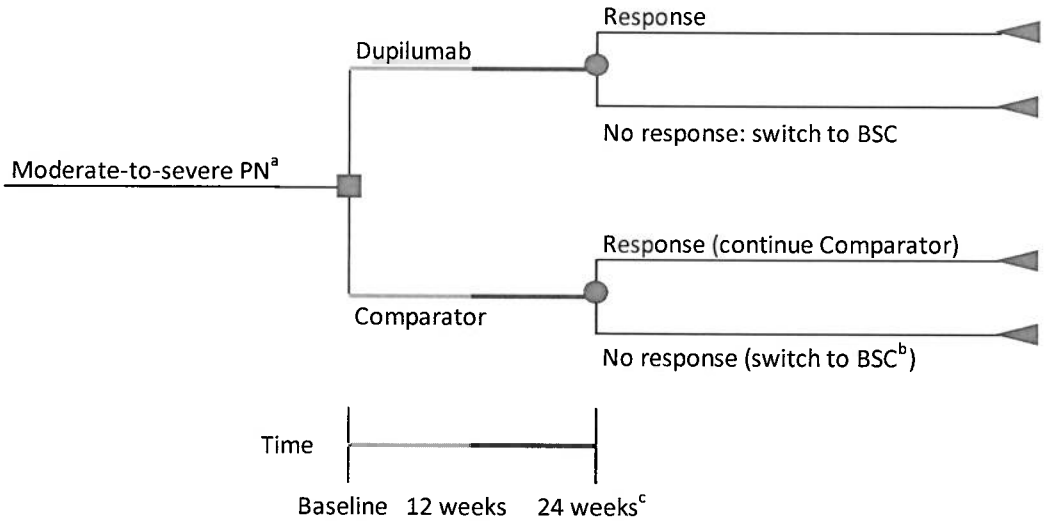
8.1 Model

8.1.1 Model structure and patient flow

A health economic model was developed with the objective of presenting the costs and outcomes associated with dupilumab as an add-on treatment and (BSC) (equal to SoC in the clinical trials) for adult patients with moderate-to-severe PN who are inadequately controlled on topical prescription therapies or when those therapies are not appropriate. The model structure for dupilumab in PN can be divided into 2 sections. It starts with a 24-week decision tree to reflect the short-term dupilumab trials, followed by a long-term treatment-based Markov model structure representing the remaining disease course. In the base case, BSC alone was selected as the comparator, as no licensed treatments are available in the indication.

In the initial decision tree, which is illustrated in Figure 4, patients with moderate to severe PN can be treated with either dupilumab plus BSC (dupilumab + BSC) or BSC alone. At the first assessment point at week 24 (shown by the blue chance nodes), a clinical check is performed to determine response in both arms. Responders move to the "Response" branch of the decision tree and continue the current treatment while non-responders move to the "No response" branch and switch to BSC. Patients receiving BSC alone upon entering the model stay on BSC treatment regardless of response status.

Figure 4: Decision Tree Structure



Based on the assessment results at week 24, patients move to the long-term Markov model. For patients in the dupilumab arm, they can enter the model within one of two treatment-based health states: "On dupilumab" or "On BSC". For patients in the BSC alone arm, they can only enter the model into one treatment-based health state: "On BSC". Mortality is assumed not to be affected by PN, and all patients are assumed to be at equal risk of general mortality, which was included in the model. The treatment-based model structure assumes that the comparator intervention does not elicit a full response. It was designed to compare dupilumab + BSC with BSC alone.

The patient flow and model structure in the treatment-based Markov model are illustrated in Figure 5 and Figure 6. The arrows are indicating, how patients can remain or move into another health state:

- For patients in the BSC arm, all of them enter "On BSC" health state and remain in that health state until death.

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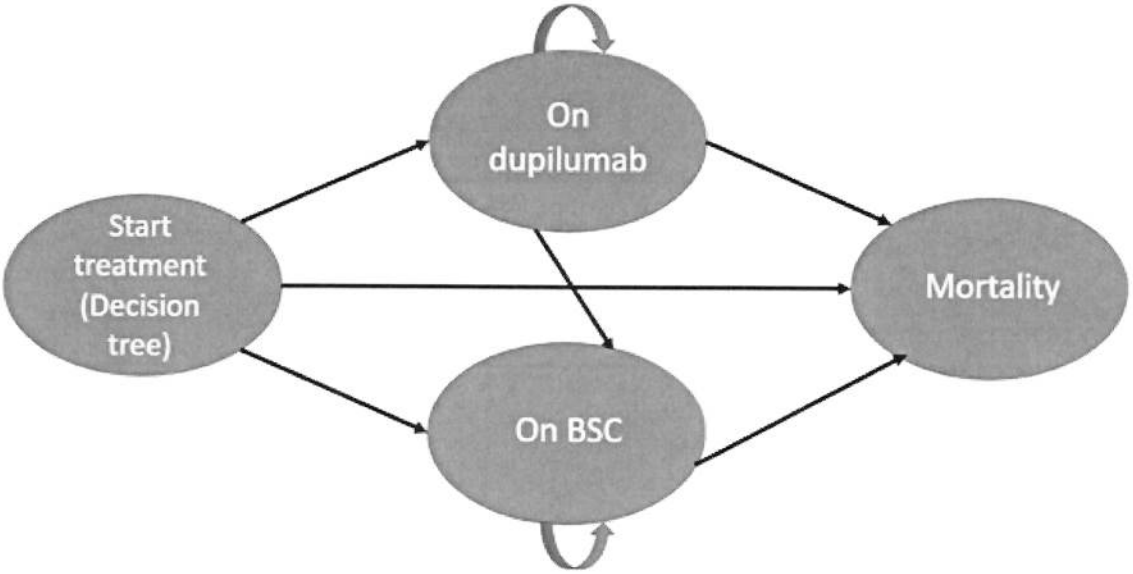
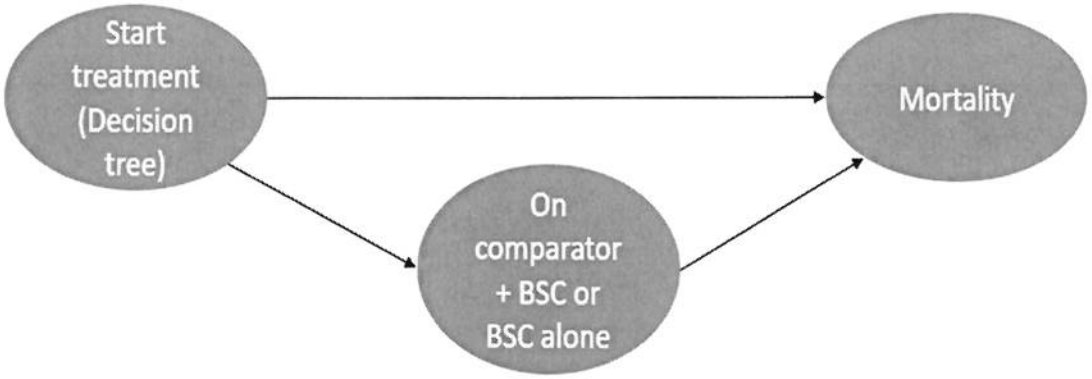
- For patients "On dupilumab", they remain in the "On dupilumab" health state until death or discontinuation for reasons such as loss of response, AEs, patient/physician preference. After discontinuation, they move to the "On BSC" health state and switch to BSC treatment alone and remain in that health state until death.

Figure 5: The Markov model structure for the dupilumab arm



BSC = Best supportive care

Figure 6: The Markov model structure for the BSC alone arm



BSC = Best supportive care

8.1.2 Patient population

The patient population for the model was based on the cohorts included in the clinical trials: patients with PN who are inadequately controlled on topical prescription therapies or when those therapies are not advisable. More precisely, "inadequately controlled" refers to patients who are unable to achieve and/or maintain remission and low disease activity (similar to IGA-PN score of ≤ 2, i.e., fewer than 20 nodules) despite treatment with a daily regimen of medium to super potent topical corticosteroid (with or without add-on topical calcineurin inhibitor, as appropriate), applied for at least 14 days, or for the maximum duration recommended by the product prescribing information, whichever is shorter. The patient baseline characteristics (e.g., age, percentage of patients who were male, body weight, and utility weight) were based on the cohorts included in the PRIME and PRIME 2 trials.

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In the model, a subpopulation of patients who have previously received systemic therapies is also included. It is possible to select either the full population or the subgroup of patients that had received systemic treatment prior to the PRIME trials.

8.1.3 Perspective, time horizon, cycle length, and discounting

The model considers a Danish restrictive societal perspective, consistent with the guidelines presented by the DMC (15). A lifetime horizon was selected to ensure the full impact of treatment in terms of cost and health outcomes are captured. A lifetime horizon of 50 years (i.e., up until patients reached the age of 100 years old) was applied in the base case. As such, the time horizon for the analysis should be long enough to capture all significant differences in effects and costs between the alternatives and an extension of the time horizon would not affect the results. The model enables the option to consider reduced time horizons. A 12-week cycle length is assumed in the Markov model and half-cycle correction has been applied to account for events not occurring at the beginning or end of every cycle. Discount rates of 3.5% until year 35, and 2.5% from year 36 onwards were applied to costs and health outcomes, as defined by the Danish Ministry of Finance and in the DMC guidelines (15, 57).

8.1.4 Interventions

The interventions included in the analysis are presented in Table 24.

Table 24: Interventions included in economic analysis

Intervention	Rationale
Dupilumab +BSC	Intervention of interest
BSC alone	Localised comparator in PRIME studies and is expected to best represent current Danish clinical practice

BSC = Best supportive care

8.1.5 Definition of response criteria

Currently, there is no consensus on a definition of treatment response. Various measures were used to evaluate the treatment efficacy in PRIME and PRIME2, including Worst-Itch Numeric Rating Scale (WI-NRS), DLQI, and Investigator Global Assessment of PN Stage (IGA PN-S). Based on Danish clinical expert feedback (30) the base case response criterion was defined as WI-NRS improvement ≥ 4 points from the baseline. In addition, the WI-NRS improvement of ≥ 4 points from baseline was the primary endpoint of the LIBERTY-PN PRIME trial (at 24 weeks) and PRIME 2 trial (at 12 weeks). The following 6 alternative definitions for response criteria were tested in scenario analyses:

- WI-NRS improvement ≥ 4
- DLQI reduction ≥ 9
- IGA-PN-S reduction ≥ 1
- IGA-PN-A reduction ≥ 1
- WI-NRS improvement ≥ 4 AND IGA-PN-S reduction ≥1
- WI-NRS improvement ≥ 4 AND IGA-PN-A reduction ≥1
- WI-NRS improvement ≥ 3 AND IGA-PN-S reduction ≥1
- WI-NRS improvement ≥ 3 AND IGA-PN-A reduction ≥1
- DLQI reduction ≥ 9 AND IGA-PN-S reduction ≥ 1
- DLQI reduction ≥ 9 AND IGA-PN-A reduction ≥ 1

The advantages and disadvantages of the different scoring systems are presented in Table 25.

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Table 25: Advantages and disadvantages of different response criteria scoring systems

Scoring system	Advantage	Disadvantage
WI-NRS improvement (reduction) ≥ 4 from baseline	**The WI-NRS was recommended as the most suitable measure of PN progress by Danish clinical expert (30). This is the primary endpoint in the PRIME and PRIME 2 trials.** As a patient-reported outcome, the WI-NRS captures the patients' self-impression on their disease. Per the inclusion criteria, all patients are enrolled in the clinical trial with a WI-NRS score ≥ 7. Thus, a drop by 4 WI-NRS units is equivalent to a move from severe itch to mild itch. This is also deemed very clinical relevant by Danish clinical experts (30) This is an attractively simple concept. This does not require a justification of the threshold values used (because the chosen cut-offs are the frequently used and widely accepted ones) The WI-NRS is the most widely adopted outcome tool in clinical trials investigating itch and should find resonance with most jurisdictions.	The WI-NRS fails to account for the impact of nodules. With the increased interest in chronic prurigo, there is a possibility that prurigo-specific tools may begin to become preferred.
IGA-PN (either A or S) reduction of ≥1	This instrument is specific to PN. Also, being a clinician-reported outcome, the IGA-PN gives an objective measure of disease staging.	The IGA-PN could be seen as too specific or too narrow for PN because only the nodular lesions are accounted for. The IGA-PN is not as popular as the WI-NRS
DLQI reduction ≥9 from baseline	The DLQI is the most widely used quality-of-life measure in dermatology. Also, it has been successfully validated in PN. The reduction ≥ 9 was the psychometrical validated threshold for PN based on internal psychometrical analysis.	The DLQI is not specific to PN
Both WI-NRS improvement (reduction) ≥ 4 points and IGA-PN reduction of ≥1	Joint consideration of WI-NRS and IGA-PN combines the individual strengths of these instruments, already mentioned above Will tend to cancel any of the individual limitations of these instruments, already mentioned above. Might prove more adequate for demonstrating dupilumab's value. This is because this approach captures both the subjective (WI-NRS) and the objective (IGA-PN) effect of dupilumab. A combination of 2 types of reported outcome: a clinician-reported outcome (IGA-PN) and a patient-reported outcome (WI-NRS). It is more objective compared with WI-NRS alone.	Joint consideration of WI-NRS and IGA-PN using the "AND" logical operator produces a smaller number of successfully treated patients compared with evaluation using WI-NRS only or IGA-PN only. This points to the imperfect overlap between clinician and patient assessment
DLQI reduction from baseline and IGA-PN reduction of ≥1	Measures a holistic improvement in quality of life	Because this is a combination of measures using the AND logical operator, this produces a smaller number of successfully treated patients compared with using either metric alone

DLQI = Dermatology Life Quality Index; IGA-PN = investigator global assessment for prurigo nodularis; PN = prurigo nodularis; WI-NRS = worst-itch numerical rating scale.

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8.1.6 Model assumptions

The model includes the following assumptions:

- 12-week cycle length is assumed in the Markov model.
- A half-cycle correction using the life method is applied in the Markov model.
- All-cause treatment discontinuation is used as a proxy for loss of response. Thus, the trial-observed discontinuation rates are used as transition probabilities from "response" to "non-response". Long-term response rates are assumed to be similar between atopic dermatitis and PN. This is because long-term response data are not yet available in PN.
- AE-related disutilities are assumed to be accounted for within patient-level EQ-5D responses collected during the PRIME and PRIME 2 trials. Therefore, no additional disutility was included to avoid double counting.
- Patients do not have an increased risk of mortality due to PN. Only adjusted population mortality is considered.
- The costs used in the model for TCSs is assumed to be the average of the cost of the individual corticosteroid creams and ointments available at medicinpriser.dk (58)
- Patients receive the first dose of subcutaneous dupilumab in a clinic and receive training on subcutaneous administration at this hospital visit. Patients are assumed to self-administer subsequent doses at home. Danish clinical experts have stated this is expected based on experience with dupilumab for other indications as well as other subcutaneous products (30).

8.1.7 Model outputs

The analyses allow benefits to be measured in terms of life-years (LYs) and QALYs. Base case results were generated using QALYs as the measure of benefit and the primary outcome was the incremental cost per QALY (ICER).

8.2 Relationship between the data for relative efficacy, parameters used in the model and relevance for Danish clinical practice

8.2.1 Presentation of input data used in the model and how they were obtained

A summary of the model inputs is presented in Table 26.

Table 26: Summary of efficacy inputs included in the economic model

Name of estimates	Results from study or indirect treatment comparison (ITC)	Input value used in the model	How is the input value obtained/estimated**
Dupilumab plus BSC			
Percentage of dupilumab + BSC responders at week 24	58.8% using the WI-NRS improvement ≥ 4 points from baseline outcome and WOCF + MI	58.8% using the WI-NRS improvement ≥ 4 points from baseline outcome and WOCF + MI	PRIME and PRIME2 pooled data; (14)
Probability of sustained response for Year 2-5+ (response waning)	Not within the time horizon of the clinical study	See section 8.2.1.2	Danish clinical expert feedback (30). See more in section 8.2.1.2.
Other cause annual discontinuation	See section 8.2.1.3	See section 8.2.1.3	PRIME and PRIME2 pooled data; (14)
Adverse events	See section 7.1.3.2.1.2	See section 8.2.2.4	PRIME and PRIME2 pooled data; (14)
Utilities	See section 8.4	See section 8.4	PRIME and PRIME2 pooled data; (14)

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BSC alone			
Percentage of BSC alone responders at week 24	19.0% using the WI-NRS improvement ≥ 4 points from baseline outcome and WOCF + MI	19.0% using the WI-NRS improvement ≥ 4 points from baseline outcome and WOCF + MI	PRIME and PRIME2 pooled data; (14)
Probability of sustained response for Year 2-5+ (response waning)	Not within the time horizon of the clinical study	See section 8.2.1.2	Danish clinical expert feedback (30). See more in section 8.2.1.2.
Other cause annual discontinuation	See section 8.2.1.3	See section 8.2.1.3	PRIME and PRIME2 pooled data; (14)
Adverse events	See section 7.1.3.2.1.2	See section 8.2.2.4	PRIME and PRIME2 pooled data; (14)
Utilities	See section 8.4	See section 8.4	PRIME and PRIME2 pooled data; (14)

BCS = Best supportive care; ITC = Indirect treatment comparison; TTD = Time to discontinuation

8.2.1.1 Response Criteria and Week-24 Response Data

The response criteria define which patients continue dupilumab treatment and influence QALYs for both treatments because utility weights for response are higher than those for nonresponse. Based on a user selection of response, the model response inputs are populated with subgroup-specific data that represent the probability of achieving the selected response criteria for each model comparator. The base case analysis used WI-NRS improvement ≥ 4 points at week 24 from baseline as response criterion.

In addition to the response criteria selection, response is further delineated by the 2 statistical analysis methods used in the trial(s) for response: 1) worst observation carried forward with multiple imputation (WOCF + MI) method and 2) as observed with multiple imputation (as observed + MI) methods. In the WOCF + MI response analysis, patients receiving rescue treatment were censored and set to non-responders. In the as observed + MI response method, rescue treatment patients that met the designated response criteria were counted as responders. The base case response data was estimated using the WOCF + MI method based on the pooled data from PRIME and PRIME2 trials. The response data inputs for the base case overall patient population under various response criteria are presented in Table 33, which is placed in section 8.2.2.4.

8.2.1.2 Response Waning

When patients lose response, those receiving active treatment discontinue the active treatment (i.e., dupilumab) and receive BSC alone for the rest of their time in the model.

In clinical trials patients tend to have a higher adherence to treatment compared to in real life. It has been described that participation in clinical trials allow for a closer follow-up of the patient which also increase the adherence to therapy as the adherence is usually better close to a clinic visit(59). In a skin condition like PN where patients are required to apply topical treatments regularly to large areas of their body, adherence may decrease over time as the application is time consuming and bothersome for the patients. In Denmark, some patients with PN receive support with applying topical treatments during day care visits and in some cases, patients even need to get hospitalized to receive the support needed. This speaks to the burden for these patients related to application of their topical treatments. In PN patients, the mental component is also of importance for the disease and may have an impact on the adherence to treatment.

In addition, as long-term response data for dupilumab in PN is not currently available and may not be available for some time, various assumptions were programmed in the model based on data from an analogue disease, AD. This is

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a common practice and AD weaning assumptions have previously been included in economic evaluations in UK, Norway, Sweden amongst others.

For these reasons, it is appropriate to consider that the response achieved in the clinical trials will not be sustained over time. In the cost-effectiveness model, response waning is included to handle this aspect.

Table 27 and Table 28 present the long-term response data for dupilumab + BSC and BSC, respectively. In the base case, response waning was based on Danish Clinical Expert feedback for both dupilumab + BSC and BSC alone (30).

The model is also programmed to disable response waning to facilitate scenario analysis, in which case, all responders remain on their treatment response unless they discontinue due to other reasons such as AEs, patient/physician preference or they die due to general mortality in the model.

Table 27: Probability of dupilumab + BSC Patients Sustained Response for Years 2-5+ used in PN model

Year	Dupilumab + BSC			
	Base case	Sensitivity analysis		
	Danish clinical expert input	AD Dermatologist survey	OLE study	AD Chronos trial
Year 2	[redacted]	[redacted]	[redacted]	[redacted]
Year 3	[redacted]	[redacted]	[redacted]	[redacted]
Year 4	[redacted]	[redacted]	[redacted]	[redacted]
Years 5+	[redacted]	[redacted]	[redacted]	[redacted]
Source	Danish clinical expect feedback (30). A Danish clinical expert was asked to validate the long-term probabilities of sustained response based on AD literature. The clinical expert suggested that the AD Chronos data was most suitable (30).	Assumptions based on physician estimates for the preparation of a CEM of dupilumab in the treatment of AD (60).	Analysis of long-term efficacy maintenance alongside the OLE study for dupilumab in AD (61).	Extrapolation of time to rescue medication or time to study drop-out in the dupilumab Chronos clinical trial in AD (62).

AD = atopic dermatitis; BSC = best supportive care; OLE = open-label extension.

Table 28: Probability of BSC Patients' Sustained Response for Years 2-5+ used in PN model

Year	BSC			
	Base case	Sensitivity analysis		
	Danish clinical expert input	NICE Assumption in AD	AD Dermatologist survey	Chronos trial
Year 2	[redacted]	[redacted]	[redacted]	[redacted]
Year 3	[redacted]	[redacted]	[redacted]	[redacted]
Year 4	[redacted]	[redacted]	[redacted]	[redacted]
Years 5+	[redacted]	[redacted]	[redacted]	[redacted]
Source	Danish clinical expect feedback (30). A Danish Clinical Expert was asked to validate the long-term probabilities of sustained response based on AD literature. The clinical expert suggested that a 20% probability each year would be more suitable for the Danish context (30)	Estimates presented by clinicians appointed by NICE (63)	Assumptions based on UK physician estimates for the preparation of a CEM of dupilumab in treating AD (60)	Extrapolation of time to rescue medication or time to study drop-out in the dupilumab Chronos clinical trial in AD (62)

AD = atopic dermatitis; BSC = best supportive care; CEM = cost-effectiveness model; NICE = National Institute for Health and Care Excellence.

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8.2.1.3 Annual Discontinuation Rates

In the base case, the model uses PRIME and PRIME2's pooled all-cause drug discontinuation as a proxy for loss of response over the model time horizon. That is, the trials' discontinuation rate is used as the transition probability from "response" to "non-response". Two data sources were programmed in the model: 1) pooled data from PRIME and PRIME2 trials (14) for dupilumab in PN (base case) and 2) Chronos clinical trial data (62) for dupilumab in AD. The data is presented in Table 29.

Table 29: Annual Discontinuation Rates Available in the Model

Treatment	Annual discontinuation rate	
	PRIME and PRIME2 trials (base case)	Chronos trial
Dupilumab	[redacted]	[redacted]
BSC	[redacted]	[redacted]
Source	Sanofi data on file, 2022 (14)	Sanofi data on file, 2017 (62)

BSC = Best supportive care

8.2.2 Relationship between the clinical documentation, data used in the model and Danish clinical practice

8.2.2.1 Patient population

A patient population summary is provided in Table 30.

The Danish patient population

The characteristics of the Danish patients with moderate to severe PN who are candidates for systemic therapy were discussed with the clinical expert who found the patient population from pooled patient characteristics from the two PRIME trialcomparable to the Danish patient population.

Patient population in the clinical documentation submitted

The pooled baseline characteristics of the patient population in PRIME trials are presented in Table 30. As seen in the table, patients in both arms had a mean age of 49.5 years with 34.7% being male patients. The average body weight was 73.9 kg. The mean pooled utility weight based on the Jensen et al. 2021 (64) was 0.653. The pooled baseline WI-NRS was the dupilumab arm and placebo arm were 8.6 and 8.4, respectively, and 8.5 on average for both arms. The mean DLQI was 17.5 for the pooled PRIME population.

Patient population in the health economic analysis submitted

The patient population included in the health economic model was based on the pooled patient characteristics of the two PRIME trials.

Table 30: Patient population

Characteristics	Clinical documentation (including source)	Used in the model (SD)	Expected Danish clinical practice (SD)
Age, years (SD)	49.5 (16.1)*	49.5 (16.1)	64.4 (14.5) (36)
% of male patients	34.7*	34.7	37.6
Body weight (SD)	73.9 (1.02)*	73.9 (1.02)	Not expected to be significant different in the Danish population

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Characteristics	Clinical documentation (including source)	Used in the model (SD)	Expected Danish clinical practice (SD)
Utility weight estimated	0.653 (0.259)**	0.653 (0.259)	Not expected to be significant different in the Danish population
WI-NRS (SD)	8.493 (1.007)*	8.493 (1.007)	Not expected to be significant different in the Danish population
DLQI (SD)	17.5 (7)*	17.5 (7)	7.0 (5.6) (36)

DLQI = Dermatology Life Quality Index; SD = standard deviation; WI-NRS = The Worst-Itch Numeric Rating Scale.
*Source: Pooled results from PRIME and PRIME2 (Sanofi data on file, 2022).
**Source: Pooled results from PRIME and PRIME2 (Sanofi data on file, 2022) based on algorithm by Jensen et al 2021., (64)

8.2.2.2 Intervention

Dupilumab as expected in Danish clinical practice

Dupilumab is indicated for adults aged >18 years with moderate to severe PN who are candidates for systemic therapy after optimal topical treatment. Dupilumab is expected to be positioned before the off-label systemic therapies, including immunosuppressants and antidepressant treatments. Dupilumab should be administered the same way as in the PRIME trials (14): subcutaneously at an initial dose of 600 mg subcutaneously, followed by 300 mg every 2 weeks.

Dupilumab in the clinical documentation submitted

In PRIME trials, dupilumab was administered subcutaneously, at an initial dose of 600 mg subcutaneously, followed by 300 mg every 2 weeks. The subcutaneous injections alternate between the different quadrants of the abdomen (avoiding navel and waist areas), upper thighs, and upper arms so that the same site is not injected for 2 consecutive administrations. The cumulative treatment exposure time for the pooled ITT population was 69.42 participant years the dupilumab + SoC group.

Dupilumab as in the health economic analysis submitted

Dupilumab was administered subcutaneously, at an initial dose of 600 mg subcutaneously, followed by 300 mg every 2 weeks. In the model, when patients lose response, those receiving active treatment discontinue their current active treatment with dupilumab and receive BSC alone for the rest of their time in the model. In the base case, this is based on WI-NRS improvement ≥4 using the WOCF + MI imputation.

Table 31: Intervention documentation

Intervention	Clinical documentation (including source)	Used in the model (number/value including source)	Expected Danish clinical practice (including source if known)
Posology	An initial dose of 600 mg, followed by 300 mg every 2 weeks. (10)	An initial dose of 600 mg, followed by 300 mg every 2 weeks. (10)	An initial dose of 600 mg, followed by 300 mg every 2 weeks per label (10)
Criteria for discontinuation	Consider end of treatment if unacceptable toxicity or lack of response. (10)	Trial-observed discontinuation rates are used. In the base case, this is based on WI-NRS improvement ≥4 using the WOCF + MI imputation.	Consider end of treatment if unacceptable toxicity or lack of response. (10)

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Intervention	Clinical documentation (including source)	Used in the model (number/value including source)	Expected Danish clinical practice (including source if known)
The pharmaceutical's position in Danish clinical practice	Adult patients with moderate-to-severe PN who are candidates for systemic therapy. (10)	Adult patients with moderate-to-severe PN who are candidates for systemic therapy. (10)	Expected to be used for adult patients with moderate-to-severe PN who are candidates for systemic therapy. (10)

8.2.2.3 Comparators

Comparators as expected in Danish clinical practice.

As discussed in section 5.2, different treatments are currently used in Denmark to treat patients, however, all of these are off-label. Based on Danish clinical expert feedback, the BSC used in Danish clinical practice aligns largely with the BSC used in PRIME trials, however, the Danish clinical expert also expected zinc bandages and light treatments to be used as BSC in Denmark.

Comparators in the clinical documentation submitted

BSC is the comparator used in the clinical documentation submitted. This is presented in section 5.2.3. The cumulative treatment exposure time for the pooled ITT population was 62.72 participant years the SoC group.

Comparators as in the health economic analysis submitted

The BSC used for the health economic model needed to be slightly modified to fit current Danish clinical practice Through the inclusion of zinc bandages and light treatments the BSC aligns with the PRIME trials. This is expected to be the best reflection of current Danish clinical practice given input from the Danish clinical expert (30).

Table 32: Comparator (BSC alone) documentation

Comparator	Clinical documentation (including source)	Used in the model (number/value including source)	Expected Danish clinical practice (including source)
Posology	Topical corticosteroids are used in a variety of skin conditions and should be applied thinly once or twice a day. For a once-daily application, it is assumed that the following quantities of topical corticosteroids will last for 2 weeks of treatment: • application to the arms, 30g to 60g • legs, 100g • trunk, 100g In the PRIME and PRIME2 clinical trials, inclusion criterion number 3 required at least 20 PN lesions in total on both legs, and/or both arms and/or trunk, at screening and at day 1. Therefore, we assume that patients will use 100g of topical glucocorticoid preparation every 2 weeks (50, 65). Tacrolimus creme/ointment should be used once or twice a day initially, however, only twice a week as maintenance treatment (66). Thus, we assume that tacrolimus is 1/3 less frequently used compared to topical corticosteroids in the model. Based on Danish clinical expert feedback (30), zinc bandages and light treatments are also used often for PN patients. Zinc bandages are expected to be used once a week for approximately 10 weeks, while the light treatment is applied 2-3 times a week for approximately 10 weeks.		

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Comparator	Clinical documentation (including source)	Used in the model (number/value including source)	Expected Danish clinical practice (including source)
Length of treatment	Consider switch of treatment if unacceptable toxicity or lack of response.	Some sort of BSC is used at any point for patients not responding.	Consider switch of treatment if unacceptable toxicity or lack of response.
The comparator's position in the Danish clinical practice	As dupilumab is the only licensed treatment of adult patients with moderate-to-severe PN, the BSC is expected to be the current first line of treatment	Treatment of adult patients with moderate-to-severe PN who are candidates for systemic therapy.	As dupilumab is the only licensed treatment of adult patients with moderate-to-severe PN, the BSC is expected to be the current first line of treatment

8.2.2.4 Relative efficacy outcomes

The clinical efficacy of dupilumab + BSC vs. BSC alone was assessed in the PRIME 1 and 2 trials. The relative efficacy outcomes in the submitted clinical documentation can be identified in section 7.1.3. The modelled values are presented below in Table 33.

Table 33: Relative efficacy documentation for the full ITT population

Clinical efficacy outcome	Clinical documentation	Used in the model (value) WOCF + MI imputation	Used in the model (value) As-observed + MI
WI-NRS improvement of ≥4 at 24 weeks	PRIME and PRIME2 pooled data; (14)	[redacted]	[redacted]
DLQI reduction of ≥9 at 24 weeks	PRIME and PRIME2 pooled data; (14)	[redacted]	[redacted]
IGA-PN-S reduction of ≥1 at 24 weeks	PRIME and PRIME2 pooled data; (14)	[redacted]	[redacted]
IGA-PN-A reduction of ≥1 at 24 weeks	PRIME and PRIME2 pooled data; (14)	[redacted]	[redacted]
WI-NRS improvement ≥ 4 AND IGA-PN-S reduction ≥ 1	PRIME and PRIME2 pooled data; (14)	[redacted]	[redacted]
WI-NRS improvement ≥ 4 AND IGA-PN-A reduction ≥ 1	PRIME and PRIME2 pooled data; (14)	[redacted]	[redacted]
WI-NRS improvement ≥ 3 AND IGA-PN-S reduction ≥ 1	PRIME and PRIME2 pooled data; (14)	[redacted]	[redacted]
WI-NRS improvement ≥ 3 AND IGA-PN-A reduction ≥ 1	PRIME and PRIME2 pooled data; (14)	[redacted]	[redacted]
DLQI reduction ≥ 9 AND IGA-PN-S reduction ≥ 1	PRIME and PRIME2 pooled data; (14)	[redacted]	[redacted]
DLQI reduction ≥ 9 AND IGA-PN-A reduction ≥ 1	PRIME and PRIME2 pooled data; (14)	[redacted]	[redacted]

BSC = best supportive care; DLQI = Dermatology Life Quality Index; IGA-PN-A = investigator global assessment for prurigo nodularis activity; IGA-PN-S = investigator global assessment for prurigo nodularis Stage; MI = multiple imputation; PN = prurigo nodularis; WI-NRS = worst-itch numerical rating scale; WOCF = worst observation carried forward

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8.2.2.5 Adverse reaction outcomes

The clinical safety information of dupilumab + BSC vs. BSC alone was assessed in the PRIME 1 and 2 trials. The relative safety outcomes in the submitted clinical documentation can be identified in section 7.1.3. The modelled values are presented below in Table 34.

Table 34: Adverse reaction outcomes

Adverse reaction outcome	Clinical documentation	Used in the model (numerical value)	Source:
Dupilumab	[redacted]	[redacted]	Pooled data from PRIME and PRIME 2 was used (14):
BSC alone	[redacted]	[redacted]	Pooled data from PRIME and PRIME 2 was used (14):

BSC = best supportive care

8.3 Extrapolation of relative efficacy

No extrapolation of study data has been used for this submission, as other data (response waning and discontinuation data) was used to predict the long-term outcomes in the Markov model. This data is presented in sections 8.2.1.2 and 8.2.1.3.

8.3.1 Time to event data – summarized:

No time extrapolations from time-to-event data were used in the health economic model.

8.4 Documentation of health-related quality of life (HRQoL)

8.4.1 Overview of health state utility values (HSUV)

8.4.1.1 Summary of utility data identified in the economic SLR

The economic SLR identified 3 utility studies, of which 1 was an abstract-only article.

Whang et al., 2022 (67) is a cohort study conducted in the US, that used the Health Utilities Index Mark 3 (HUI3) to measure the QOL burden of PN to compare with that of other disease states. Thirty-six patients with PN were included with a mean (standard error [SE]) age of 56.3 (2.7), and normative data of 4,187 controls from the general US population were collected from the 2002-2003 Joint Canada/US Survey of Health, with a mean (SE) age of 48.9 (0.3). The HUI was completed by patients, and the average HUI3 score of the PN cohort compared with the general population was significantly lower with means (SD) of 0.52 (0.06) and 0.86 (0.003), respectively.

Whang et al., 2019 (68) is a cross-sectional survey conducted in the US that also used the HUI3 questionnaire. Ninety-five patients with chronic PN, and 4,187 healthy US adults from the 2002-2003 Joint Canada/United States Survey of Health were included, and HUI3 scores were compared between the groups and stratified by race. Among the subset of chronic pruritus patients diagnosed with PN, Black patients were associated with decreased overall health performance in multivariate regression adjusting for demographics and itch severity (coefficient −0.49,

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95% confidence intervals [CIs], −0.98 to −0.01). This association was not observed in other diagnosis classes for chronic pruritus. Black chronic pruritus patients had a significantly higher average QALY loss, calculated based on HUI3 scores, than White chronic pruritus patients (7.66 vs. 6.18 years, $P = 0.003$). The QALY loss by Black chronic pruritus patients translates to an increased individual lifetime financial burden of $383,036 compared with $309,011 for White chronic pruritus patients.

Todberg et al., 2020 (36) is a cross-sectional survey conducted in Denmark that used the VAS and DLQI. The VAS scale and DLQI were completed by 52 patients with moderate to severe pruritis who responded to a survey sent out to the Department of Dermatology and Allergy, Herlev and Gentofte Hospital, University of Copenhagen. The mean (SD) VAS and DLQI scores were 6.6 (2.4) and 7.0 (5.6), respectively.

Although the HUI3 scores reported by Whang et al., 2022 (67) and Whang et al., 2019 (68) are a useful indicator of the lower utility associated with PN compared with the general population, HUI3 is not the preferred utility, with most HTA bodies preferring EQ-5D utility measures. Whang et al. 2019 (68) was also an abstract only that did not give overall scores or domain scores for HUI3, meaning it is not suitable for use in the model. Furthermore, although the data reported by Todberg et al. 2020 (36, 67) and Whang et al., 2019 (68) are a useful indicator of the lower utility associated with PN compared with the general population, HUI3 is not the preferred utility, with most HTA bodies preferring EQ-5D utility measures. Whang et al. 2019 (68) was also an abstract only that did not give overall scores or domain scores for HUI3, meaning it is not suitable for use in the model. Furthermore, although the data reported by Todberg et al. 2020 (36) is European, limited information is provided by the study. Despite this, the DLQI could be mapped to EQ-5D making it suitable for a European model.

8.4.1.2 Utilities from clinical trial

A post-hoc analysis of PRO pooled data from PRIME and PRIME2 showed that the most impacted EQ-5D-5L dimensions at baseline were pain/discomfort and anxiety/depression. The percentage of patients reporting severe/extreme problems was 35% and 12%, respectively.

At Week 12 and Week 24, a higher percentage of patients in the dupilumab group compared to the placebo group reported improvement for the EQ-5D-5L Pain/Discomfort dimension (59.9% vs. 44.4% and 60.5% vs. 36.8%, respectively) and for the EQ-5D-5L Anxiety/Depression dimension (32.9% vs. 20.9% and 38.2% vs. 19.4%) (14). The data is presented Table 35.

Table 35: Percentage improvement of all EQ-5D-5L dimensions assessed from baseline at Week 12 and Week 24 – Pooled ITT analysis

Most impacted dimensions at baseline (patients with severe/extreme problems)		% of patients reporting ≥1 category improvement			
		Week 12		Week 24	
Dimensions[a]	% All	Dupilumab (%)	Placebo (%)	Dupilumab (%)	Placebo (%)
Pain/ Discomfort	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Anxiety/ Depression	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mobility	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Selfcare	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Usual activities	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[a] EQ-5D-5L dimensions in bold were the most impacted at baseline.

EQ-5D-5L = EuroQoL 5 dimensions 5 levels; ITT = intent-to-treat.

Source: Sanofi 2022 (Data on file – PRO post-hoc analyses).

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Changes in all EQ-5D-5L health state dimensions from baseline to Week 12 and Week 24 were summarised according to Paretian classification[8]. Improvement was assigned when outcomes were better on at least one dimension and not worse on any other dimension, worsening was assigned when outcomes were worse in at least one dimension and no improvement was reported in any other dimension, mixed change was assigned when outcomes were improved in at least one dimension while at the same time outcomes were worse in at least one other dimension, and finally no change was assigned when no improvement or worsening was reported in any dimension. Paretian classification of health change for all EQ-5D-5L dimensions demonstrated that improvement in the dupilumab group was reported by 52.0% of patients at Week 12 and 57.2% of patients at Week 24 compared to 36.6% and 35.4%, respectively, in the placebo group. Worsening profile was reported by 16.4% of patients at Week 12 and 12.5% of patients at Week 24 in the dupilumab group compared to 12.4% and 9.7%, respectively, in the placebo group (14). This is presented in Table 36.

Table 36: Summary of EQ-5D-5L health state according to Paretian classification from baseline at Week 12 and Week 24 – Pooled ITT analysis

EQ-5D-5L	Week 12		Week 24	
	Dupilumab (%)	Placebo (%)	Dupilumab (%)	Placebo (%)
Improvement[a]	[redacted]	[redacted]	[redacted]	[redacted]
No change[b]	[redacted]	[redacted]	[redacted]	[redacted]
Worsening[c]	[redacted]	[redacted]	[redacted]	[redacted]
Mixed change[d]	[redacted]	[redacted]	[redacted]	[redacted]

a Better on at least one dimension and no worse on any other dimension. b No change in any dimension. c Worse in at least one dimension and no better in any other dimension. d Better in at least one dimension but worse in at least one other.

EQ-5D-5L = EuroQoL 5 dimensions 5 levels; ITT = intent-to-treat.
Source: Sanofi 2022 (Data on file – PRO post-hoc analyses) (14).

The data was used to derive health state utilities via the algorithm from Jensen et al., 2021, (64) with Danish preference weights.

Table 37: Overview of utilities from the clinical trials captured with EQ-5D-5L and converted using the Danish tariff value set (64)

	Arm	SE of arithmetic mean utility CFB	Arithmetic mean utility CFB	Resulting utility at follow-up
Baseline	**Pooled**	[redacted]	[redacted]	[redacted]
Week 12, pooled response	**Dupilumab**	[redacted]	[redacted]	[redacted]
	BSC	[redacted]	[redacted]	[redacted]
Week 24, pooled response	**Dupilumab**	[redacted]	[redacted]	[redacted]
	BSC	[redacted]	[redacted]	[redacted]
Week 24, separate response	**Dupilumab, responders**	[redacted]	[redacted]	[redacted]
	BSC, responders	[redacted]	[redacted]	[redacted]
	Dupilumab, non-responders	[redacted]	[redacted]	[redacted]
	BSC, non-responders	[redacted]	[redacted]	[redacted]
Week 24, pooled arms	**Responders**	[redacted]	[redacted]	[redacted]
	Non responders	[redacted]	[redacted]	[redacted]

BSC = best supportive care; CFB = change from baseline; EQ-5D-5L = EuroQol-5 Domain 5 level.

8.4.1.3 Mapped utilities

No mapping was needed.

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8.4.2 Health state utility values used in the health economic model

Two different approaches can be used in the model, and as per DMC's guidelines, the utilities were all adjusted to Danish preferences using the Jensen et al. algorithm (64). The two different approaches are:

- Trial-observed utilities using means (follow-up utilities calculated by considering the mean change from baseline
- Trial-observed utilities using least squares means (follow-up utilities calculated by considering the least squares mean change from baseline).

The base case used the utilities derived by trial-observed means using. The base case values are presented in Table 38.

Table 38: Base case health state utility values in the health economic model

	Health state	Utility value (CI 95%)	SE	Change from baseline
	Baseline	[redacted]	[redacted]	[redacted]
Week 12, pooled response	Dupilumab	[redacted]	[redacted]	[redacted]
	BSC	[redacted]	[redacted]	[redacted]
Week 24, pooled response	Dupilumab	[redacted]	[redacted]	[redacted]
	BSC	[redacted]	[redacted]	[redacted]
Week 24, separate response	Dupilumab, responders	[redacted]	[redacted]	[redacted]
	BSC, responders	[redacted]	[redacted]	[redacted]
	Dupilumab, non-responders	[redacted]	[redacted]	[redacted]
	BSC, non-responders	[redacted]	[redacted]	[redacted]
Week 24, pooled treatment arms	Responders	[redacted]	[redacted]	[redacted]
	Non responders	[redacted]	[redacted]	[redacted]

BSC = best supportive care; CFB = change from baseline; EQ-5D-5L = EuroQol-5 Domain 5 level.

8.5 Resource use and costs

8.5.1 Drug cost

All drug costs were identified at medicinpriser.dk (58). A pack of dupilumab with two syringes were identified to cost DKK 8,677.40. The unit cost per dose was multiplied by the treatment frequency (a loading dose of 600 mg, followed by 300 mg every 2 weeks) to estimate the cycle-specific drug costs. Table 39 presents the estimated drug costs for the first model cycle and subsequent model cycle.

Table 39: Drug-acquisition costs for dupilumab per model cycle

Model cycle	Dupilumab drug-acquisition costs, DKK
1st model cycle	[redacted]
2nd model cycle and onwards	[redacted]

The cost of BSC treatments was estimated by cost of mild/moderate potency TCS and TCI. Hydrocortisone, betamathasone, and hydrocontison-17-butyrat are applied to represent TCS products. While further TCS products may be used in practice, these products were chosen as a proxy to represent the TCS products as they have the lowest price. E.g., Betamethasone is used as a proxy for other moderate topical corticosteroids incl. Mometasonfuroat, as it has the lowest price.

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The average acquisition costs of TCS and TCI were estimated based on the prices presented in Table 40 and Table 41, respectively. TCS and TCI treatment frequencies were estimated based on the assumptions presented in Table 42.

Table 40: Average Acquisition Costs of TCS

	Pack size (g)	Acq. cost per pack, DKK	Acq. cost of a 100g pack, DKK
Mild TCS			
Hydrocortisone 0.1%, cream	90	155.00	172.22
Hydrocortisone 1%, cream	90	155.00	172.22
Moderate TCS			
Betamethasone val. 0.1%, cream	120	227.49	189.58
Betamethasone val. 0.1%, ointment	30	24.23	80.77
Hydrocortison-17-butyrat 0.1% creme	90	155.00	172.22
Hydrocortison-17-butyrat 0.1%, ointment	30	35.12	117.07
Average Acq. Costs of a 100g pack of TCS			**139.58**

Acq = acquisition; TCS = topical corticosteroids.

Source: BNF, 2022.

Table 41: Average Acquisition Costs of TCI

	Pack size, g	Acq. cost per pack, DKK	Acq. cost of a 100g pack, DKK
Tacrolimus 0.03%, ointment	30	212.57	708.57
Tacrolimus 0.1%, ointment	60	450.00	750.00
Average Acq. Costs of a 100g pack of TCI			**729.28**

Acq = acquisition; TCI = topical calcineurin inhibitors.

Source: BNF, 2022.

Tacrolimus is used as a proxy for Topical calcineurin inhibitors incl. Pimecrolimus as it has the lowest price.

Table 42: Assumed TCS and TCI Treatment Frequencies

	Treatment frequency	Assumption
TCS	100g every 2 weeks	Topical corticosteroids are used in a variety of skin conditions and should be applied thinly once or twice a day. For a once-daily application, it is assumed that the following quantities of topical corticosteroids will last for 2 weeks of treatment: • application to the arms, 30g to 60g • legs, 100g • trunk, 100g In the PRIME and PRIME2 clinical trials, inclusion criterion number 3 required at least 20 PN lesions in total on both legs, and/or both arms and/or trunk, at screening and at day 1. Therefore, we assume that patients will use 100g of topical glucocorticoid preparation every 2 weeks (50, 65).
TCI	100g every 6 weeks	Tacrolimus creme/ointment should be used once or twice a day initially, however, only twice a week as maintenance treatment (63). Thus, we assume that tacrolimus is 1/3 less frequently used compared to topical corticosteroids in the model.

TCI = topical calcineurin inhibitors; TCS = topical corticosteroids.

Based on the average acquisition costs and treatment frequencies for TCS and TCI, BSC treatment costs were estimated to be DKK 2,296.03 per cycle.

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8.5.2 Rescue drugs

Rescue drugs were included in the model based on the number of patients receiving the drug during the PRIME clinical trials (14). This was validated by a Danish clinical expert (30). If a drug used as rescue treatment was not found at medicinpriser.dk, it was not included in the model. The drugs used for rescue treatments are presented in Table 43. The cost per pack is presented in Table 44. The cost per patient per year and per model cycle is presented in Table 45.

Table 43: Rescue medication used

Drug	Dupilumab + BSC	BSC	Dose
Dexamethasone	1	3	0.5 mg once a day for 14 days
Prednisolone	1	1	10 mg once a day for 14 days
Ciclosporin	0	4	100 mg twice a day for 56 days
Hydroxychloroquine sulfate	0	1	200 mg once a day for 14 days
Methotrexate	0	1	10 mg once weekly for 14 days
Methylprednisolone	0	2	2 mg once a day for 14 days
Thalidomide	0	1	200 mg once a day for 14 days
Triamcinolone acetonide	0	1	40 mg once a day for 1 day
Tramadol	2	0	50 mg four times a day for 14 days
Tapentadol	1	0	50 mg four times a day for 14 days
Amitriptyline	1	0	25 mg once a day for 42 days
Fexofenadine	0	1	180 mg once a day for 14 days
Levocetirizine	0	1	5 mg once a day for 14 days
Clobetasol proprionate, cream	3	26	100 g used in 14 days
Betamethasone dipropionate 0.05%, cream	1	0	100 g used in 14 days
Fluocinonide 0.05%, cream	1	1	100 g used in 14 days
Calcipotriol 0.005% + betamethasone dipropionate 0.05%, ointment	0	2	100 g used in 14 days
Betamethasone valerate 0.1%, cream	0	1	100 g used in 14 days
Clobetasol, 0.5 mg/g	0	6	100 g used in 14 days
Mometasone, 1 mg/g	0	3	100 g used in 14 days
Tacrolimus	0	3	100 g used in 14 days

BSC = Best supportive care

Table 44: Packages used for the rescue medication costs

Drug	Pack size	Dose unit	Cost per pack (DKK)
Dexamethasone	20 tablets	1mg	133.00
Prednisolone	100 tablets	5mg	37.31
Ciclosporin	30 capsules	50mg	371.59
Hydroxychloroquine sulfate	100 tablets	200mg	98.00
Methotrexate	100 tablets	2.5mg	22.00
Methylprednisolone	100 tablets	4mg	142.54
Thalidomide	28 tablets	50mg	2,049.00
Triamcinolone acetonide	1 vial	40mg	38.00

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Tramadol	20 capsules	50mg	4.20
Tapentadol	30 tablets	50mg	136.45
Amitriptyline	100 tablets	25mg	35.07
Fexofenadine	100 tablets	180mg	130.95
Levocetirizine	100 tablets	5mg	72.00
Clobetasol proprionate, cream	1 pack	100 g used in 14 days	58.83
Betamethasone dipropionate 0.05%, cream	1 pack	100 g used in 14 days	46.00
Fluocinonide 0.05%, cream	1 pack	100 g used in 14 days	104.00
Calcipotriol 0.005% + betamethasone dipropionate 0.05%, ointment	1 pack	100 g used in 14 days	69.21
Betamethasone valerate 0.1%, cream	1 pack	100 g used in 14 days	66.07
Clobetasol, 0.5 mg/g	1 pack	100 g used in 14 days	58.83
Mometasone, 1 mg/g	1 pack	100 g used in 14 days	38.00
Tacrolimus	See tacrolimus treatment in section 8.5.1	100 g used in 14 days	See tacrolimus treatment in section 8.5.1

DKK = Danish Kroners

Table 45: Cost per patient of rescue drugs per year and per model cycle

Comparator	Cost per year	Cost per model cycle
Dupilumab + BSC	DKK 21.89	DKK 5.05
BSC	DKK 1,199.38	DKK 276.78

8.5.3 Disease management cost

The model considers the disease management costs associated with PN, based on response status. In the base case, responders were assumed to incur reduced disease management costs based on the number of healthcare visits per year. The unit costs were derived from the Danish DRG-tariff system (69). The number of visits per year was identified via clinical expert interviews and using the Danish Landspatientregistreret (70) divided by the number of expected Danish PN patients. Responders were not assumed to go to the hospital based on feedback from the Danish clinical expert (30). The expected number of visits per patient is presented in Table 46 and the cost per visit is presented in Table 47.

Table 46: Expected number of visits per patient per year

Type of visit	Responders	Non-responders	Source
	Number of visits per year		
Dermatology visits	3	3	Danish clinical expert feedback (30)
Inpatient	0	0.009	Responders assumed not to visit hospital. Number of PN inpatient admissions found in Landspatientregisteret (2021) divided by the prevalence of PN (70)
Outpatient	0	0.884	Responders assumed not to visit hospital. Number of PN outpatient visits found in Landspatientregisteret (2021) divided by the prevalence of PN (70)

PN = Prurigo nodularis

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Table 47: Cost per visit

Type of visit	Cost (DKK)	Source
Dermatology visit	553.19	Takstkort 21A: Dermato-venerologi. 1. konsultation dermatologi
Inpatient	19,941.00	DRG 2023: 09MA03 Lettere eller moderat hudsygdom, u. kompl. Bidiag, langliggertakst, (DL281) Prurigo nodularis
Outpatient	1,634.00	DRG 2023: 09MA98 MDC09 1-dagsgruppe, pat. mindst 7 år, (DL281) Prurigo nodularis.

DRG = Diagnosis-related group

The model also considers the additional treatments used to manage the disease. As stated earlier, this includes the use of zinc bandages and light treatment. Based on Danish clinical expert feedback, it was estimated that 40% of patients receive a zinc bandage regime and 25% receive a light treatment regime on an annual basis. The number of treatments, time interval, and time duration of treatment was based on the Danish clinical expert feedback, which is presented in Table 48. These are quite conservative estimates which seen in light of the small Danish study of PN patients where zinc dressing and phototherapy was used on 71.2% and 88.4% of the PN population respectively(26). The input aligns with 10 bandages per regime for zinc treatment and 25 treatments per regime for light treatment (30).

The cost of the zinc bandages was identified via apopro.dk, and the light treatment cost was identified via interactive DRG, which is presented in Table 49.

Table 48: Inputs for zinc bandages and light treatment disease management

Treatment	#	Source
Zinc bandages		
Treatments per week		Danish clinical expert feedback (30)
Treatment duration		
Annual % of patient being treated		
Light treatment		
Treatments per week		Danish clinical expert feedback (30)
Treatment duration		
Annual % of patient being treated		

Table 49: Cost of zinc bandages and light treatment disease management

Treatment	Cost per pack (DKK)	Cost per unit	Source
Zinc bandages	166.55	33.31	Apopro.dk Duoderm Extra Tynd 10 x 10 cm - 5 bandages
Light treatment	N/a	1,634.00	DRG 2023: 09MA98 MDC09 1-dagsgruppe, pat. mindst 7 år, (DL281) Prurigo nodularis. (BNGA2) Lysbehandling, UV-B, bredspektret

This results in DKK 30.75 and DKK 2,356.73 per model cycle for zinc bandages and light treatments, respectively.

8.5.4 Patient time and transport cost

The patient time cost and transport cost are calculated in line with DMC guidelines and using the Unit cost catalogue from DMC (71). The total number of healthcare visits is calculated based on the total number of management visits. A Danish clinical expert provided the estimate for time spent per visit (30). The number of visits was based on response to treatment. The transport cost is presented in Table 50 and the patient time cost is presented in Table 51. The cost per year for the patient time and transport is presented in Table 52.

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Table 50: Transport cost

Item	Number of units		Reference
	Responders	Non-responders	
Number of healthcare visits per year	3.00	3.89	Calculation of total management visits
Kilometres per visit	40	40	Værdisætning af enhedsomkostninger v. 1.6 (Medicinrådet) (71)
Transport cost per kilometre	DKK 3.51	DKK 3.51	Værdisætning af enhedsomkostninger v. 1.6 (Medicinrådet) (71)

Table 51: Patient time cost

Item	Number of units		Reference
	Responders	Non-responders	
Number of healthcare visits per year	3.00	3.89	Calculation of total management visits
Hours per visit	0.17	0.17	Danish clinical expert feedback (30)
Cost of patient time per hour	DKK 181.00	DKK 181.00	Værdisætning af enhedsomkostninger v. 1.6 (Medicinrådet) (71)

Table 52: Cost per year per patient for transport and patient time

Costs	Responders	Non-responders
Transport cost per year per patient	DKK 421.20	DKK 546.59
Patient time cost per year	DKK 90.50	DKK 117.44

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8.6 Results

8.6.1 Base case overview

The main base case settings are listed in Table53.

Table 53: Base case input data used in the model

Variable	Value	Measurement of uncertainty (distribution)	Reference
Mean age, years	49.5	SE = 0.91 (lognormal)	PRIME and PRIME2 pooled data; (14)
Percentage male	34.7%	n/N = 108/311 (beta)	
Body weight, kg	73.9	SE = 1.02 (lognormal)	
Baseline EQ-5D-5L utility estimated based on algorithm by Jensen et al., 2021	0.667	SE = 0.01 (beta)	
Baseline WI-NRS	8.493	SE = 0.06 (lognormal)	
Baseline DLQI	17.5	SE = 0.39 (lognormal)	
Age-specific mortality rate	Danish national life tables rates by age and sex	N/A	Statbank.dk Dødelighedstavle (2-års tavler) (72)
Response criteria	WI-NRS improvement ≥ 4 points from baseline	N/A	Danish clinical expert feedback (30)
Response rates			
Decision tree			
Percentage of dupilumab + BSC responders at week 24	58.8%	Beta – based on the percentage	PRIME and PRIME2 pooled data; (14)
Percentage of BSC responders at week 24	19.0%	As above	
Markov model			
Probability of dupilumab + BSC patients sustained response for Year 2-5+ (response waning)	[redacted]	As above	Chronos data due to preference from Danish clinical expert (30, 62)
Probability of BSC patients sustained response for Year 2-5+ (response waning)	[redacted]	As above	Danish clinical expert feedback (30)
Dupilumab annual other-cause discontinuation	[redacted]	As above	PRIME and PRIME2 pooled data; (14)

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Utility (EQ-5D-5L)			
Decision tree			
Utility weight during weeks 0-12 for all patients	[redacted]		
Utility weight during weeks 12-24 for all dupilumab + BSC patients	[redacted]	Cholesky and uncertainty in the patient baseline characteristics	Week 12 utility of all dupilumab + BSC patients generated by a regression model
Utility weight during weeks 12-24 for all BSC patients	[redacted]	As above	Week 12 utility of all BSC patients generated by a regression model
Markov model using treatment-based health states			
Dupilumab responders (on active treatment)	[redacted]	As above	Week 24 utility of dupilumab responders generated by a regression model
Dupilumab non-responders (not on active treatment)	[redacted]	As above	Week 12 utility of all BSC patients generated by a regression model
On BSC	[redacted]	SE = 0.01 (beta)	Baseline pooled arms utility; PRIME and PRIME2 pooled data; Sanofi data on file (14)

AD = atopic dermatitis; BSC = best supportive care; CEM = cost-effectiveness model; SE = standard error; QoL = quality of life; TCS = topical corticosteroids; TCI = topical calcineurin inhibitors; UK = United Kingdom; WI-NRS = The Worst-Itch Numeric Rating Scale.

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8.6.2 Base case results

The overall aggregated discounted model results for the base case indicate an incremental cost of [redacted] and incremental QALYs of 0.50 for dupilumab + BSC vs. BSC alone, resulting in an ICER [redacted]. This is presented in Table 54. The disaggregated discounted QALY, life year, and cost outcomes are presented in Table 55, Table 56, and Table 57, respectively.

Table 54: Base case discounted model results

Discounted model outcomes	Dupilumab + BSC	BSC	Increment	ICER
Costs	[redacted]	[redacted]	[redacted]	
QALYs	[redacted]	[redacted]	[redacted]	[redacted]
Life years	[redacted]	[redacted]	[redacted]	[redacted]
Years in response	[redacted]	[redacted]	[redacted]	[redacted]

BSC = Best supportive care; QALY = Quality-adjusted life-years

Table 55: Base case model discounted QALY outcomes

Discounted QALY outcomes	Dupilumab + BSC	BSC	Increment
Total QALYs	[redacted]	[redacted]	[redacted]
[redacted]			
QALYs in decision tree	[redacted]	[redacted]	[redacted]
[redacted]			
QALYs on dupilumab + BSC	[redacted]	[redacted]	[redacted]
QALYs on BSC	[redacted]	[redacted]	[redacted]

BSC = Best supportive care; QALY = Quality-adjusted life-years

Table 56: Base case model discounted life year outcomes

Discounted life year outcomes	Dupilumab + BSC	BSC	Increment
Total Life years	[redacted]	[redacted]	[redacted]
[redacted]			
Life years in decision tree	[redacted]	[redacted]	[redacted]
[redacted]			
Life years on dupilumab + BSC	[redacted]	[redacted]	[redacted]
Life years on BSC	[redacted]	[redacted]	[redacted]

BSC = Best supportive care

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Table 57: Base case model discounted cost outcomes

Discounted cost outcomes (DKK)	Dupilumab + BSC	BSC	Increment
[redacted]			
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]			
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]			
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]			

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8.7 Sensitivity analyses

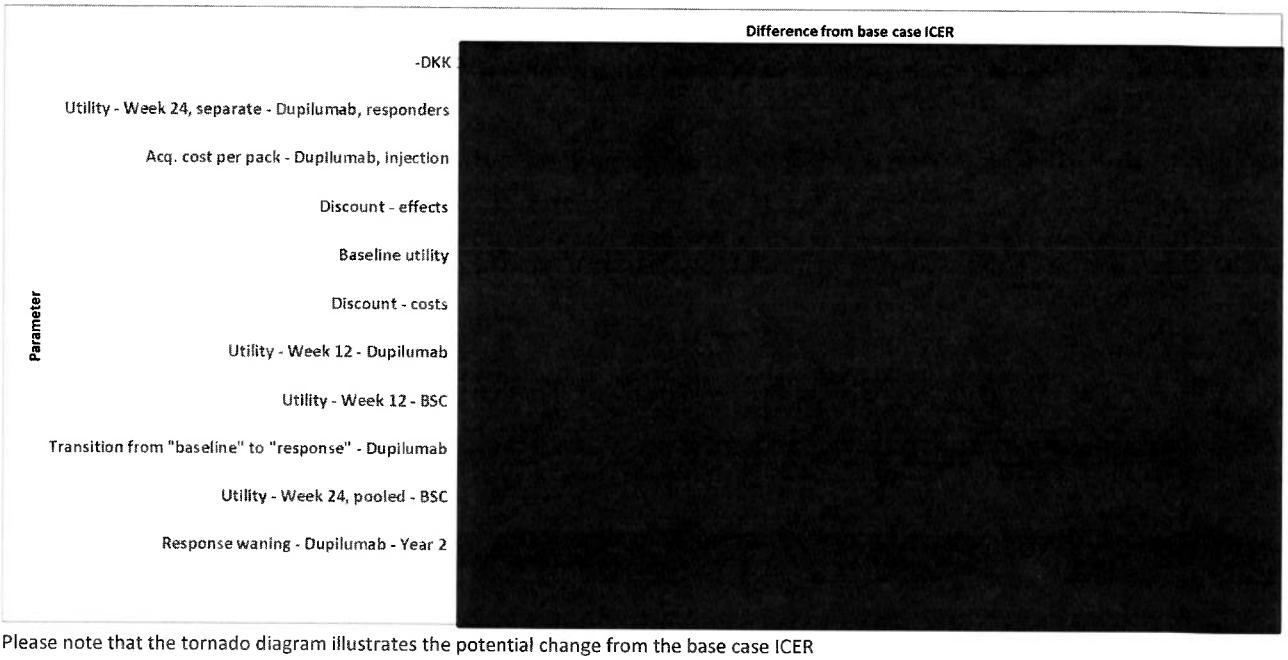
8.7.1 Deterministic sensitivity analyses

The model results were tested for parameter uncertainty in using one-way deterministic sensitivity analyses. The results of one-way sensitivity analyses are presented in Table 58 with the 10 parameters with the potential biggest impact on the results. The results are also illustrated in the tornado diagram presented in Figure 7. The impact of the price per pack for dupilumab is provided in Table 59.

Table 58: One-way sensitivity analysis

Parameter	Parameter lower and upper value	ICER lower bound (DKK per QALY)	ICER upper bound (DKK per QALY)	Difference in incremental ICER
[redacted]				

Figure 7: Tornado diagram illustrating one-way sensitivity analysis results



Please note that the tornado diagram illustrates the potential change from the base case ICER

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Table 59: Analysis on the impact of the dupilumab price per pack

Parameter	Pack price (DKK)	ICER (DKK per QALY)
[redacted]	[redacted]	[redacted]

8.7.1.1 Scenario analyses

A series of scenario analyses were conducted to explore the impact of different response criteria, the choice of either the overall population or only patients with prior systemic immunosuppressants, and the statistical imputation method are presented in Table 60. The results indicate a rather conservative base case ICER.

Table 60: Scenarios for different response criteria, population, and statistical imputation.

ICER (DKK per QALY) with different response criteria	WOCF + MI		As observed + MI	
	Overall population	Prior systemic immunosuppressants	Overall population	Prior systemic immunosuppressants
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

*Base case result

Furthermore, the impact of different sets of response waning numbers were explored. The response waning inputs were presented in section 8.2.1.2, and the impact of each set is presented below in Table 61.

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Table 61: Scenarios with different response waning options

ICER (DKK per QALY) with response waning		
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

8.7.2 Probabilistic sensitivity analyses

The probabilistic sensitivity analysis (PSA) was conducted with 10,000 iterations. All PSA inputs can be identified in Table 78 placed in 'Appendix J Probabilistic sensitivity analyses'. The results of the PSA, presented in Table 62, align with the deterministic base case results. The results are also illustrated in the incremental cost-effectiveness scatterplot in Figure 8. The cost-effectiveness of dupilumab using different willingness-to-pay (WTP) thresholds were investigated in the cost-effectiveness acceptability curve, presented in Figure 9. The figure illustrates that at a WTP threshold of 525,000 dupilumab would be cost-effective in 29.99%% of the iterations, at a WTP threshold of 575,000 dupilumab would be cost-effective in 53.24% of the iterations, and at a WTP threshold of 650,000 dupilumab would be cost-effective in 76.81% of the iterations.

Table 62: Aggregated results from the PSA

PSA model outcomes	Dupilumab + BSC	BSC	Increment
Costs (DKK)	[redacted]	[redacted]	[redacted]
QALYs	[redacted]	[redacted]	[redacted]
ICER			[redacted]

Figure 8: The incremental cost-effectiveness scatterplot

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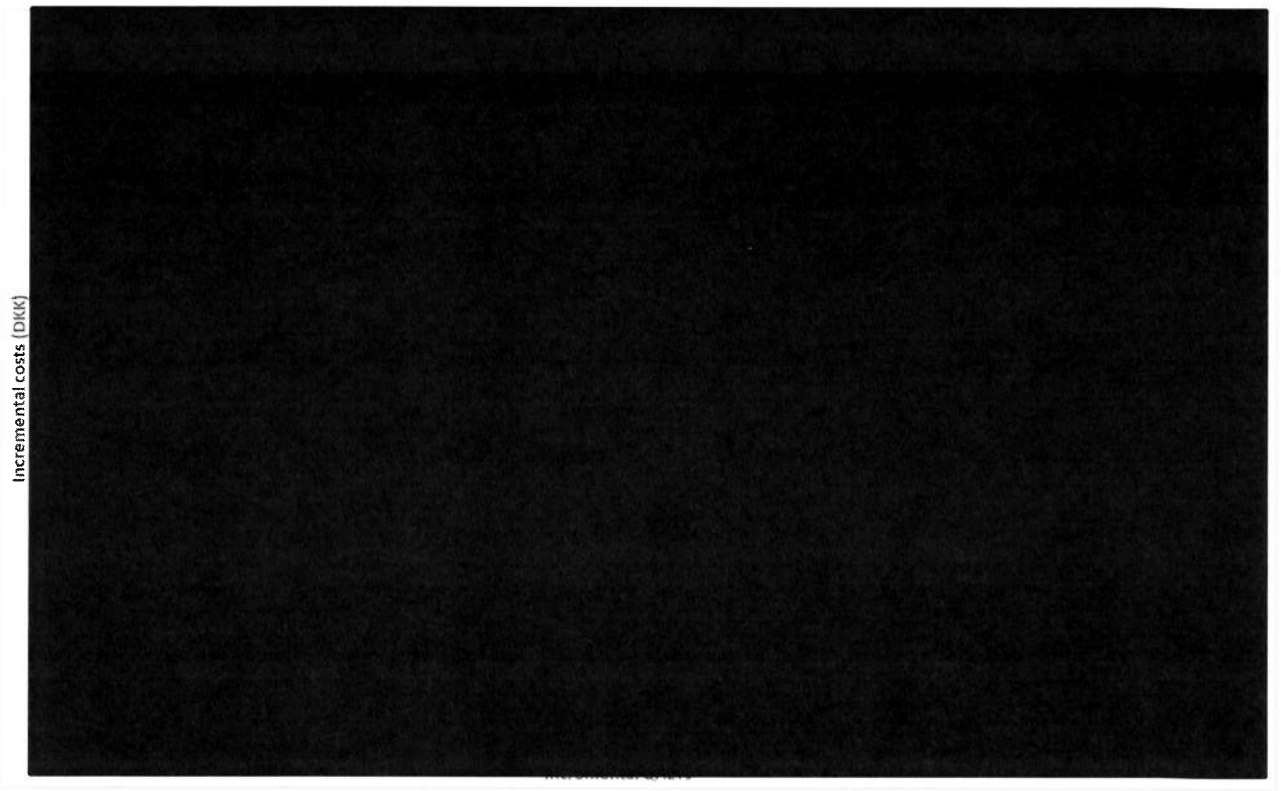
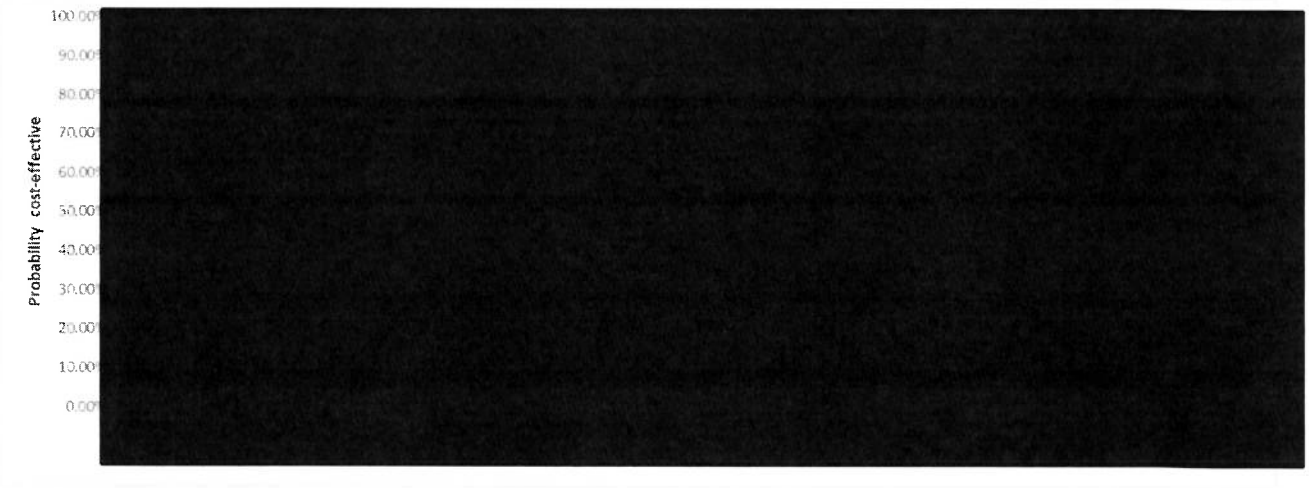


Figure 9: The cost-effectiveness acceptability curve



9. Budget impact analysis

The budget impact model was developed to estimate the expected budget impact of recommending dupilumab + BSC as the standard treatment for patients with PN in Denmark. The budget impact was estimated per year for the first 5 years after the introduction of the dupilumab + BSC regime in Denmark. It has been assumed that approximately 40% of eligible patients will receive dupilumab + BSC in the first year if made available, while the remainder of patients is assumed to receive BSC alone. This was based on feedback from the Danish clinical expert (30). As experience with dupilumab for this patient population increases, the market share is expected to increase by 10% per year. This is

presented in Table 63. In the current scenario where dupilumab + BSC is not available, it is assumed that 100% of patients are receiving BSC alone. The patient numbers are based on the data presented in section 5.1.3.

The budget impact model was linked through the decision tree and Markov traces in the cost-effectiveness model, and therefore, any changes in the settings of the cost-effectiveness model would affect the results of the budget impact model.

The budget impact analysis was developed by comparing the costs for the Danish healthcare system per year over five years in the scenario where the dupilumab + BSC regime is recommended as a standard treatment and the scenario where the dupilumab + BSC regime is not recommended as standard treatment. The total budget impact per year is the difference between the two scenarios, which is presented in Table 67..

Market share

Table 63: Market share split for dupilumab and the comparator

	Year 1	Year 2	Year 3	Year 4	Year 5
Dupilumab + BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BSC alone	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Number of patients

Table 64: Number of patients expected to be treated over the next five-year period - if dupilumab + BSC is introduced

	Year 1	Year 2	Year 3	Year 4	Year 5
Dupilumab + BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BSC alone	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total number of patients	**63**	**67**	**71**	**74**	**78**

Table 65: Number of patients expected to be treated over the next five-year period - if dupilumab + BSC is NOT introduced

	Year 1	Year 2	Year 3	Year 4	Year 5
Dupilumab + BSC	0	0	0	0	0
BSC alone	63	67	71	74	78
Total number of patients	**63**	**67**	**71**	**74**	**78**

Expenditure per patient

The cost per patient was linked to the decision tree and Markov trace, and the cost per patient, presented in Table 66, represents the average cost per patient for the 1st, 2nd, 3rd, 4th, and 5th year following treatment initiation.

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Table 66: Costs per patient per year

	1st year	2nd year	3rd year	4th year	5th year
Dupilumab + BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BSC alone	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Budget impact

Table 67: Expected budget impact of recommending dupilumab + BSC for the treatment of PN (DKK)

	Year 1	Year 2	Year 3	Year 4	Year 5
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

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10. Discussion on the submitted documentation

Results from both the pooled ITT analysis and individual pivotal phase 3 studies demonstrated the efficacy and safety of dupilumab versus placebo in improving the outcomes of adult patients with moderate to severe PN who are candidates for systemic therapy (51, 52). Statistical significance was achieved for the primary endpoint of both studies as measured by a reduction in WI-NRS by ≥4 points (12, 13, 51). A greater proportion of patients in the dupilumab group compared to the placebo group achieved a weekly average reduction of WI-NRS by ≥4 at Week 12 (<0.0001) and Week 24 (<0.0001) (51). Furthermore, the treatment benefit magnitude was greater at Week 24 than at Week 12 within the dupilumab group (40.5% vs. 58.8%) (51).

Key secondary endpoints were also met across the studies:

- The proportion of patients with healing PN skin lesions (IGA PN-S score of 0 or 1) and concomitant itch and skin lesions improvement (WI-NRS reduction by ≥4 points and IGA PN-S score of 0 or 1) at Week 24 in the dupilumab group was significantly higher than in the placebo group (51).
- In terms of prurigo activity, the proportion of patients in the dupilumab group with an IGA PN-A score of 0 or 1 was significantly higher compared to the placebo group as early as Week 4, with the highest difference being reported at Week 24 (55.6% vs. 19%) (51).
- Treatment with dupilumab resulted in a greater decrease in weekly average Skin Pain-NRS score as early as Week 2 and gradually decreased over time with the greatest difference observed at Week 24 (51).
- Nominally significant improvement in weekly average Sleep-NRS score from baseline at Week 24 was reported in the dupilumab group compared to the placebo group in the pooled ITT analysis and the PRIME results (12, 51). The difference in treatment effect reported in the weekly average Sleep-NRS score in PRIME2 between the dupilumab and the placebo group, although trending towards improvement, was not statistically significant (13).

Dupilumab resulted in a statistically significant improvement in HRQoL in terms of DLQI decrease, as well as improvement in mental health by a greater reduction in mean HADS scores compared to placebo from baseline at Week 24 (51). These results were confirmed in post-hoc analyses with dupilumab resulting in significant improvement in patient-reported HRQoL, as shown by a significant difference between the proportion of patients with improvements in ≥1 DLQI items (55).

Consistent with data in patients with asthma, AD, CRSwNP and EOE, treatment with dupilumab was well tolerated and had a favourable profile in patients with PN in the PRIME and PRIME2 studies (45, 52, 73).

The health economic model indicated that recommending dupilumab as standard care for the treatment of moderate-to-severe PN patients eligible for systemic treatments would result in an [redacted] indicating that dupilumab could be a cost-effective treatment in this population. For the subpopulation that had received systemic treatments before, [redacted] One-way sensitivity analysis indicated that the utility for dupilumab responders at week 24 and the cost of dupilumab were the most influential parameters concerning cost-effectiveness. [redacted]

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11. List of experts

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Version log

Version	Date	Change
1.0	27 November 2020	Application form for assessment made available on the website of the Danish Medicines Council.
1.1	9 February 2022	Appendix K and onwards have been deleted (company specific appendices) Color scheme for text highlighting table added after table of contents Section 6: Specified requirements for literature search Section 7: Stated it explicitly that statistical methods used need to be described Section 8.3.1: Listed the standard parametric models Section 8.4.1: Added the need for description of quality of life mapping Appendix A: Specified that the literature search needs to be specific for the Danish context and the application Appendices B and D: Stated it explicitly that statistical methods need to be described in the tables in the appendices
1.2	20 June 2022	Clarification of the introduction, including instructions on how to complete the form.

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Appendix A Literature search for efficacy and safety of intervention and comparator(s)

In accordance with the DMC guidance, if a head-to-head study with the relevant comparator for the indication in question for the application, the literature search can be omitted (48). There is currently no labelled systemic treatment for the indication. As such, **SoC (moisturizers, low to medium potent topical corticosteroids and topical calcineurin inhibitors)** is considered the relevant comparator in Danish clinical setting.
Sanofi have conducted two similarly designed multicentre, randomised, double-blind, placebo-controlled, parallel group, 24-week-treatment phase 3 studies, LIBERTY-PN PRIME (49) and PRIME2 (50) (see 7.1.2.1 and 7.1.2.2).

The evidence of the two studies (LIBERTY-PN PRIME and PRIME2) are considered to provide the best possible basis to inform the comparison of dupilumab + SoC with the relevant comparator in Danish clinical practice (SoC (moisturizers, low to medium potent topical corticosteroids and topical calcineurin inhibitors)) for adults with moderate-to-severe prurigo nodularis who are candidates for systemic therapy.

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Appendix B Main characteristics of included studies

Table 68: LIBERTY-PN PRIME

Trial name: 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)	NCT number: NCT04183335
Objective	**Primary Objective:** ´ • To demonstrate the efficacy of dupilumab on itch response in patients with PN, inadequately controlled on topical prescription therapy or when those therapies are not advisable. **Secondary Objectives:** • To demonstrate the efficacy of dupilumab on additional itch endpoints in patients with PN, inadequately controlled on topical prescription therapy or when those therapies are not advisable. • To demonstrate efficacy of dupilumab on skin lesions of PN. • To demonstrate the improvement in health-related quality of life. To evaluate safety outcome measures. • To evaluate immunogenicity of dupilumab
Publications – title, author, journal, year	Dupilumab in patients with prurigo nodularis: two randomized, double-blind, placebo-controlled phase 3 trials, Yosipovitch, Nat Med, 2023(11)
Study type and design	Interventional phase 3 trial. Randomized, double blind, placebo-controlled, multicentre (63 study locations), parallel group study
Sample size (n)	151 participants

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Trial name: 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)	NCT number: NCT04183335

Main inclusion and exclusion criteria

Inclusion:

Must be 18 to 80 years of age, at the time of signing the informed consent. With a clinical diagnosis of PN defined by all of the following:

- Diagnosed by a dermatologist for at least 3 months before the Screening visit
- On the worst-itch numeric rating scale (WI-NRS) ranging from 0 to 10, patients must have an average worst itch score of ≥7 in the 7 days prior to Day1.
- 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 Day 1
- History of failing a 2-week course of medium-to-superpotent topical corticosteroids (TCS) or when TCS are not medically advisable
- 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
- Must be willing and able to complete a daily symptom eDiary for the duration of the study

Exclusion:

Participants are excluded from the study if any of the following criteria apply:

- Presence of skin morbidities other than PN and mild atopic dermatitis that may interfere with the assessment of the study outcomes
- PN secondary to medications
- PN secondary to medical conditions such as neuropathy or psychiatric disease
- Within 6 months before the screening visit, or documented diagnosis of moderate to severe AD from screening visit to randomization visit
- Severe concomitant illness(es) under poor control that, in the investigator's judgment, would adversely affect the patient's participation in the study
- Severe renal conditions (e.g., patients with uremia and/or on dialysis)
- Participants with uncontrolled thyroid disease.
- Active tuberculosis or non-tuberculous mycobacterial infection, or a history of incompletely treated tuberculosis unless documented adequately treated
- 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.
- Active chronic or acute infection (except HIV infection) requiring treatment with systemic antibiotics, antivirals, antiprotozoals, or antifungals within 2 weeks before the screening visit or during the screening period
- Known or suspected immunodeficiency
- 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.

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Trial name: 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)	NCT number: NCT04183335

Intervention	**Treatment regimen:**
	• Dupilumab administration
	  o initial loading dose – 600mg
	  o Subsequent dose – 300mg every 2 weeks
	• Moisturizers
	• Low to medium potent topical corticosteroids
	• Topical calcineurin inhibitors
	
	Number of patients: 75

Comparator(s)	• Matched subcutaneous placebo • Moisturizers • Low to medium potent topical corticosteroids • Topical calcineurin inhibitors **Number of patients:** 76
Follow-up time	The duration of study for each participant will include 2-4 weeks of screening period, 24 weeks of treatment period and 12 weeks of post treatment follow up period.
Is the study used in the health economic model?	Yes

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Trial name: 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)	NCT number: NCT04183335

Primary, secondary and exploratory endpoints

Primary endpoint(s):

1. Proportion of participants with improvement (reduction) in WI-NRS by ≥4 from baseline to Week 24 [Time Frame: Baseline to Week 24] *

Secondary endpoint(s):

1. Time to onset of effect on pruritus as measured by proportion of participants with an improvement (reduction) in WI-NRS by ≥4 from baseline during the 24-week treatment period [Time Frame: Baseline to Week 24] *
2. Change from baseline in WI-NRS [Time Frame: Baseline to Week 12 and Week 24] *
3. Percent change from baseline in WI-NRS [Time Frame: Baseline to Week 2, Week 4, Week 12 and Week 24] *
4. Percent change from baseline in WI-NRS over time [Time Frame: Baseline to overtime until Week 24] *
5. Proportion of participants with improvement (reduction) in WI-NRS reduction ≥4 [Time Frame: Week 4 and Week 12] *
6. Proportion of participants with WI-NRS reduction ≥ 4 over time until Week 24 [Time Frame: Baseline to overtime until Week 24] *
7. Onset of action in change from baseline in WI-NRS [Time Frame: Baseline to overtime until Week 12] * [*Onset of action in change from baseline in WI-NRS (first p<0.05 difference from placebo in the daily WI-NRS that remains significant at subsequent measurements) until Week 12.]*
8. Proportion of participants with Investigator's Global Assessment for Prurigo Nodularis (IGA PN) 0 or 1 score for PN-stage (IGA PN-S) at Week 24 [Time Frame: Week 24] †
9. Proportion of participants with IGA PN-S 0 or 1 score at Week 4, 8 and 12 [Time Frame: Week 4, Week 8 and Week 12] †
10. Change from baseline in IGA PN-S score [Time Frame: Baseline to Week 4, Week 8, Week 12 and Week 24] †
11. Proportion of participants with IGA 0 or 1 score for PN-Activity (IGA PN-A) [Time Frame: Week 4, Week 8, Week 12, and Week 24] ‡
12. Change from baseline in health-related quality-of-life, (HRQoL), as measured by Dermatology Life Quality Index (DLQI) [Time Frame: Baseline to Week 12 and Week 24]§
13. Percentage of participants experiencing treatment-emergent adverse events (TEAEs) or serious adverse events (SAEs) from baseline through Week 24 [Time Frame: Baseline through Week 24]
14. Incidence of treatment-emergent antidrug antibodies against dupilumab over time [Time Frame: Baseline through Week 24]

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Trial name: 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)	NCT number: NCT04183335
Method of analysis	For the comparison between dupilumab and placebo, multiplicity-controlled statistical hierarchical testing, with a 2-sided significance level of 0.05, was applied to primary, key secondary, and other selected endpoints. Nominal p-values were reported for endpoints tested outside of the statistical hierarchy. The intention-to-treat (ITT) population included all randomized patients and efficacy was analysed based on the treatment allocated at randomisation. The safety analysis set included all randomised patients who received any study drug; in safety analyses, patients were analysed as treated. For the primary endpoint and binary secondary endpoints assessments, the Cochran–Mantel–Haenszel (CHM) test was used, adjusted for randomisation strata (documented history of atopy, stable use of TCS/TCI, and region) and baseline antidepressant use. Non-responders were considered patients receiving rescue treatment or with missing values. Time to first WI-NRS improvement was analysed using a Cox proportional hazards model, which included treatment, stratification factors, and baseline antidepressant use. Continuous secondary endpoints were analysed using an analysis of covariance (ANCOVA) model; efficacy data after rescue treatment were set to missing and imputed by worst-observation carried forward (WOCF). Missing data after treatment discontinuation for lack of efficacy were imputed by WOCF, and other missing data were imputed by multiple imputation. A hierarchical testing procedure was used to control the overall type-1 error rate at 0.05 for the primary, key secondary, and selected other endpoints for dupilumab versus placebo.
Subgroup analyses	No subgroup analyses
Other relevant information	

Table 69: PRIME2

Trial name: 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)	NCT number: NCT04202679
Objective	**Primary Objective:** ´ • To demonstrate the efficacy of dupilumab on itch response in patients with PN, inadequately controlled on topical prescription therapy or when those therapies are not advisable. **Secondary Objectives:** • To demonstrate the efficacy of dupilumab on additional itch endpoints in patients with PN, inadequately controlled on topical prescription therapy or when those therapies are not advisable. • To demonstrate efficacy of dupilumab on skin lesions of PN. • To demonstrate the improvement in health-related quality of life. To evaluate safety outcome measures. • To evaluate immunogenicity of dupilumab

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Trial name: 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)	NCT number: NCT04202679
Publications – title, author, journal, year	Dupilumab in patients with prurigo nodularis: two randomized, double-blind, placebo-controlled phase 3 trials, Yosipovitch, Nat Med, 2023(11)
Study type and design	Interventional phase 3 trial. Randomized, double blind, placebo-controlled, multicentre (63 study locations), parallel group study
Sample size (n)	160 participants

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Trial name: 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)	NCT number: NCT04202679

Main inclusion and exclusion criteria

Inclusion:

Must be 18 to 80 years of age, at the time of signing the informed consent. With a clinical diagnosis of PN defined by all of the following:

- Diagnosed by a dermatologist for at least 3 months before the Screening visit
- On the worst-itch numeric rating scale (WI-NRS) ranging from 0 to 10, patients must have an average worst itch score of ≥7 in the 7 days prior to Day1.
- 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 Day 1
- History of failing a 2-week course of medium-to-superpotent topical corticosteroids (TCS) or when TCS are not medically advisable
- 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
- Must be willing and able to complete a daily symptom eDiary for the duration of the study

Exclusion:

Participants are excluded from the study if any of the following criteria apply:

- Presence of skin morbidities other than PN and mild atopic dermatitis that may interfere with the assessment of the study outcomes
- PN secondary to medications
- PN secondary to medical conditions such as neuropathy or psychiatric disease
- Within 6 months before the screening visit, or documented diagnosis of moderate to severe AD from screening visit to randomization visit
- Severe concomitant illness(es) under poor control that, in the investigator's judgment, would adversely affect the patient's participation in the study
- Severe renal conditions (e.g., patients with uremia and/or on dialysis)
- Participants with uncontrolled thyroid disease.
- Active tuberculosis or non-tuberculous mycobacterial infection, or a history of incompletely treated tuberculosis unless documented adequately treated
- 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.
- Active chronic or acute infection (except HIV infection) requiring treatment with systemic antibiotics, antivirals, antiprotozoals, or antifungals within 2 weeks before the screening visit or during the screening period
- Known or suspected immunodeficiency
- 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.

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Trial name: 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)	NCT number: NCT04202679

Intervention	**Treatment regimen:**
	• Dupilumab administration
	  ○ initial loading dose – 600mg
	  ○ Subsequent dose – 300mg every 2 weeks
	• Moisturizers
	• Low to medium potent topical corticosteroids
	• Topical calcineurin inhibitors
	
	Number of patients: 78

Comparator(s)	• Matched subcutaneous placebo • Moisturizers • Low to medium potent topical corticosteroids • Topical calcineurin inhibitors **Number of patients:** 82
Follow-up time	The duration of study for each participant will include 2-4 weeks of screening period, 24 weeks of treatment period and 12 weeks of post treatment follow up period.
Is the study used in the health economic model?	Yes

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Trial name: 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)	NCT number: NCT04202679

Primary, secondary and exploratory endpoints

Primary endpoint(s):

1. Proportion of participants with improvement (reduction) in WI-NRS by ≥4 from baseline to Week 12 [Time Frame: Baseline to Week 12] *

Secondary endpoint(s):

1. Time to onset of effect on pruritus as measured by proportion of participants with an improvement (reduction) in WI-NRS by ≥4 from baseline during the 24-week treatment period [Time Frame: Baseline to Week 24] *
2. Change from baseline in WI-NRS [Time Frame: Baseline to Week 12 and Week 24] *
3. Percent change from baseline in WI-NRS [Time Frame: Baseline to Week 2, Week 4, Week 12 and Week 24] *
4. Percent change from baseline in WI-NRS over time [Time Frame: Baseline to overtime until Week 24] *
5. Proportion of participants with improvement (reduction) in WI-NRS reduction ≥4 [Time Frame: Baseline to Week 24] *
6. Proportion of participants with WI-NRS reduction ≥4 at Week 4 [Time Frame: Baseline to Week 4] *
7. Proportion of participants with WI-NRS reduction ≥ 4 over time until Week 24 [Time Frame: Baseline to overtime until Week 24] *
8. Onset of action in change from baseline in WI-NRS [Time Frame: Baseline to overtime until Week 12] * [*Onset of action in change from baseline in WI-NRS (first p<0.05 difference from placebo in the daily WI-NRS that remains significant at subsequent measurements) until Week 12.*]
9. Proportion of participants with Investigator's Global Assessment for Prurigo Nodularis (IGA PN) 0 or 1 score for PN-stage (IGA PN-S) at Week 24 [Time Frame: Week 24] †
10. Proportion of participants with IGA PN-S 0 or 1 score at Week 4, 8 and 12 [Time Frame: Week 4, Week 8 and Week 12] †
11. Change from baseline in IGA PN-S score [Time Frame: Baseline to Week 4, Week 8, Week 12 and Week 24] †
12. Proportion of participants with IGA 0 or 1 score for PN-Activity (IGA PN-A) [Time Frame: Week 4, Week 8, Week 12, and Week 24] ‡
13. Change from baseline in health-related quality-of-life, (HRQoL), as measured by Dermatology Life Quality Index (DLQI) [Time Frame: Baseline to Week 12 and Week 24]§
14. Percentage of participants experiencing treatment-emergent adverse events (TEAEs) or serious adverse events (SAEs) from baseline through Week 24 [Time Frame: Baseline through Week 24]
15. Incidence of treatment-emergent antidrug antibodies against dupilumab over time [Time Frame: Baseline through Week 24]

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Trial name: 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)	NCT number: NCT04202679
Method of analysis	For the comparison between dupilumab and placebo, multiplicity-controlled statistical hierarchical testing, with a 2-sided significance level of 0.05, was applied to primary, key secondary, and other selected endpoints. Nominal p-values were reported for endpoints tested outside of the statistical hierarchy. The intention-to-treat (ITT) population included all randomized patients and efficacy was analysed based on the treatment allocated at randomisation. The safety analysis set included all randomised patients who received any study drug; in safety analyses, patients were analysed as treated. For the primary endpoint and binary secondary endpoints assessments, the Cochran–Mantel–Haenszel (CHM) test was used, adjusted for randomisation strata (documented history of atopy, stable use of TCS/TCI, and region) and baseline antidepressant use. Non-responders were considered patients receiving rescue treatment or with missing values. Time to first WI-NRS improvement was analysed using a Cox proportional hazards model, which included treatment, stratification factors, and baseline antidepressant use. Continuous secondary endpoints were analysed using an analysis of covariance (ANCOVA) model; efficacy data after rescue treatment were set to missing and imputed by worst-observation carried forward (WOCF). Missing data after treatment discontinuation for lack of efficacy were imputed by WOCF, and other missing data were imputed by multiple imputation. A hierarchical testing procedure was used to control the overall type-1 error rate at 0.05 for the primary, key secondary, and selected other endpoints for dupilumab versus placebo.
Subgroup analyses	No subgroup analyses
Other relevant information	

Appendix C Baseline characteristics of patients in studies used for the comparative analysis of efficacy and safety

Table 70: Baseline characteristics and demographics (LIBERTY-PN PRIME, PRIME2, Pooled ITT)

Characteristic	LIBERTY-PN PRIME		PRIME2		Pooled ITT analysis	
	Dupilumab 300 mg Q2W (N=75)	Placebo (N=76)	Dupilumab 300 mg Q2W (N=78)	Placebo (N=82)	Dupilumab 300 mg Q2W (N=153)	Placebo (N=158)
Age, years, mean (SD)	[redacted]					
Male (%)						
Race, n (%)						
White						
Black or African American						
Asian						
Hispanic or Latino ethnicity, n (%)						
Weight, kg, mean (SD)						
BMI, kg/m2, mean (SD)						
Duration of PN, years, mean (SD)[a]						
History of atopy, n (%)[b]						

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Characteristic	LIBERTY-PN PRIME		PRIME2		Pooled ITT analysis	
	Dupilumab 300 mg Q2W (N=75)	Placebo (N=76)	Dupilumab 300 mg Q2W (N=78)	Placebo (N=82)	Dupilumab 300 mg Q2W (N=153)	Placebo (N=158)
Stable use of TCS/ TCI, n (%) [c]						
WI-NRS score, mean (SD)						
IGA PN-S score, mean (SD)						
IGA PN-S categorical score, n (%)						
3 (moderate)						
4 (severe)						
IGA PN-A score, mean (SD)						
IGA PN-A categorical score, n (%)						
0 (clear)						
1 (almost clear)						
2 (mild)						
3 (moderate)						
4 (severe)						
Skin pain – NRS score, mean (SD)						
Sleep – NRS score, mean (SD)						
Number of lesions from PAS, n (%)						
20-100						
>100						
Exact number of lesions in representative area from PAS, mean (SD)						
Healed lesions from PAS, n (%)						
0-24%						
25-49%						
50-74%						
75-99%						
DLQI score, mean (SD)						
HADS total score, mean (SD)						
HADS-A subscale score ≥8, n (%)[d]						
HADS-D subscale score ≥8, n (%)[d]						
EQ-5D visual analogue scale score, mean (SD)						
Antidepressant use at baseline, n (%)						

Footnote: [a] Derived as (Year of randomisation – Year of first diagnosis of PN) + (month of randomisation – month of first diagnosis of PN)/12.
[b] Defined as having a medical history of AD, allergic rhinitis/rhinoconjunctivitis, asthma, food allergy or eosinophilic esophagitis.
[c] Stable regimen for TCS is defined as maintaining the same medicine (low to medium potency TCS) and maintaining the same frequency of treatment (once or twice daily) used from 2 weeks prior to screening. Stable regimen for TCI is defined as maintaining the same medicine and treatment frequency (once or twice daily) used from 2 weeks prior to screening.
[d] A score of ≥8 in HADS-A and HADS-D subscales is the recommended within-participant minimum cut-off score for an abnormal score to indicate anxiety and depression, respectively.
Note: A low score indicates good outcome for WI-NRS (range 0-10), IGA PN-S (range 0-4), IGA PN-A (range 0-4), DLQI (range 0-30), Skin Pain-NRS (range 0-10) and HADS total score (range 0-42); A high score indicates good outcome for Sleep-NRS (range 0-10) and EQ-5D visual analogue scale score (range 0-100).
Abbreviations: AD, atopic dermatitis; BMI, body mass index; DLQI, dermatology life quality index; EQ-5D, EuroQoL 5 dimensions; HADS, hospital anxiety and depression scale; HADS-A, HADS-Anxiety; HADS-D, HADS-Depression; IGA PN-A, Investigator's global assessment for prurigo nodularis – activity; IGA PN-S, Investigator's global assessment for prurigo nodularis – stage; ITT, intent-to-treat; NRS, numeric rating scale; PAS, prurigo activity score; PN, prurigo nodularis; SD, standard deviation; TCI, topical calcineurin inhibitors; TCS, topical corticosteroids; Q2W, every 2 weeks; WI-NRS,

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worst-itch numeric rating scale.
Source: (12, 13)

Table 71: Baseline characteristics and demographics (post-hoc analysis - pooled ITT participants by prior IS use)

Characteristic	Patients with prior systemic immunosuppressants (N=114)			Patients without prior systemic immunosuppressants (N=197)		
Age, years, mean (SD)						
Male (%)						
Race, n (%)						
White						
Black or African American						
Asian						
Hispanic or Latino ethnicity, n (%)						
Weight, kg, mean (SD)						
BMI, kg/m2, mean (SD)						
Duration of PN, years, mean (SD) [a]						
History of atopy, n (%) [b]						
Stable use of TCS/ TCI, n (%) [c]						
WI-NRS score, mean (SD)						
IGA PN-S score, mean (SD)						
IGA PN-S categorical score, n (%)						
3 (moderate)						
4 (severe)						
IGA PN-A score, mean (SD)						
IGA PN-A categorical score, n (%)						
0 (clear)						
1 (almost clear)						
2 (mild)						
3 (moderate)						
4 (severe)						
Skin pain – NRS score, mean (SD)						
Sleep – NRS score, mean (SD)						
Number of lesions from PAS, n (%)						
20-100						
>100						

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Characteristic	Patients with prior systemic immunosuppressants (N=114)			Patients without prior systemic immunosuppressants (N=197)		
	[redacted]					
Exact number of lesions in representative area from PAS, mean (SD)	[redacted]					
Healed lesions from PAS, n (%)						
0-24%	[redacted]					
25-49%	[redacted]					
50-74%	[redacted]					
75-99%	[redacted]					
DLQI score, mean (SD)	[redacted]					
HADS total score, mean (SD)	[redacted]					
HADS-A score, mean (SD)	[redacted]					
HADS-D score, mean (SD)	[redacted]					
EQ-5D visual analogue scale score, mean (SD)	[redacted]					
Antidepressant use at baseline, n (%)	[redacted]					

Footnote: [a] Derived as (Year of randomisation - Year of first diagnosis of PN) + (month of randomisation - month of first diagnosis of PN)/12.
[b] Defined as having a medical history of AD, allergic rhinitis/rhinoconjunctivitis, asthma, food allergy or eosinophilic esophagitis.
[c] Stable regimen for TCS is defined as maintaining the same medicine (low to medium potency TCS) and maintaining the same frequency of treatment (once or twice daily) used from 2 weeks prior to screening. Stable regimen for TCI is defined as maintaining the same medicine and treatment frequency (once or twice daily) used from 2 weeks prior to screening.
Note: A low score indicates good outcome for WI-NRS (range 0-10), IGA PN-S (range 0-4), IGA PN-A (range 0-4), DLQI (range 0-30), Skin Pain-NRS (range 0-10) and HADS total score (range 0-42); A high score indicates good outcome for Sleep-NRS (range 0-10) and EQ-5D visual analogue scale score (range 0-100).
Abbreviations: AD, atopic dermatitis; BMI, body mass index; DLQI, dermatology life quality index; EQ-5D, EuroQoL 5 dimensions; HADS, hospital anxiety and depression scale; HADS-A, HADS-Anxiety; HADS-D, HADS-Depression; IGA PN-A, Investigator's global assessment for prurigo nodularis - activity; IGA PN-S, Investigator's global assessment for prurigo nodularis - stage; ITT, intent-to-treat; NRS, numeric rating scale; PAS, prurigo activity score; PN, prurigo nodularis; SD, standard deviation; TCI, topical calcineurin inhibitors; TCS, topical corticosteroids; Q2W, every 2 weeks; WI-NRS, worst-itch numeric rating scale.
Source: (56)

Comparability of patients across studies

LIBERTY-PN PRIME, PRIME2

A review of the baseline characteristics of the two phase-III trials, LIBERTY-PN PRIME and PRIME2, demonstrated that the two trials had similar baseline characteristics. No differences in baseline characteristics were observed between the arms of the two studies. It was noticed that the LIBERTY-PN PRIME had a higher percentage of participants of Hispanic or Latino ethnicity. However, this did not influence the balance between the two arms in the pooled analysis and was not deemed consequential.

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Comparability of the study populations with Danish patients eligible for treatment

The characteristics of the study population from the studies LIBERTY-PN PRIME and PRIME 2 are comparable to patients eligible for treatment in the Danish setting.

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Appendix D Efficacy and safety results per study

Definition, validity and clinical relevance of included outcome measures

Outcome measure	Definition	Validity	Clinical relevance
Proportion of participants with improvement (reduction) in WI-NRS by ≥4 from baseline	WI-NRS is a patient-reported outcome comprised of a single item rated on a scale from 0 ("No itch") to 10 ("Worst imaginable itch").	The WI-NRS has been developed as a simple, single item with which to assess the patient-reported severity of this symptom at its most intense during the previous 24-hour period. The method has previously been validated in PN. (74, 75)	The WI-NRS is a single-item patient-reported outcome measure in which patients indicate the intensity of the worst itching they experienced over the past 24 h
Proportion of participants with IGA PN-S 0 or 1 score at Week 24	IGA PN is a clinician-reported outcomes report that allows clinicians to assess IGA PN-S using a 5-point scale from 0 (clear) to 4 (sever	IGA PN-S is a validated tool for assessment of stage of chronic prurigo disease. (75)	The number of lesions is representative of the stage of the disease, while the presence of excoriations reflects the scratching activity.
Proportion of participants with both an improvement (reduction) in WI-NRS by ≥4 points from baseline to Week 24 and an IGA PN-S 0 or 1 score at Week 24	See definitions above	See validity above	See clinical relevance above

Results per study/analysis

LIBERTY-PN PRIME (NCT04183335)

Outcome	Study arm	N	Result (responder)	Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
				Difference	95% CI	P value	Difference (experimental vs. comparator)	95% CI	P value		
Proportion of participants with WI-NRS improvement (reduction) by ≥4 points from baseline to Week 24	Experimental (Dupilumab + SoC)	75	45 (60.0%)	NA	NA	NA	OR= 6.5	2.78, 15.41	<0.0001	OR derived from the Mantel-Haenszel estimator. CMH test was performed on the association between the responder status and intervention group, adjusted by documented history of atopy (atopic or non-atopic), stable use of TCS/TCI (yes or no), region and baseline anti-depressant use (yes or no).	LIBERTY-PN PRIME (12)
	Comparator (Matched placebo + SoC)	76	14 (18.4%)								
Proportion of participants with IGA PN-S 0 or 1 score at Week 24	Experimental (Dupilumab + SoC)	75	36 (48.0%)	NA	NA	NA	OR= 4.0	1.81, 8.98	0.0004	OR derived from the Mantel-Haenszel estimator. CMH test was performed on the association between the responder status and intervention group, adjusted by	LIBERTY-PN PRIME (12)
	Comparator (Matched placebo + SoC)	76	14 (18.4%)								

				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	Study arm	N	Result (responder)	Difference	95% CI	P value	Difference (experimental vs. comparator)	95% CI	P value		
										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).	
Proportion of participants with both an improvement (reduction) in WI-NRS by ≥4 points from baseline to Week 24 and an IGA PN-S 0 or 1 score at Week 24	Experimental (Dupilumab + SoC)	75	29 (38.7%)	NA	NA	NA	OR = 6.9	2.49, 19.05	<0.0001	OR derived from the Mantel-Haenszel estimator. CMH test was performed on the association between the responder status and intervention group, adjusted by documented history of atopy (atopic or non-atopic), stable use of TCS/TCI (yes or no), region and baseline anti-depressant use (yes or no).	Liberty-PN PRIME (12)
	Comparator (Matched placebo + SoC)	76	7 (9.2%)								

PRIME2 (NCT04202679)

Outcome	Study arm	N	Result (responder)	Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
				Difference	95% CI	P value	Difference (experimental vs. comparator)	95% CI	P value		
Proportion of participants with WI-NRS improvement (reduction) by ≥4 points from baseline to Week 12	Experimental (Dupilumab + SoC)	78	29 (37.2%)	NA	NA	NA	OR= 2.3	1.08, 5.00	<0.0216	OR derived from the Mantel-Haenszel estimator. CMH test was performed on the association between the responder status and intervention group, adjusted by documented history of atopy (atopic or non-atopic), stable use of TCS/TCI (yes or no), region and baseline anti-depressant use (yes or no).	PRIME2 (13)
	Comparator (Matched placebo + SoC)	82	18 (22.0%)								
Proportion of participants with WI-NRS improvement (reduction) by ≥4 points from baseline to Week 24	Experimental (Dupilumab + SoC)	78	45 (57.7%)	NA	NA	NA	OR= 9.0	3.56, 22.66	<0.0001	OR derived from the Mantel-Haenszel estimator. CMH test was performed on the association between the responder status and intervention group, adjusted by documented history of atopy (atopic or non-atopic), stable use of TCS/TCI (yes or no), region and baseline anti-depressant use (yes or no).	PRIME2 (13)
	Comparator (Matched placebo + SoC)	82	16 (19.5%)								
Proportion of participants with IGA PN-	Experimental (Dupilumab + SoC)	78	35 (44.9%)	NA	NA	NA	OR= 4.4	2.02, 9.55	<0.0001	OR derived from the Mantel-Haenszel estimator. CMH test was performed on	PRIME2 (13)

Outcome	Study arm	N	Result (responder)	Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
				Difference	95% CI	P value	Difference (experimental vs. comparator)	95% CI	P value		
S 0 or 1 score at Week 24	Comparator (Matched placebo + SoC)	82	13 (15.9%)							the association between the responder status and intervention group, adjusted by documented history of atopy (atopic or non-atopic), stable use of TCS/TCI (yes or no), region and baseline anti-depressant use (yes or no).	
Proportion of participants with both an improvement (reduction) in WI-NRS by ≥4 points from baseline to Week 24 and an IGA PN-S 0 or 1 score at Week 24	Experimental (Dupilumab + SoC)	78	25 (32.1%)	NA	NA	NA	OR = 6.1	2.03, 18.11	<0.0001	OR derived from the Mantel-Haenszel estimator. CMH test was performed on the association between the responder status and intervention group, adjusted by documented history of atopy (atopic or non-atopic), stable use of TCS/TCI (yes or no), region and baseline anti-depressant use (yes or no).	PRIME2 (13)
	Comparator (Matched placebo + SoC)	82	7 (8.5%)								

Pooled ITT population of LIBERTY-PN PRIME and PRIME2 (NCT04183335, NCT04202679)

				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	Study arm	N	Result (responder)	Difference	95% CI	P value	Difference (experimental vs. comparator)	95% CI	P value		
Proportion of participants with improvement (reduction) in WI-NRS by ≥4 from baseline to Week 24 [Time Frame: Baseline to Week 24	Experimental (Dupilumab + SoC)	153	90 (58.8%)	NA	NA	NA	OR= 7.6	4.03, 14.24	<0.0001	OR derived from the Mantel-Haenszel estimator. CMH test was performed on the association between the responder status and intervention group, adjusted by documented history of atopy (atopic or non-atopic), stable use of TCS/TCI (yes or no), region and baseline anti-depressant use (yes or no).	LIBERTY-PN (12), PRIME2 (13)
	Comparator (Matched placebo + SoC)	158	30 (19.0%)								
Proportion of participants with WI-NRS improvement (reduction) by ≥4 points from baseline to Week 12	Experimental (Dupilumab + SoC)	153	62 (40.5)	NA	NA	NA	OR= 3.1	1.77, 5.43	<0.0001	OR derived from the Mantel-Haenszel estimator. CMH test was performed on the association between the responder status and intervention group, adjusted by documented history of atopy (atopic or non-atopic), stable use of TCS/TCI (yes or no), region and baseline anti-depressant use (yes or no).	LIBERTY-PN (12), PRIME2 (13)
	Comparator (Matched placebo + SoC)	158	30 (19.0)								

				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	Study arm	N	Result (responder)	Difference	95% CI	P value	Difference (experimental vs. comparator)	95% CI	P value		
Patients with IGA PN-S 0 or 1 at Week 24 (Key secondary endpoint)	Experimental (Dupilumab + SoC)	153	71 (46.4)	NA	NA	NA	OR= 4.2	2.42, 7.37	<0.0001	OR derived from the Mantel-Haenszel estimator. CMH test was performed on the association between the responder status and intervention group, adjusted by documented history of atopy (atopic or non-atopic), stable use of TCS/TCI (yes or no), region and baseline anti-depressant use (yes or no).	LIBERTY-PN (12), PRIME2 (13)
	Comparator (Matched placebo + SoC)	158	27 (17.1)								
Patients with both an improvement (reduction) in WI-NRS by ≥4 points and IGA PN-S score of 0 or 1 at Week 24 (Key secondary endpoint)	Experimental (Dupilumab + SoC)	153	54 (35.3)	NA	NA	NA	OR= 6.5	3.05, 13.67	<0.0001	OR derived from the Mantel-Haenszel estimator. CMH test was performed on the association between the responder status and intervention group, adjusted by documented history of atopy (atopic or non-atopic), stable use of TCS/TCI (yes or no), region and baseline anti-depressant use (yes or no).	LIBERTY-PN (12), PRIME2 (13)
	Comparator (Matched placebo + SoC)	158	14 (8.9)								

Pooled ITT population of LIBERTY-PN PRIME and PRIME2 (NCT04183335, NCT04202679) by prior systemic use

Outcome	Population	Study arm	N	Result (responder)	Estimated absolute difference in effect			Estimated relative difference in effect			Overall p-value for interaction	Description of methods used for estimation	References
					Difference	95% CI	P value	Difference (dupilumab vs. comparator)	95% CI	P value			
[redacted]													

Outcome	Population	Study arm	N	Result (responder)	Estimated absolute difference in effect			Estimated relative difference in effect			Overall p-value for interaction	Description of methods used for estimation	References
					Difference	95% CI	P value	Difference (dupilumab vs. comparator)	95% CI	P value			

Appendix E Safety data for intervention and comparator(s)

LIBERTY-PN PRIME, PRIME2 (Pooled ITT population)

TEAEs

The most commonly reported TEAE in the pooled safety analysis belonged to the System Organ Classes (SOC)[ix] infections and infestations, skin and subcutaneous tissue disorders and nervous system disorders (≥10% in either treatment group) (Table 72) (52). Infections and infestations were also the most common TEAE reported in both treatment groups in PRIME2 and LIBERTY-PN PRIME (12, 13). At the system organ class level, musculoskeletal and connective tissue disorders and gastrointestinal disorders were reported more frequently in the dupilumab group than in the placebo group in the pooled safety analysis (52).

At the preferred term (PT) level[x], TEAEs with a ≥1% higher incidence in the dupilumab group than in the placebo group and ≥2% incidence in either treatment group were nasopharyngitis, dizziness, diarrhoea, eczema, blood creatine phosphokinase increased, conjunctivitis and conjunctivitis allergic, myalgia and accidental overdose (46). TEAEs with a ≥1% higher incidence in the placebo group than in the dupilumab group and ≥2% incidence in either treatment group were coronavirus disease 2019 (COVID-19), neurodermatitis, injection site pain and folliculitis (52).

In the pooled safety population, skin infections (excluding herpes) were reported by seven (4.6%) patients in the dupilumab group (PRIME2: four patients; PRIME: three patients) and in 14 (8.9%) patients in the placebo group (PRIME2: seven patients; PRIME: seven patients) (52). Five (3.3%) patients in the dupilumab group (PRIME2: five patients; PRIME: no patients) experienced herpes viral infections (including genital herpes simplex, herpes zoster, ophthalmic herpes zoster and oral herpes) compared to no patients in the placebo group (52).

Table 72: TEAEs reported in ≥2% in either treatment group – pooled safety analysis

Primary system organ class Preferred term, n (%)	Placebo (N=157)	Dupilumab (N=152)	Dupilumab vs. placebo RR (95% CI)
[redacted]			
[redacted]			
[redacted]			
[redacted]			
[redacted]			
[redacted]			
[redacted]			
[redacted]			
[redacted]			
[redacted]			
[redacted]			

[ix] System Organ Classes (SOCs) are groupings by aetiology, manifestation site or purpose.76. MedDRA. Medical Dictionary for Regulatory Activities (MedDRA) Hierarchy 2022 [Available from: https://www.meddra.org/how-to-use/basics/hierarchy.

[x] Preferred Terms (PTs) are distinct descriptors for a symptom, sign, disease diagnosis, therapeutic indication, investigation, surgical or medical procedure, and medical social or family history characteristic.76. Ibid.

Abbreviations: CI, confidence interval; COVID-19, coronavirus disease 2019; NC, not calculated; RR, relative risk; TEAE, Treatment emergent adverse event.
Sources: (12, 13)

AESIs and other selected AEs

In the pooled safety analysis, one (0.7%) patient in the dupilumab group (PRIME2: one patient; PRIME: no patients) and two (1.3%) patients in the placebo group (PRIME2: one patient; PRIME: one patient) experienced an adverse event of special interest (AESI) of systemic hypersensitivity reaction (Table 73). Other selected AEs that occurred less frequently in the dupilumab group than in the placebo group in the pooled safety analysis were potential drug-related hepatic disorders and injection site reactions, while conjunctivitis occurred more frequently in the dupilumab group than in the placebo group (52).

There were no events reported for the following AESIs and other selected AEs: anaphylactic reaction, helminthic infection, severe type of conjunctivitis, severe type of blepharitis, keratitis, clinically symptomatic eosinophilia, pregnancy, significant alanine aminotransferase (ALT) elevation, symptomatic overdose with the investigational medicinal product (IMP)/non-IMP, serious or severe injection site reactions lasting longer than 24 hours and suicidal behaviour (12, 13, 52).

The exposure-adjusted incidence rate for other selected AE groupings was higher in the dupilumab group compared to the placebo group (17.7 and 14.1 patients with at least one event per 100 patient-years, respectively) in PRIME2 (13). However, the exposure-adjusted incidence rate for other selected AE groupings was lower in the dupilumab group compared to the placebo group (17.1 and 30.5 patients with at least one event per 100 patient-years, respectively) in LIBERTY-PN PRIME (12).

Table 73: AESIs and other selected AEs – safety population from PRIME, PRIME2 and pooled safety analysis.

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Footnote: [a] The AE categories and associated footnotes are aligned with the AMCP dossier. [b] Conjunctivitis cluster includes conjunctivitis, allergic conjunctivitis, bacterial conjunctivitis, viral conjunctivitis, giant papillary conjunctivitis, eye irritation and eye inflammation. [c] Keratitis cluster includes keratitis, ulcerative keratitis, allergic keratitis, atopic keratoconjunctivitis and ophthalmic herpes simplex.
Abbreviations: AE = adverse event; AESI = adverse event of special interest; ALT = alanine transaminase; CMQ = custom MedDRA query; IMP = investigational medicinal product; NIMP = non-investigational medicinal product

Appendix F Comparative analysis of efficacy and safety

No comparative analysis was conducted.

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Appendix G Extrapolation

No extrapolation of study data has been used for this submission, as other data (response waning and discontinuation data) was used to predict the long-term outcomes in the Markov model. This data is presented in sections 8.2.1.2 and 8.2.1.3.

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Appendix H Literature search for HRQoL data

Electronic Databases

RTI-HS performed literature searches of the following electronic databases:

- Embase (using Elsevier Platform)
- MEDLINE and MEDLINE In-Process (using PubMed platform)
- EconLit
- Cochrane Library
- The Cochrane Central Register of Controlled Trials (CENTRAL)
- The Cochrane Database of Systematic Reviews
- Centre for Reviews and Dissemination (CRD)
- National Health Service (NHS) Economic Evaluation Database (EED)
- School of Health and Related Research Health Utilities Database
- Websites and Other Resources

Many of the medical literature databases, particularly Embase, provide comprehensive coverage of conference abstracts; thus, most abstracts were identified through the database searches. However, conducting hand searches on selected websites helped to ensure that the SLR identified the most recent abstracts that may not be indexed in the databases. Websites of the following professional organisations were searched:

- International Society for Pharmacoeconomics and Outcomes Research (ISPOR): https://www.ispor.org/ (meetings that have not yet been indexed in Embase)
- European Academy of Dermatology and Venereology Congress: https://www.eadv.org/congress
- American Academy of Dermatology: https://www.aad.org/member/meetings-education
- British Association of Dermatologists: https://www.bad.org.uk/events/annualmeeting
- International Conference on Dermatology and Dermatologic Diseases: https://waset.org/dermatology-and-dermatological-diseases-conference
- Australasian College of Dermatologists: https://acdasm.delegateconnect.co/
- The following websites were all searched to identify model structures and available utility, resource-use, and cost data:
- National Institute for Health and Care Excellence (NICE): https://www.nice.org.uk/
- Scottish Medicines Consortium (SMC): https://www.scottishmedicines.org.uk/
- Canadian Agency for Drugs and Technologies in Health (CADTH): https://www.cadth.ca/
- Haute Autorité de Santé (HAS): has-sante.fr (High Authority of Health – Portal HAS Professionals)
- International HTA Database (INAHTA): inahta.org (HTA Database – Home)
- Tufts Medical Center Cost-Effectiveness Analysis (CEA) Registry: https://cevr.tuftsmedicalcenter.org/databases/cea-registry
- European Network for Health Technology Assessment (EUnetHTA): https://www.eunethta.eu/

Reference lists of identified economic analyses, systematic reviews, and health technology assessments were searched for further studies of interest, because such reference lists typically

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are good sources of additional material that can supplement the articles identified from the medical literature databases.

Searches were conducted on 28 July 2021 and were not limited by date. No geographical or language restrictions were imposed on these searches. Searches of conference proceedings were limited to abstracts published in the last 2 years (2019-2021) because it was expected that all studies of a reasonable quality reported in abstract form before this date would have been published in a peer-reviewed journal.

Search terms included combinations of free text and Medical Subject Headings (MeSHs). For example, the following sets of terms were used:

- Population: Search terms relating to the overarching population of interest (e.g., 'prurigo nodularis'/exp OR 'prurigo nodularis':ti,ab,de OR 'nodular prurigo':ti,ab,de)
- Study type(s): Economic models, using 'cost'/exp OR 'cost benefit analysis'/exp OR 'health economics'/exp OR 'pharmacoeconomics'/exp OR 'cost analysis':ti,ab,de
- Exclusionary terms: Unwanted publication types, using terms for comments, editorials, letters, and case reports, and studies in animals but not in humans.

Table 74 presents the inclusion and exclusion criteria that were used for screening the identified studies. The inclusion and exclusion criteria identified the population and disease condition, interventions, comparators, outcomes, and study types (also known as the PICOS criteria).

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Table 74: eSLR inclusion and exclusion

Criteria	Included	Excluded
Population	▪ Patients with PN	▪ Patients without PN
Interventions and comparators	▪ All	▪ Nonpharmacological studies (e.g., exercise, Chinese medicine)
Outcomes	▪ Direct costs of interest may include the following: – Medication costs – Outpatient visit costs – Hospitalisation costs (ED or hospital visits) – Laboratory costs – Diagnostic costs (e.g., MRI) – Physician costs – Cost per treatment success or per response or per QALY gained ▪ Indirect or other costs of interest, including the following: – Productivity losses for patients; for parents or caregivers (e.g., wages lost because of travel or because of absences from work, changes to work status) – Out-of-pocket expenses – Travel costs for patients and caregivers ▪ Days lost from work for caregivers ▪ Resource-use estimates (e.g., number of hospitalisations and length of stay, drug utilisation, physician visits) ▪ Utility outcomes: – EQ-5D – SF-36 – HUI – HRQOL measures (when used to underpin utility estimates)	▪ Studies that report only clinical efficacy and safety data ▪ Resource-use or cost studies that do not report per-patient or per–health state results (e.g., studies that report annual national disease costs only) ▪ Studies reporting quality-of-life data but not health utility estimates
Study design	▪ Economic analyses (cost-effectiveness, cost-utility, cost benefit, cost-consequence, and cost-minimisation analyses) ▪ Utility studies (including studies where utility weights were mapped from other instruments, e.g., disease-specific patient-reported outcome measures) ▪ Prospective studies reporting utility, resource-use, or cost data (e.g., observational studies, clinical trials) ▪ Retrospective studies reporting resource-use or costs (e.g., database studies, medical record abstraction studies) ▪ Systematic reviews of economic analyses, utility, resource-use, or cost studies[a]	▪ Commentaries and letters (publication type) ▪ Consensus reports ▪ News articles ▪ Nonsystematic reviews ▪ Articles reporting cost estimates that are not based on data (e.g., commentaries making general reference to cost burden) ▪ Commentaries and letters (publication type) ▪ Editorials ▪ Genetic or pathological studies ▪ Case reports
Language	▪ No language limits[b]	▪ No language limits
Date	▪ No time limit for published manuscripts ▪ Conference proceedings from 2019 onwards	▪ No time limit ▪ Conference proceedings before 2019

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ED = emergency department; HRQOL = health-related quality of life; HUI = Health Utilities Index; MRI = magnetic resonance imaging; PN = prurigo nodularis; QALY = quality-adjusted life-year; SF-36 = 36-Item Short Form Health Survey.
Note: If it was unclear whether a study met any criterion during the level 1 screening process, the study was progressed to full-text screening to confirm its inclusion in the review.
[a] Systematic reviews were included at level 1 screening, used for identification of primary studies, and then excluded at level 2 screening.
[b] Need for data extraction from any included non–English language articles to be discussed with Sanofi.

Study Selection Process

Citations were downloaded using EndNote X8.0 (Clarivate Analytics; Philadelphia, PA) and then exported into Microsoft Excel (Microsoft Corporation; Redmond, Washington). Once all abstracts of potentially relevant published articles were identified, the screening of titles and abstracts was performed to determine study eligibility based on the inclusion and exclusion criteria.

The study selection process was performed in the following 2 phases:

Level 1 screen: Titles and abstracts of studies identified from the electronic databases and internet searches were double screened by 2 independent researchers to determine eligibility according to the inclusion and exclusion criteria described in Table 74. If there was disagreement about study relevance, consensus was reached through a third researcher.

Level 2 screen: For the studies selected at level 1, full texts were obtained and double screened by 2 independent researchers to determine eligibility according to the inclusion and exclusion criteria described in Table 74. If there was disagreement about study relevance, consensus was reached through a third researcher.

The inclusion and exclusion processes were thoroughly documented, including completion of a PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flow chart (77, 78) detailing the volume of articles included and excluded at each screening level. A list of studies excluded at level 2 screening, and the reason for each exclusion, was developed in Microsoft Excel.

Data Extraction

Data were extracted from full-text publications, where available (i.e., abstracts and posters were not used unless an abstract or poster was the terminal source document). When a full-text journal publication was not available, the source used (e.g., abstract or poster) was noted. References to other publications within a study were traced to original sources, where appropriate. Data were extracted into Microsoft Word (Microsoft Corporation; Redmond, Washington) tables.

All studies that reported relevant utility-weight estimates were tabulated to summarise the method of elicitation, study population, health state descriptions, and utility estimates.

A quality assessment was performed for each economic analysis (treatment studies), using the Drummond Checklist (79), which is recommended by NICE (80) (Appendix 12, Section 5.1.3), CADTH (81), and HAS (82). For utility estimates, an assessment of compliance with the NICE reference case was performed.

Search Results

The electronic database searches, performed using a predefined search strategy, were conducted on 28 July 2021, and were not limited by date for published manuscripts. No limits were imposed regarding the publication language or geographical location. These searches yielded a total of 91 titles (Embase = 46; PubMed = 29; Cochrane = 16; and EconLit = 0), of which 11 records were duplicates. Ultimately, 80 titles and/or abstracts were eligible for screening. The titles and

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abstracts were exported from EndNote X8.0 to a Microsoft Excel format for screening purposes. The titles and abstracts were then reviewed independently by 2 researchers for inclusion and exclusion. This is illustrated in Table 75.

Table 75: Search records

Database	Records	Unique records	Range in EndNote
Embase	46	46	1-46
PubMed	29	18	47-75
Cochrane	16	16	76-91
EconLit	0	0	NA
CRD & NHS EED	0	0	NA
ScHarrHud	0	0	NA
Totals	**91**	**80**	

CRD = Centre for Reviews and Dissemination; EED = Economic Evaluation Database; NA = not applicable; NHS = National Health Service.

Internet Searches and hand searches

Searches of internet websites were performed on 28 July 2021 and yielded a total 29 studies in the initial search, 2 of which were potentially relevant. One researcher screened the titles or abstracts online or in PDF format, where available, and downloaded onto an Excel sheet the titles that were potentially relevant for the review, to be screened by a second researcher. Bibliographic lists from 3 relevant systematic reviews and meta-analyses identified in the database searches were screened for relevant studies that were not identified in the electronic searches; Table 76 presents the sources that were searched. These searches returned 7 hits, all of which were unique references identified as being potentially relevant for our review and were progressed for formal screening. In addition, 3 articles were identified from reference lists of the included studies and were progressed for detailed screening.

Table 76: Sources searched in the hand searches

Full reference	Number of potentially relevant studies	Number screened after exclusion of duplicates
Hendricks AJ, Yosipovitch G, Shi VY. Dupilumab use in dermatologic conditions beyond atopic dermatitis–a systematic review. J Dermatolog Treat. 2021;32(1):19-28. Doi:http://dx.doi.org/10.1080/09546634.2019.1689227.	5	5
Janmohamed SR, Gwillim EC, Yousaf M, Patel KR, Silverberg JI. The impact of prurigo nodularis on quality of life: a systematic review and meta-analysis. Arch Dermatol Res. 2020. Doi:http://dx.doi.org/10.1007/s00403-020-02148-0.	2	2
Ekelem C, Juhasz M, Khera P, Mesinkovska NA. Utility of naltrexone treatment for chronic inflammatory dermatologic conditions: a systematic review. JAMA Dermatol. 2019 Feb 1;155(2):229-36. Doi:http://dx.doi.org/10.1001/jamadermatol.2018.4093.	0	0
Total	**7**	**7**

Screening Process and Results

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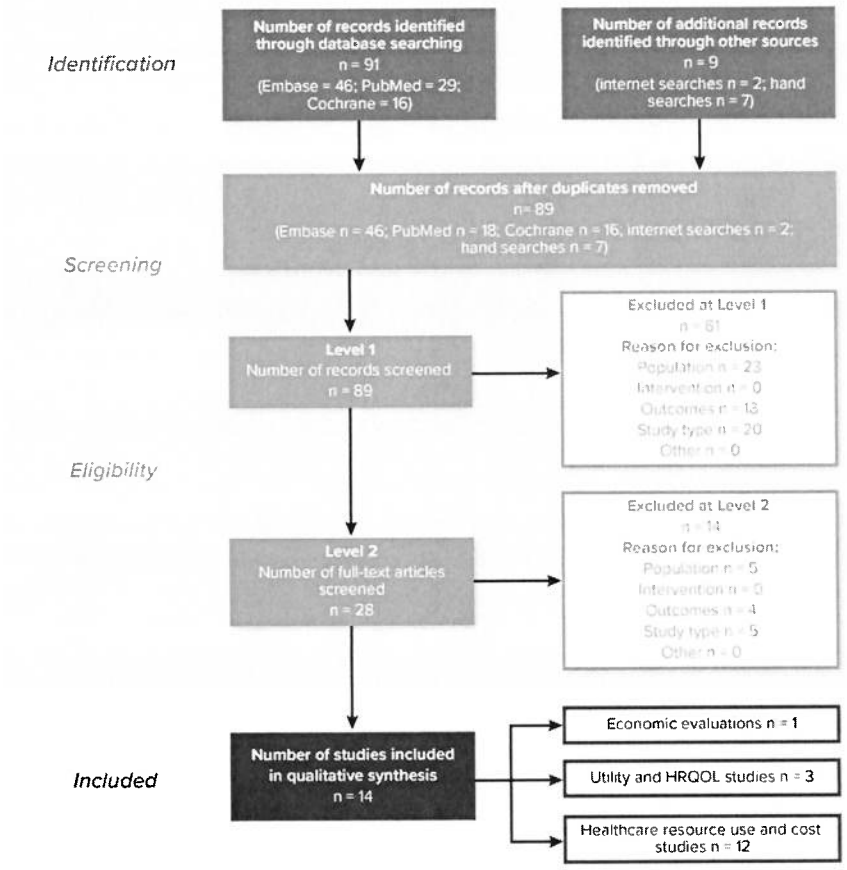
A total of 89 records (titles and abstracts) were selected for manual screening (databases = 80; internet searches = 2; hand searches = 7). Titles and abstracts were reviewed for eligibility using the predefined inclusion and exclusion criteria presented in the protocol. The titles and abstracts were reviewed independently by 2 researchers for inclusion and exclusion. Any discrepancies were resolved by consensus.

After the initial (level 1) screening of titles and abstracts, 28 publications (database searches = 28; internet searches = 0; hand searches = 0) were progressed for further screening of the full-text articles (level 2). At the level 2 screening, 14 publications (database searches = 14; internet searches = 0; hand searches = 0) met the predefined inclusion criteria and were selected for data extraction.

The volume of studies included and excluded at each stage of screening is shown in the PRISMA flow chart (77, 78) presented in Figure 10. The three utility and HRQoL studies are presented in Table 77.

Figure 10: PRISMA diagram



HRQOL = health-related quality of life; PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-Analyses.
Note: Some included studies are counted in more than 1 study type category
Source: Adapted from Moher, Liberati (77) and Page, McKenzie (78).

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Table 77: Utility Estimates Included in the Review

Ref ID	Primary reference (source)	Secondary reference(s) (source)
11	Whang KA, Le TK, Khanna R, Williams KA, Roh YS, Sutaria N, et al. Health-related quality of life and economic burden of prurigo nodularis. J Am Acad Dermatol. 2021. Doi: http://dx.doi.org/10.1016/j.jaad.2021.05.036.	NA
18	Whang K, Semenov Y, Khanna R, Williams K, Mahadevan V, Kwatra S. 723 Racial differences in the health-related quality of life of chronic pruritus patients. J Investig Dermatol. 2020;140(7):S97. Doi: http://dx.doi.org/10.1016/j.jid.2020.03.736.	NA
20	Todberg T, Zachariae C, Skov L. Treatment and burden of disease in a cohort of patients with prurigo nodularis: a survey-based study. Acta Dermato-Venereologica. 2020;100(8):1-5. Doi: http://dx.doi.org/10.2340/00015555-3471.	NA
Total articles included: primary references = 3; secondary references = 0; total = 3		

NA = not applicable; Ref ID = reference identification number.

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Appendix I Mapping of HRQoL data

As EQ-5D-5L was available in the clinical studies, mapping was not used to estimate the HRQoL.

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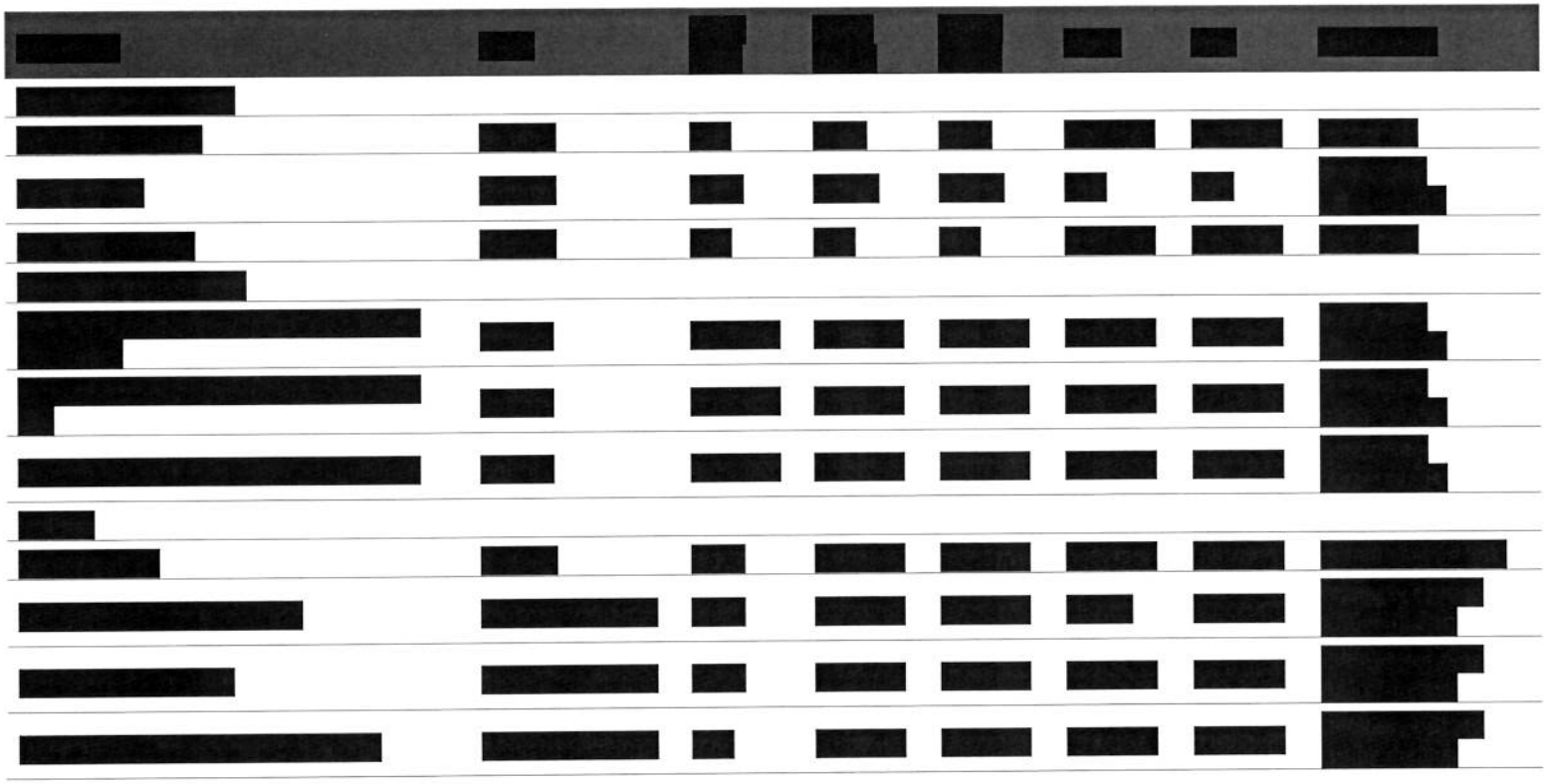
Appendix J Probabilistic sensitivity analyses

Table 78: PSA inputs



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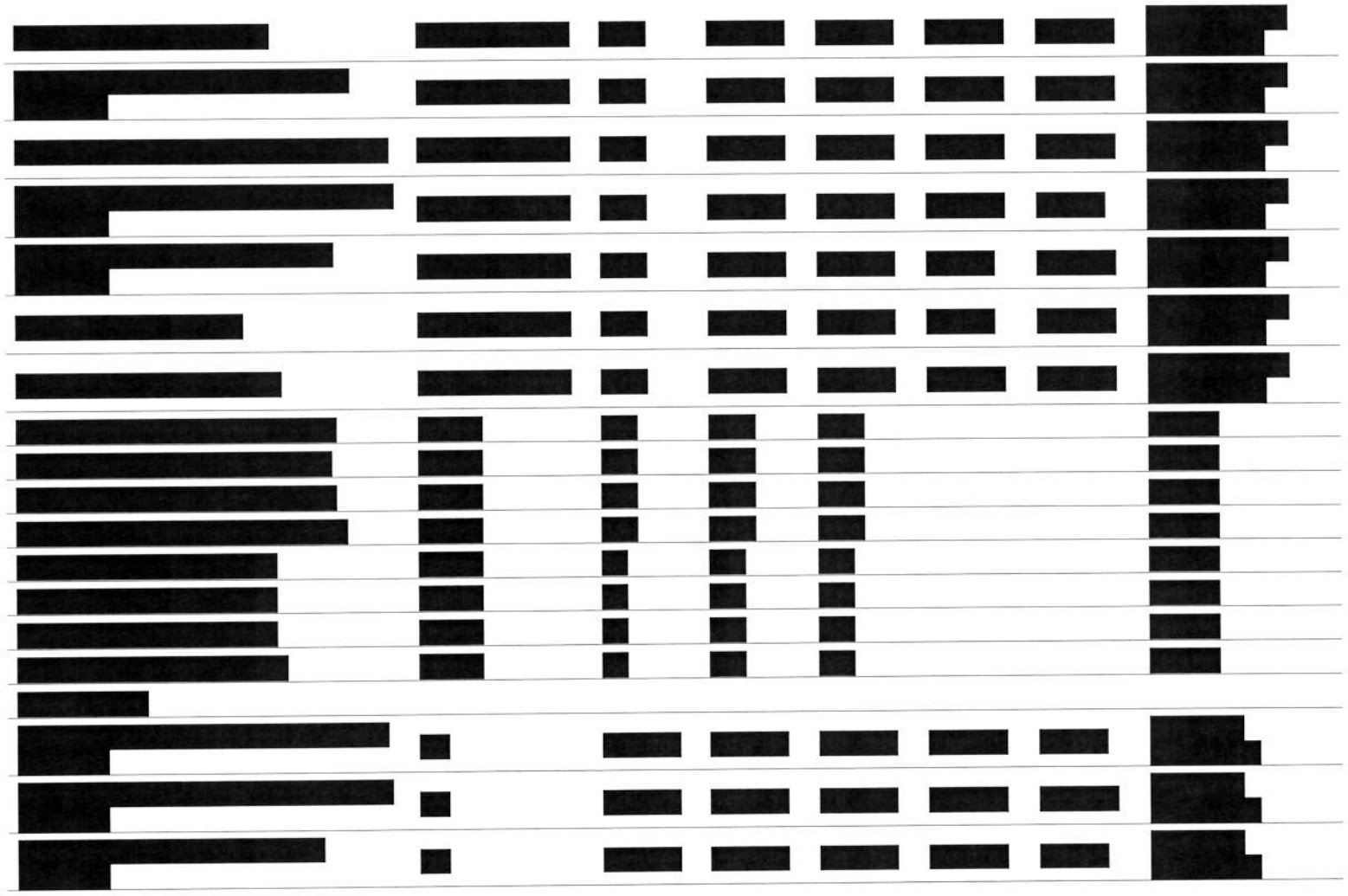

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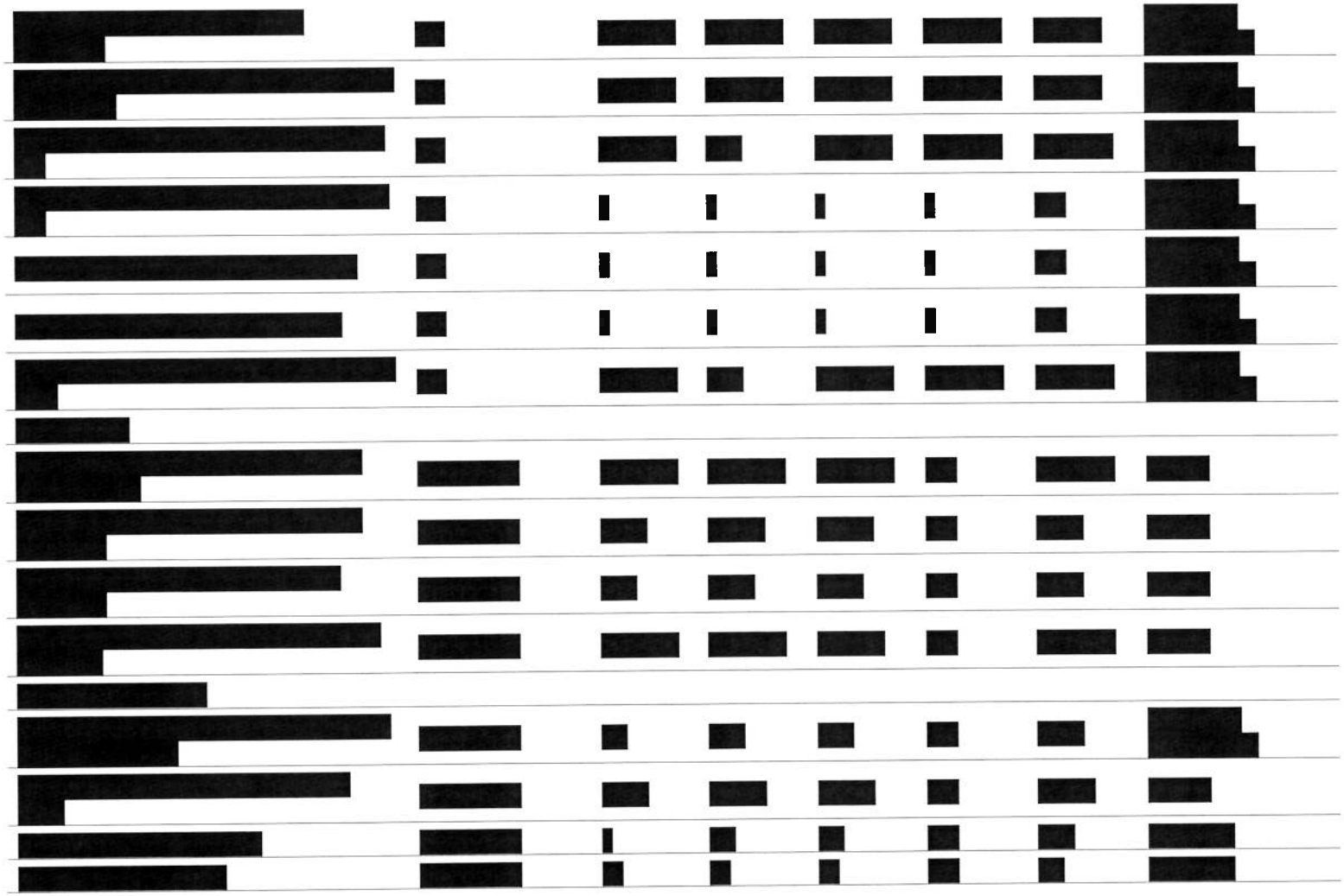

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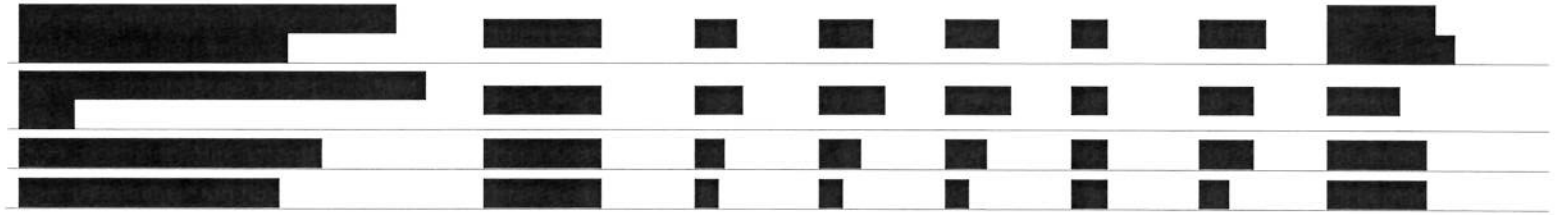

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