10 November 2022
EMA/9410/2023
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Dupixent

International non-proprietary name: dupilumab

Procedure No. EMEA/H/C/004390/II/0063

Note

Variation assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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List of abbreviations

AD	atopic dermatitis
ADA	antidrug antibody
ADR	adverse drug reaction
AE	adverse event
AESI	adverse event of special interest
ALT	alanine aminotransferase
AST	aspartate aminotransferase
BMI	body mass index
CI	confidence interval
ClinRO	clinician-reported outcome
CMH	Cochran-Mantel Haenszel
CMQ	custom MedDRA query
COA	clinical outcome assessment
COVID-19	coronavirus disease 2019
CRSwNP	chronic rhinosinusitis with nasal polyposis
CSR	clinical study report
DLQI	Dermatology Life Quality Index
EOS	end of study
FDA	Food and Drug Administration
HADS	hospital anxiety and depression scale
HADS-A	HADS-Anxiety
HADS-D	HADS-Depression
HIV	human immunodeficiency virus
HLGT	high level group term
HLT	high level term
HR	hazard ratio
HRQoL	health-related quality of life
Ig	Immunoglobulin
IGA	Investigator's Global Assessment
IGA PN	IGA for prurigo nodularis
IGA PN A	IGA PN-Activity
IGA PN-S	IGA PN-Stage
IL	interleukin
IMP	investigational medicinal product
ISE	integrated summary of effectiveness
ITT	intent-to-treat
KM	Kaplan-Meier
LLOQ	lower limit of quantification
LS	least square
MedDRA	Medical Dictionary for Regulatoy Activities
NAb	neutralizing antibody
Nab	neutralizing antibody
NRS	numeric rating scale
OR	odds ratio

PAS	prurigo activity score
PD	pharmacodynamic(s)
PGIC	Patient Global Impression of Change
PGIS	Patient Global Impression of Severity
PK	pharmacokinetic(s)
PN	prurigo nodularis
PRIME	EFC16459
PRIME2	EFC16460
PRO	patient-reported outcome
PT	preferred term
PY	participant-years
Q2W	every 2 weeks
SAP	statistical analysis plan
SC	subcutaneous(ly)
SCE	summary of clinical efficacy
SD	standard deviation
SOC	system organ class
SUSAR	suspected unexpected serious adverse reaction
TCI	topical calcineurin inhibitors
TCS	topical corticosteroids
TEAE	treatment-emergent adverse event
VAS	visual analogue score
WI-NRS	worst-itch numeric rating scale

1. Background information on the procedure

1.1. Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, sanofi-aventis groupe submitted to the European Medicines Agency on 4 April 2022 an application for a variation.

The following variation was requested:

Variation requested		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I and IIIB

Extension of indication to include treatment of adults with moderate to severe prurigo nodularis (PN) who are candidates for systemic therapy, based on results from studies EFC16459 and EFC16460 (PRIME and PRIME2); these are two phase 3, 24-week, randomized, double-blind, placebo-controlled, multi-centre, parallel group studies undertaken to evaluate the efficacy and safety of dupilumab in patients 18 years of age and older with moderate to severe PN, who are inadequately controlled on topical prescription therapies or when those therapies are not advisable. As a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1, 5.2 of the SmPC are updated. The Package Leaflet is updated in accordance. Version 8.0 of the RMP has also been submitted.
As part of this application, the MAH is also requesting a 1-year extension of the market protection.

The variation requested amendments to the Summary of Product Characteristics and Package Leaflet and to the Risk Management Plan (RMP).

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision (P/0394/2020) on the granting of a (product-specific) waiver.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the MAH did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

MAH request for additional market protection

The MAH requested consideration of its application in accordance with Article 14(11) of Regulation (EC) 726/2004 - one year of market protection for a new indication.

Scientific advice

The MAH received Scientific Advice on the development for their product Dupilumab for treatment of adult patients with moderate to severe PN who are candidates for systemic therapy from the CHMP on 27 February 2020 (EMEA/H/SA/2744/11/2020/II). The Scientific Advice pertained to the following clinical aspects:

The design of two replicate (EFC16459 and EFC16460) phase 3 studies to support a MAA, and specifically: patient population; primary endpoint and secondary endpoints; dose rationale and duration of exposure; sample size and statistical approach; background treatment, prohibited medications, and rescue treatment.

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Jan Mueller-Berghaus Co-Rapporteur: Finbarr Leacy

Timetable	Actual dates
Submission date	04 April 2022
Start of procedure:	23 April 2022
CHMP Rapporteur Assessment Report	20 June 2022
PRAC Rapporteur Assessment Report	20 June 2022
CHMP Co-Rapporteur Critique	29 June 2022
PRAC members comments	29 June 2022
PRAC Outcome	07 July 2022
CHMP members comments	11 July 2022
Updated CHMP Rapporteur(s) (Joint) Assessment Report	14 July 2022
Request for supplementary information (RSI)	21 July 2022
CHMP Rapporteur Assessment Report	17 October 2022
PRAC Rapporteur Assessment Report	14 October 2022
PRAC members comments	n/a
PRAC Outcome	27 October 2022
CHMP members comments	28 October 2022
Updated CHMP Rapporteur Assessment Report	03 November 2022
Opinion	10 November 2022
The CHMP adopted a report on the novelty of the indication/significant clinical benefit for Dupixent in comparison with existing therapies (Appendix 1)	10 November 2022

2. Scientific discussion

2.1. Introduction

2.1.1. Problem statement

Disease or condition

Prurigo nodularis (PN) is a subtype of chronic prurigo and can also be referred to as nodular prurigo or chronic nodular prurigo, and is defined by pruriginous nodular skin lesions in symmetrically distributed areas of the trunk and extremities. Chronic prurigo is defined by the presence of chronic pruritus for at least 6 weeks and multiple localized or generalized pruriginous cutaneous lesions Clinically, PN is characterized by severe pruritus that leads to prolonged, repetitive, and often uncontrollable rubbing and scratching that culminates in hyperkeratotic nodules on the skin.

Pruritus is the central manifestation in PN and the main driver of disease burden resulting in a significant quality of life impairment. In patients with PN, the itching is characteristically intense, causing people to scratch themselves and leading to the development of an itch–scratch cycle, which exacerbates the cellular damage in skin lesions and facilitates secondary infections. Patients with PN report chronic sleep loss due to constant itching, often experience constant burning, stinging, and pain at affected areas, and are often afflicted by chronic depression and anxiety. This constellation of symptoms results in a large impact on their quality of life. Psychiatric conditions are common in patients with chronic pruritus, with approximately 70% of chronic pruritus patients having a psychiatric comorbidity. In those patients with chronic pruritus and depression, the severity of depression correlates with the intensity of itch.

A variety of comorbidities is associated with PN, including mental health disorders, obesity, endocrine/metabolic disorders, autoimmune/auto-inflammatory disorders, cardiovascular disorders, renal disorders, malignancy, and atopy have been identified through case series and epidemiologic studies with PN have a higher comorbidity burden compared to age- and gender-matched controls as well as patients with AD or psoriasis, and higher healthcare utilization of specialty care services. Many of the associated comorbidities are characterized by pruritus and underlying neuronal and immune dysregulation, and likely contribute to the development of PN.

Approximately 20-60% of PN patients have either past or current history of AD or other atopic disorders. Those patients with a history of atopic disorders exhibit cutaneous hypersensitivity to various environmental allergens. In contrast, PN patients with no history of atopy do not show hypersensitive reactions against these allergens. Patients with a history of atopy also demonstrate high total IgE levels in serum and the presence of eosinophils in the dermis of skin biopsies.

The MAH's initially claimed therapeutic indication was:

Dupixent is indicated for the treatment of adults with moderate-to-severe prurigo nodularis (PN) who are candidates for systemic therapy.

Epidemiology

Broad epidemiological data for PN are lacking. A recent European study in a German population found an overall incidence rate of PN of 0.1%. The prevalence in Poland has been estimated to be 6.52 cases per 100 000 individuals. Prurigo nodularis is predominantly observed in older patients (median age of

>50 years), and rarely occurs in children. PN affects both genders, however there is a female predominance. Black patients are disproportionately affected with PN compared to Caucasian patients. While PN patients demonstrated higher all-cause mortality than control patients without PN, likely due to the high comorbidity burden seen in patients with PN, Black PN patients had the highest all-cause mortality compared to other races.

Pathogenesis

The pathophysiology of PN is dependent on, and driven by, the itch-scratch cycle irrespective of the initial underlying aetiology, and is characterized by synergistic neuronal- and immune-mediated mechanisms that lead to neuronal hypersensitization. Studies of the lesional skin of patients with PN revealed increased dermal nerve fiber density, increased expression of the neuropeptides and production of pro-inflammatory cytokines and mediators from keratinocytes and cutaneous immune cells, such as T cells, mast cells, and eosinophils. Pro-inflammatory Th2 cytokines are involved in PN. IL-4 and IL-13 can directly activate pruriceptors and cause neuronal sensitization leading to chronic itch. Type 2 cytokines, such as IL-4 and IL-31, are upregulated in the skin of patients with PN. Binding of IL-4 and IL-31 to these neuronal receptors may perpetuate the chronic activation of neurons and neuronal hypersensitization. In addition, IL-4 and IL-13 are pro-fibrotic cytokines and may play key roles in the fibrosis in PN lesions and drive chemotaxis of mast cells and eosinophils to the skin.

Clinical presentation, diagnosis

The diagnosis of PN is clinically determined and based on a history of chronic, severe pruritus, and the clinical finding of characteristic excoriated, hyperkeratotic, firm dome-shaped, smooth topped, or crusted nodules that are often symmetrically distributed. Core symptoms are the presence of multiple pruriginous lesions (localized or generalized), the presence of chronic pruritus (obligatory: itch ≥6 weeks) and the history and/or sign of a prolonged scratching behaviour.

Lesions may be grouped, can vary in number from one lesion to hundreds, and are present in areas that can be scratched or rubbed. The histologic features include prominent compact orthokeratosis, focal parakeratosis, hypergranulosis, irregular epidermal hyperplasia, thick collagen bundles arrayed perpendicularly to the overlying epidermis, and scattered fibroblasts in the papillary dermis.

Management

There are no approved systemic therapies available for the treatment of PN and approved treatment options for PN are limited to a few specific topical corticosteroids TCS of which some are authorised nationally in the EU. Identifying and treating an underlying cause, if present, is essential to minimize recurrent pruritus and to avoid any treatments which may be contraindicated. The current consensus guideline of International Forum for the Study of Itch (IFSI) recommends to follow a multimodal stepwise approach including general strategies to control pruritus, treatment of concomitant, potentially pruritogenic diseases and therapy of pruriginous lesions.

Topical therapies, such as topical corticosteroids (TCS) and topical calcineurin inhibitors (TCI) are used as first-line therapy alone or in combination. Continuous use of emollients as supportive antipruritic care is recommended. Other topical therapies such as Vitamin D3 analogues, topical anesthetics, topical capsaicin are also used but data regarding efficacy are lacking.

Additional therapies used to treat PN include intralesional injections of corticosteroids, cryotherapy, and phototherapy. UV phototherapy is a viable therapeutic option, in particular for elderly patients with multi-morbidities and multi-medications. Antihistamines are often used in PN treatment but evidence of an antipruritic effect is low.

Other systemic treatment options for patients with severe PN and a non-satisfactory response to the initial first line of therapies are neuromodulatory agents such as gabapentinoids, NKR 1 antagonists, antidepressants, and μ-opioid receptor antagonists and systemic immunosuppressants such as oral corticosteroids, cyclosporine, and methotrexate.

Prurigo nodularis is a chronic skin disease with a high disease burden due to the central manifestation of pruritus and hyperkeratotic nodules with a substantial impact on the quality of life. There are currently no approved systemic therapies. The currently available effective treatment options for PN are limited and do not always achieve satisfactory response in PN patients. The therapy of PN remains challenging and of prolonged course. Based on the currently available therapies, there is an important unmet need for treatment options for patients with PN that cannot be controlled with the current treatment options.

2.1.2. About the product

Dupilumab is a human monoclonal IgG4 antibody that inhibits IL-4 and IL-13 signaling by specifically binding to the IL 4Rα subunit shared by the IL-4 and IL-13 receptor complexes. Dupilumab inhibits IL 4 signaling via the Type I receptor (IL4Rα/γc) and both IL-4 and IL-13 signaling through the Type II receptor (IL 4Rα/IL 13Rα1). Blocking IL-4Rα with dupilumab can reduce the absolute number of Th2 cells and inhibits IL-4 and IL-13 cytokine-induced type 2 inflammatory responses, including the release of proinflammatory cytokines, chemokines, nitric oxide, and IgE.

Dupilumab is currently approved for the following indications: atopic dermatitis (AD), asthma, chronic rhinosinusitis with nasal polyposis (CRSwNP).

2.1.3. The development programme/compliance with CHMP guidance/scientific advice

A Scientific Advice, with implications for the present Application was received from the CHMP in 2020 (EMEA/H/SA/2744/11/2020/II).

2.1.4. General comments on compliance with GCP

The MAH states that the clinical studies presented in this dossier were conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with the International Council for Harmonisation guidelines for Good Clinical Practice and applicable regulatory requirements.

2.2. Quality aspects

No new quality data have been submitted in this application, which was considered acceptable by the CHMP.

2.2.1. Justification regarding existing Drug-Device Combination

In *3.2.R Regional information* justifications have been provided regarding the use of the existing Medical Device Part of the Drug-Device Combination (DDC) 300 mg PFS, PFS-S and PFP for the introduction of the Prurigo nodularis indication for the adult patient population.

Change assessment towards MDR Article 117 (PFS, PFS-S, PFP)

The MAH has determined that there are no changes to the design or intended purpose of the device (part), nor is there a new medical device being introduced. Therefore, a Notified Body opinion is not required. The details of the MAH´s assessment are as follows:

• There is no impact on the medical device clinical use; as it will still be administered with the same procedure and at the same injection sites (abdomen, upper thigh regions and upper arm).

• There are no changes to the medical device instructions for use related to the new therapeutic indication.

• There is no change to the intended users; the self-administration patient characteristics (functional capabilities/impairment such as perceptual, cognitive, manual dexterity, other comorbidities) are equal to the currently approved population.

Table 1 Intended users and patient populations of Dupilumab 300 mg PFS, PFS-S and PFP for the new therapeutic indication

Dupixent® 300 mg (2mL) PFS, PFS-S and PFPs for the Prurigo Nodularis indication	
Intended Users	Healthcare Professionals (HCP) & Lay Caregivers Patient self-administration: Adults
Patient population	Adults

Usability Studies

The MAH has determined that there is no need for additional Usability Studies.

The quality, safety and/or efficacy of the DDC product are not affected as the assessment results conclude the following:

• There are no changes to the medical device instructions for use related to the new therapeutic indication.

• There are no changes to the performance requirements, nor the specifications of the medical device.

• No new or different risks in relation to the medical device use have been identified, therefore no new mitigations need to be introduced. The existing Risk Management File will be updated as part of the life cycle management activities. The hazard list is already covering this new therapeutic indication.

No need for additional Usability Studies; usability for the PFS, PFS-S and PFP is supported by human factors data that could be bridging data to the same identical device part used with the patient populations tested to support the approved indications.

The intended user population is unchanged versus the DDC currently authorised, as the self-administration patient characteristics (functional capabilities/impairment such as perceptual, cognitive, manual dexterity, other comorbidities) are equivalent to the currently approved populations. Therefore, the bridging data can demonstrate the effective use of the DDC by the same intended user population.

2.2.2. Discussion on quality

No new quality data have been submitted in this application.

The proposed new Prurigo nodularis indication for adults does not result in the introduction of a new medical device or a modification to the design, or aforementioned intended use/purpose of the medical device part of the Drug Device Combination (DDC). Therefore, it is agreed that the variation application supporting the new therapeutic indication does not require a Notified Body Opinion (NBOp) for the currently authorised DDC.

It is agreed that there is no need for additional Usability Studies as the new therapeutic indication has no impact on the 1) intended users, 2) the clinical use, and 3) use-related risks. In addition, there is no difference in the medical device instructions for use compared with the authorised instructions.

From a quality point of view, the MAH´s justifications regarding the use of the existing Medical Device Part of the DDC 300 mg PFS, PFS-S and PFP for the new therapeutic indication in adults is accepted.

2.2.3. Conclusion on the quality aspects

The available quality data do not raise concern in the indication.

2.3. Non-clinical aspects

No new non-clinical data have been submitted in this application, which was considered acceptable by the CHMP.

2.3.1. Ecotoxicity/environmental risk assessment

The environmental risk assessment provided in Module 1.6 has been updated.

A claim of exclusion from submission of environmental risk assessment studies is made according to Section 2 of the 2006 CHMP Guideline on the Environmental Risk Assessment of Medicinal Products for Human Use (ERA Guideline corr 2) because dupilumab is a monoclonal antibody consisting of linked naturally occurring amino acids. Per the ERA Guideline, vitamins, electrolytes, amino acids, peptides, proteins, carbohydrates and lipids are exempt from ERA study requirements because by their nature they are unlikely to result in significant risk to the environment.

2.3.2. Discussion on non-clinical aspects

No new non-clinical data have been submitted in this application.

The claim for ERA exemption by the MAH is justified and in conformity with the ERA guideline since the extension indication variation request concerns a monoclonal antibody consisting of naturally occurring amino acids. Dupilumab is significantly metabolized in-vivo and is expected to be readily and rapidly degraded in wastewater treatment systems and in the environment. The antibody’s structure and mode of action do not indicate any specific risk to the environment.

2.3.3. Conclusion on the non-clinical aspects

The available non-clinical data do not raise concern in the indication.

The updated data submitted in this application do not lead to a significant increase in environmental

exposure further to the use of dupilumab.

- Considering the above data, dupilumab is not expected to pose a risk to the environment.

2.4. Clinical aspects

2.4.1. Introduction

GCP

The Clinical trials were performed in accordance with GCP as claimed by the MAH.

The MAH has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

- Tabular overview of clinical studies

Study number/Status at study cut-off date	Summary of key study information	Planned study duration	Participants randomized/ treated
EFC16460 (LIBERTY-PN PRIME2) Ongoing (24-week intervention period completed; follow-up period ongoing) Cut-off date for the integrated safety analysis: 30 August 2021	A randomized, multi-center, 24-week treatment, parallel group, double-blind, placebo-controlled study to evaluate the use of dupilumab in participants with PN whose disease was inadequately controlled on topical prescription therapies or when those therapies were not advisable. Population: adults (18 to 80 years of age) Dose regimen: 300 mg Q2W, after an initial loading dose of 600 mg (2 injections of 300 mg)	24 weeks of treatment + 12 weeks of follow-up	Randomized=160 Treated=159 (Placebo: 82; dupilumab 300 mg: 77 treated)
EFC16459 (LIBERTY-PN PRIME) Ongoing (24-week intervention period completed; follow-up period ongoing) Cut-off date for the integrated safety analysis: 12 November 2021	A randomized, multi-center, 24-week treatment, parallel group, double-blind, placebo-controlled study to evaluate the use of dupilumab in participants with PN whose disease was inadequately controlled on topical prescription therapies or when those therapies were not advisable. Population: adults (18 to 80 years of age) Dose regimen: 300 mg Q2W, after an initial loading dose of 600 mg (2 injections of 300 mg)	24 weeks of treatment + 12 weeks of follow-up	Randomized=151 Treated=150 (Placebo: 75; dupilumab 300 mg: 75 treated)

2.4.2. Pharmacokinetics

Dupilumab concentrations in serum were measured in studies EFC16459 and EFC16460 using sparse sampling (samples collected at predose, during treatment at Week 4, Week 8, Week 12 and Week 24, and at the end of the follow-up period at Week 36). Descriptive statistics were used to summarize the concentration data over time in patients with PN in the individual studies.

The PK of dupilumab in healthy subjects and in patients with AD, asthma, and CRSwNP is also extensively described in the original marketing application for AD and the subsequent applications for asthma and CRSwNP.

Dupilumab concentrations determined in the PN population were compared to the dupilumab concentrations in AD, asthma, and CRSwNP populations as well as in healthy subjects using both descriptive analysis from the observed data and a model-based approach.

A Pop PK analysis was conducted, using the MAP Bayesian approach (Study POH0779), based on a previously established global Pop PK base model from the CRSwNP submission (see Section 2.4.4). This global Pop PK structural model was developed using dupilumab data pooled from Phase 1 to Phase 3 studies in healthy subjects (adults), patients with AD (adults), and asthma (adults and adolescents). Data from Studies EFC16459 and EFC16460 were not included in the global Pop PK model development, but were evaluated using the MAP Bayesian approach, which allows the incorporation of prior information into the analysis for the PK data in patients with PN. The adequacy of the Bayesian approach based on the global model to describe the PK data in patients with PN was first confirmed by standard diagnostic criteria (external validation). The post hoc exposure estimates from the model were then used to assess the effect of intrinsic and extrinsic factors on dupilumab PK in the PN population.

Pharmacokinetic parameters in patients with PN

The observed C_{trough} and Pop PK model-based post hoc estimates of dupilumab exposure at steady state (C_{max}, C_{trough}, and AUC) are shown below. Dupilumab steady-state exposure at 300 mg Q2W was similar for the two studies. The Pop PK model estimates were consistent with the observed values for C_{trough}, demonstrating a robust model performance in describing dupilumab PK in the PN-patient population.

Table 2. Mean (SD) steady-state exposure of dupilumab in patients with PN (Studies EFC16460 and EFC16459)

Study identifier	Dose	$C_{max,ss}$ (mg/L)		$AUC_{\tau,ss}$ (mg•day/L)	$C_{trough,ss}$ (mg/L)		
		N	Predicted[a]	Predicted[a]	Predicted[a]	N	Observed
EFC16460	300 mg Q2W	74	93.1 (37.6)	1170 (505)	69.2 (33.4)	67	68.6 (36.7)
EFC16459	300 mg Q2W	65	85.0 (35.8)	1070 (482)	61.7 (32.0)	65	60.2 (34.7)

a Predicted: summary statistics of post hoc estimates of exposure parameters in Study POH0779

$AUC_{\tau,ss}$ = AUC[Week 22 – Week 24] for 300 mg Q2W

$C_{trough,ss}$ represents the mean trough concentration at Week 24

N: number of patients; $AUC_{\tau,ss}$: area under the concentration time curve over the dosing interval (τ) at steady state; $C_{max,ss}$: maximum concentration at steady state; $C_{trough,ss}$: trough concentration at steady state; Q2W: every 2 weeks; SD: standard deviation

Sources: Study POH0779 PN Pop PK analysis report, see 5.3.3.5 Study POH0779; PK appendices of Studies EFC16459 and EFC16460, see 5.3.5.1 Studies EFC16459 and EFC16460, Appendix 16.2.5 Compliance and drug concentration data [16.2.5.4]

Table 3. Summary of observed dupilumab concentrations of dupilumab in serum in patients with PN (Studies EFC16459 and EFC16460)

Study identifier	Dupilumab dose (N)	Mean (SD) C_{trough} (mg/L)					
		Week 0	Week 4	Week 8	Week 12	Week 24	Week 36
EFC16460	300 mg Q2W SC (76)	0.00 (0.00)	54.8 (25.7)	61.3 (28.4)	65.3 (32.7)	68.6 (36.7)	0.460 (1.10)[a]

Study identifier	Dupilumab dose (N)	Mean (SD) C_{trough} (mg/L)					
		Week 0	Week 4	Week 8	Week 12	Week 24	Week 36
EFC16459	300 mg Q2W SC (67)	0.00 (0.00)	48.6 (22.6)	55.1 (26.1)	59.8 (29.5)	60.2 (34.7)	1.94 (6.12)[a]

a Represents the concentration at follow-up visits where the last dose was at Week 22.

C_{trough}: trough concentration; N: number of patients; Q2W: every 2 weeks

Absorption, Distribution and Elimination

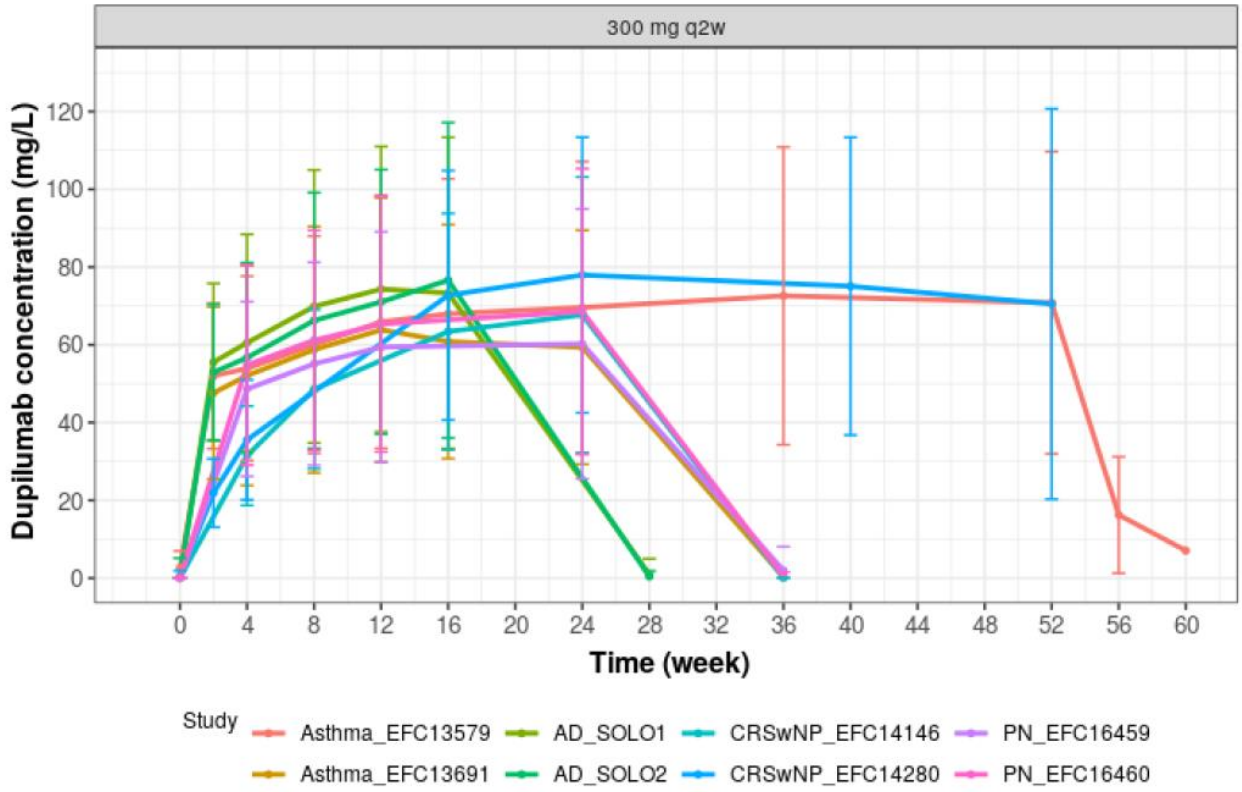
The disposition of dupilumab in patients with PN was similar with that reported for the AD, asthma, and CRSwNP populations based on Pop PK analysis. It is well-absorbed, distributes primarily within the vascular compartment, and exhibits saturable target-mediated elimination. After the last dose of a 300 mg Q2W SC regimen, the model-predicted median time for dupilumab concentration to decline from PK steady state to below LLOQ (0.078 mg/L) in a typical adult patient with PN is 12 weeks. Steady state was achieved by Week 12 for the 300 mg Q2W regimen. The mean steady-state trough concentrations at Week 12 and Week 24 (end of treatment) were 59.8-65.3 mg/L and 60.2-68.6 mg/L, respectively.

Comparison between adult PN population and other adult disease populations

As shown in the figure below, the observed concentration-time profiles in adult patients with PN are similar across the 2 PN studies and similar to those observed in adult patients with AD, asthma, and CRSwNP, except for lower concentrations over the first few weeks in patients with CRSwNP due to the absence of a loading dose in this population. The observed dupilumab steady-state exposure (C_{trough}) at 300 mg Q2W was similar across PN, AD, asthma, and CRSwNP patient populations with various dupilumab-treatment durations. In patients with PN, steady state was achieved by Week 12 for the 300 mg Q2W regimen.

Based on the PN Pop PK model, the median time to steady-state was 10 weeks for 300 mg Q2W with a loading dose in a typical individual, which is similar to AD and asthma studies (figure below). The model-based predictions, which are not dependent on study design, represent a more robust assessment of the time to steady state than those derived from observed data, which are in part dependent on the PK sampling scheme.

Figure 1. Mean (SD) trough concentration-time profiles of dupilumab at 300 mg Q2W in patients with PN, AD, asthma, and CRSwNP



Abbreviation: AD_SOLO1: study AD-1314; AD_SOLO2: study AD-1416; q2w: every two weeks.

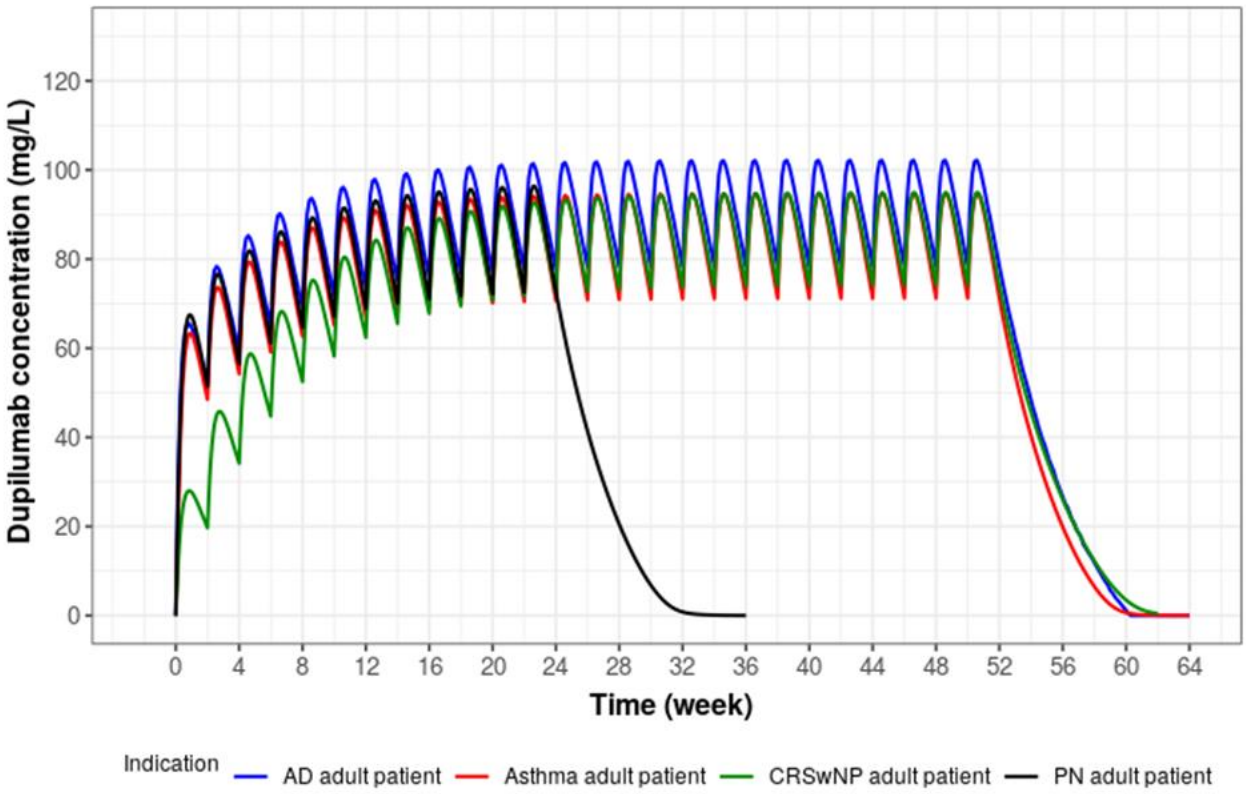
Table 4. Mean (SD) observed steady state exposure of dupilumab in adults with PN, AD, asthma, and CRSwNP

Population	Study identifier	Dose regimen	$C_{trough,ss}$ (mg/L)	
			N	Observed[a]
PN	EFC16459	300 mg Q2W with a	65	60.2 (34.7)
	EFC16460	loading dose of 600 mg	67	68.6 (36.7)
AD	R668-AD-1334	300 mg Q2W with a	219	73.3 (40.0)
	R668-AD-1416	loading dose of 600 mg	219	76.6 (40.5)
	R668-AD-1224		101	79.9 (39.2)
Asthma	EFC13579	300 mg Q2W with a	544	69.0 (37.8)
	EFC13691	loading dose of 600 mg	99	58.8 (31.4)
CRSwNP	EFC14146	300 mg Q2W	136	69.2 (36.9)
	EFC14280	without a loading dose	95	75.5 (33.5)

a The observed $C_{trough,ss}$ at Week 24 in PN, asthma,and CRSwNP populations, and at Week 16 in AD population.
AD: atopic dermatitis; CRSwNP: chronic rhinosinusitis with nasal polyposis; $C_{trough,ss}$: trough concentration at steady state; N: number of patients; PN: prurigo nodularis; Q2W: every 2 weeks; SD: standard deviation
Source: 5.3.5.1 Study EFC16461, Appendix 16.2.5 [16.2.5.4.1.1] of the current submission and 5.3.5.1 Studies R668-AD-1334, R668-AD-1416, R668-AD-1224, previously submitted in the marketing application for adults with AD,
5.3.5.1 Studies EFC13579 and EFC13691, previously submitted in the marketing application for adults and adolescents with asthma,
5.3.5.1 Studies EFC14146 and EFC14280, previously submitted in the marketing application for adults and adolescents with CRSwNP

The similarity in the PK of dupilumab between PN, AD, asthma, and CRSwNP populations was investigated using Pop PK analysis where a previously developed global base model using data from healthy subjects and patients with AD and asthma (study POH0668) was used to describe the PK in patients with PN (see figure below). Based on the PN Pop PK model, the median time to steady-state was 10 weeks for 300 mg Q2W with a loading dose in a typical individual, which is similar to AD and asthma studies. Besides body weight that was already included in the base model, no other covariates were identified as sources of PK variability in patients with PN (study POH0779).

Figure 2. Comparison of dupilumab typical concentration-time profiles at 300 mg Q2W in adult patients with PN, AD, asthma, and CRSwNP as predicted by population pharmacokinetic models



Note: The typical profile simulation was conducted at 300 mg Q2W with a 600 mg loading dose (in AD, asthma, and PN) and without a loading dose (in CRSwNP) using Pop PK models for AD (REGN668-MX-16103-CP-01V1), asthma (POH0530), CRSwNP (POH0611), and PN (POH0779) for a typical (adult) Caucasian patient with median values of the covariates for the respective populations as follows: weight of 75 kg for AD and asthma (79 kg for CRSwNP and 73 kg for PN), albumin of 45 g/L, body mass index of 25.1 kg/m^2, creatinine clearance normalized to body surface area of 111 mL/min/1.73 m^2, and eczema area severity index of 29.5 (AD only) and negative ADAs.
ADA: anti-drug antibody; AD: atopic dermatitis; CRSwNP: chronic rhinosinusitis with nasal polyposis; PN: prurigo nodularis; Pop PK: population pharmacokinetic; Q2W: every 2 weeks
Source: POH0779, POH0611, POH0530, REGN668-MX-16103-CP-01V1

Sources of pharmacokinetic variability

The mean and SD of steady-state exposures (i.e., $AUC_{\tau,ss}$, $C_{max,ss}$, and $C_{trough,ss}$) of dupilumab in patients with PN after 300 mg Q2W in studies EFC16460 and EFC16459 as a function of selected intrinsic/extrinsic factors are provided in the table below. Boxplots of dupilumab predicted steady-state exposures in patients with PN as a function of intrinsic/extrinsic factors are provided below.

Among the evaluated factors, only body weight exerted a noticeable effect explaining variability source in dupilumab PK in patients with PN. Patients in lower body weight group exhibited higher exposures of dupilumab.

All other tested factors, including baseline demographics (gender, age, and race), baseline lab parameters (creatinine clearance and albumin), immunogenicity, ethnicity, and baseline biomarker and disease characteristics (IgE, IGA score, WINRS, duration of PN) had no apparent effect on dupilumab PK exposure based on available data. Some apparent difference in PK exposure across ADA, race and albumin categories were inclusive, which may be due to limited data (<10% patients in certain categories). The impact of comorbidity (atopic comorbidities) and concomitant medication (use of TCS / TCI) on dupilumab PK exposure was found to be minimal based on available data.

Table 5. Mean (SD) for post hoc estimates of steady state exposure of dupilumab in patients with PN from EFC16459 and EFC16460 by covariates tested in population pharmacokinetic analysis (POH0779)

Intrinsic and extrinsic factors		N[b] (mean weight)	$AUC_{\tau,ss}$[c] (mg.day/L)	$C_{max,ss}$[c] (mg/L)	$C_{trough,ss}$[c] (mg/L)
All (300 mg q2w[a])		139 (75.0 kg)	1120 (496)	89.3 (36.9)	65.7 (32.8)
Age (year)	18-<65	107 (75.3 kg)	1160 (489)	91.6 (36.4)	67.8 (32.4)
	65-<75	26 (76.8 kg)	980 (553)	78.7 (41.1)	56.4 (36.4)
	≥75	6 (62.5 kg)	1170 (243)	93.8 (17.6)	67.8 (17.0)
Weight (kg)	≤60	30 (54.0 kg)	1670 (466)	131 (34.2)	101 (31.5)
	60 -< 90	84 (74.1 kg)	1070 (369)	85.6 (27.3)	62.5 (24.7)
	≥ 90	25 (103 kg)	632 (206)	52.2 (15.0)	33.7 (13.8)
Stationary ADA	Negative ADA	126 (74.2 kg)	1170 (487)	92.5 (36.2)	68.6 (32.3)
	Positive ADA	13 (83.1 kg)	702 (380)	57.9 (28.4)	37.8 (24.9)
Sex	Male	46 (81.4 kg)	956 (370)	76.5 (27.8)	54.7 (24.4)
	Female	93 (71.9 kg)	1210 (530)	95.6 (39.2)	71.1 (35.1)
Race[d]	White	79 (76.8 kg)	1120 (513)	89.2 (38.0)	66.0 (34.1)
	Black	11 (94.3 kg)	645 (278)	53.0 (20.7)	34.4 (18.4)
	Asian	44 (67.1 kg)	1220 (402)	97.0 (30.0)	71.7 (26.5)
	Other	5 (75.2 kg)	1300 (799)	103 (59.0)	76.8 (53.5)
Ethnicity	Japanese	7 (60.0 kg)	1270 (331)	101 (24.7)	74.1 (21.9)
	Non-Japanese	132 (75.8 kg)	1120 (503)	88.7 (37.4)	65.3 (33.3)
	Chinese[f]	12 (69.5 kg)	1160 (484)	92.2 (36.4)	67.1 (31.4)
	Non-Chinese	127 (75.6 kg)	1120 (498)	89.0 (37.0)	65.6 (33.1)
Albumin (g/L)	30-< 40	7 (77.5 kg)	747 (284)	62.3 (20.4)	40.4 (18.7)
	40-<50	123 (75.8 kg)	1120 (478)	88.8 (35.6)	65.3 (31.6)
	>=50	9 (63.3 kg)	1500 (643)	117 (47.3)	90.5 (43.3)
CLCRN (mL/min/1.73 m^2)	Normal	106 (76.3 kg)	1130 (494)	89.4 (36.8)	66.0 (32.7)
	Mild RI	26 (70.8 kg)	1090 (418)	86.9 (31.1)	62.8 (27.6)
	Moderate RI	7 (72.1 kg)	1220 (794)	96.0 (58.7)	71.7 (53.1)
CLCR (mL/min)	Normal	105 (77.3 kg)	1090 (476)	86.9 (35.4)	63.7 (31.5)
	Mild RI	27 (69.8 kg)	1180 (511)	93.3 (38.1)	68.7 (33.8)
	Moderate RI	7 (61.4 kg)	1400 (687)	110 (50.6)	83.6 (46.4)
IgE[e] (IU/mL)	≤312	71 (73.9 kg)	1170 (544)	92.9 (40.4)	68.8 (36.2)
	>312	68 (76.3 kg)	1070 (438)	85.5 (32.7)	62.5 (28.7)
IGA	3	92 (74.4 kg)	1130 (512)	89.9 (38.1)	66.0 (33.9)
	4	47 (76.3 kg)	1110 (467)	88.0 (34.7)	65.1 (30.9)
Duration of PN	< 3 years	62 (76.6 kg)	1070 (509)	85.1 (37.9)	62.0 (33.8)
	≥ 3 years	77 (73.8 kg)	1170 (483)	92.6 (35.9)	68.7 (31.9)

a 300 mg Q2W with an initial loading dose of 600 mg.

b Two patients each from Studies EFC16459 and EFC16560 were not included due to dose discontinuation before Week 24

c Predicted $AUC_{\tau,ss}$ = AUC [Week 22 – Week 24] for 300 mg Q2W. $C_{max,ss}$ and $C_{trough,ss}$ were calculated over Week 22 and Week 24 for 300 mg Q2W in Studies EFC16459 and EFC16460.

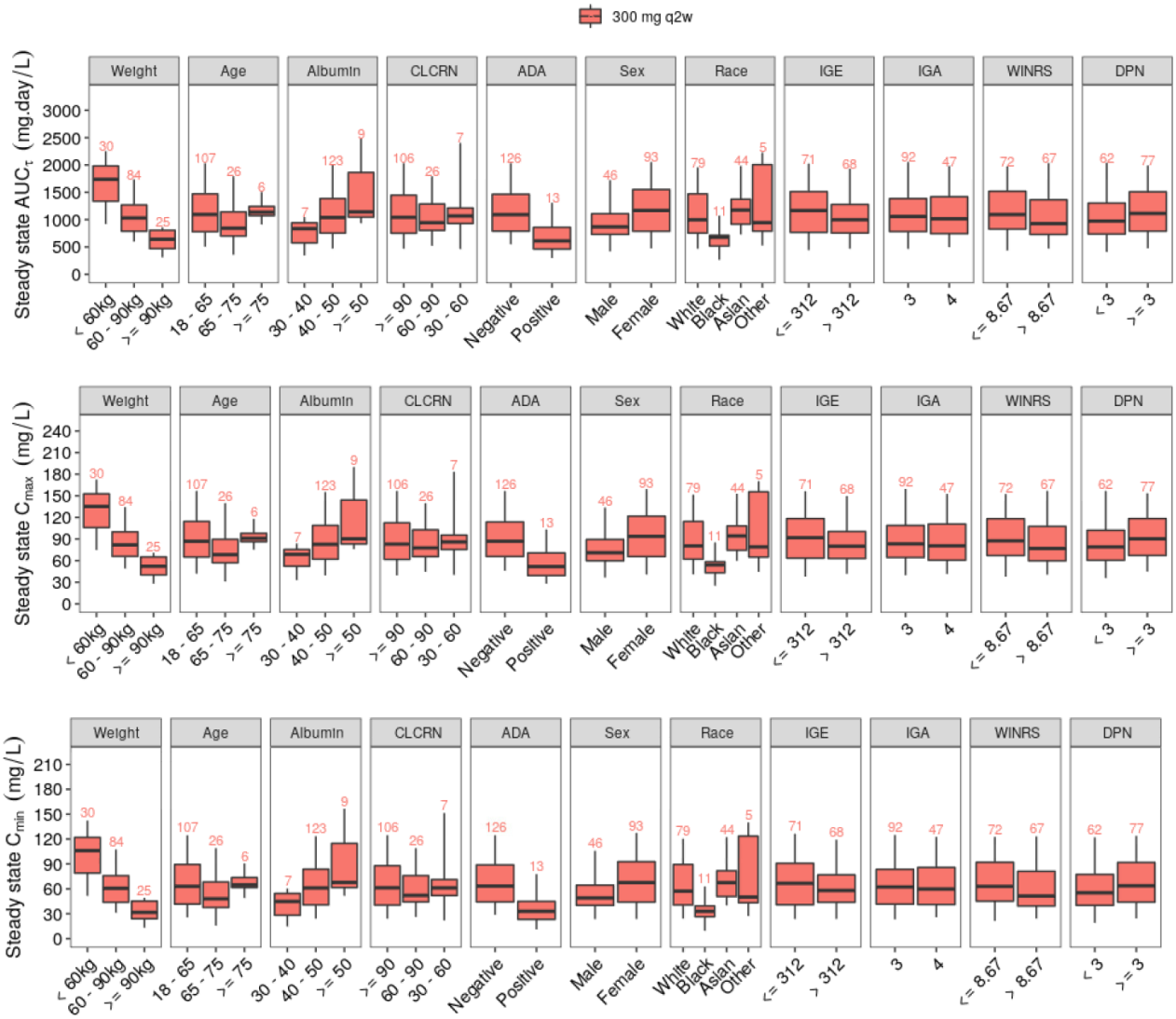
d The mean weight for Non-Asian (N=95) is 78.8 kg. The mean (SD) $AUC_{\tau,ss}$, $C_{max,ss}$ and $C_{min,ss}$ for Non-Asian are 1080 (529) mg·day/L, 85.7 (39.3) mg/L and 62.9 (35.1) mg/L, respectively.

e One patient each from Studies EFC16459 and EFC16460 with missing information for baseline IgE were excluded from the summary.

f Chinese patients from Taiwan only, No PK data Chinese patients from China.

ADA: anti-drug antibody; $AUC_{\tau,ss}$: area under the concentration time curve over the dosing interval (τ) at steady state; CHIN: Chinese patients; CLCR: creatinine clearance; CLCRN: creatinine clearance normalized by body size; $C_{max,ss}$: maximum concentration at steady state; $C_{min,ss}$: minimum concentration at steady state; $C_{trough,ss}$: trough concentration at steady state; IGA: Investigator's Global Assessment; IgE: immunoglobulin E; JAPN: Japan as study site; N: number of patients; PK: pharmacokinetic; Q2W/q2w: every 2 weeks; SD: standard deviation.

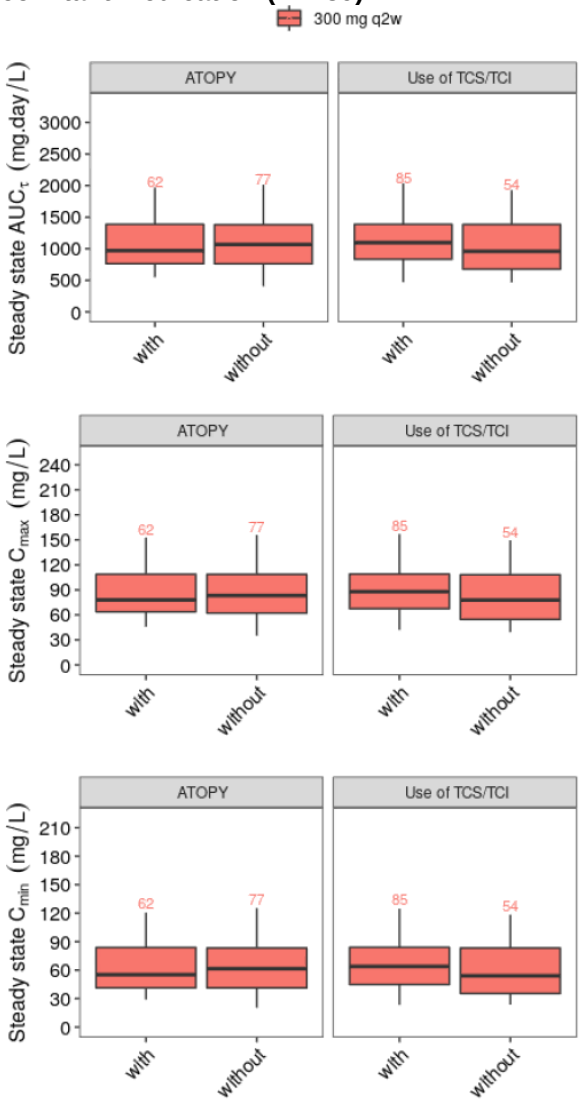
Figure 3. Boxplot of dupilumab predicted $AUC_{t,ss}$, $Cmax_{,ss}$ and $Ctrough_{,ss}$ in patients with PN as a function of intrinsic/extrinsic factors (N=139)



Abbreviation: AUC_{τ}: $AUC_{\tau,ss}$, area under the concentration-time curve from 0 to τ at steady state; C_{max}: $C_{max,ss}$, maximum concentration at steady state ; C_{mm}: $C_{trough,ss}$, minimum concentration at steady state; CLCRN: creatinine clearance normalized by body size; DPN: duration of prurigo nodularis; IGA: Investigator's Global Assessment; IGE: IgE, immunoglobulin E; q2w: every two weeks; WINRS: worst-itch numeric rating scale.

Note: Lower and upper end of whisker indicated 5th and 95th percentile of $AUC_{\tau,ss}$, $C_{max,ss}$ and $C_{trough,ss}$ (Week 22 to Week 24). Number inside plot panel indicate patient numbers in each bin of covariate; Weight (kg), Age (year), Albumin (g/L), CLCRN (mL/min/1.73 m^2), Negative ADA = negative ADA at all the time, Positive ADA = positive ADA at any time; IGE (IU/mL); DPN (years). One patient from study EFC16459 and one patient from study EFC16460 with missing information for baseline IgE. In this summary, the missing values for baseline IgE were imputed using the population median (312 IU/mL).

Figure 4. Boxplot of dupilumab predicted $AUC_{t,ss}$, $Cmax_{,ss}$ and $Ctrough_{,ss}$ in patients with PN by comorbidity and concomitant medication (N=139)



Abbreviation: AUC_{τ}: $AUC_{\tau,ss}$, area under the concentration-time curve from 0 to τ at steady state; ATOPY: atopic comorbidities; N: subject number; $AUC_{\tau,ss}$, area under the concentration-time curve from 0 to τ at steady state; C_{max}: $C_{max,ss}$, maximum concentration at steady state ; C_{min}: $C_{trough,ss}$, minimum concentration at steady state; q2w: every two weeks; TCI: topical calcineurin inhibitors; TCS: topical corticosteroids.
Note: Lower and upper end of whisker indicated 5th and 95th percentile of $AUC_{\tau,ss}$ $C_{max,ss}$ and $C_{trough,ss}$ (Week 22 to Week 24). Number inside plot panel indicate the counts of patients in each bin of concomitant medication.

Body weight

Body weight is the primary factor explaining between-subject variability of dupilumab PK in patients with PN, consistent with previous findings in different disease/age populations. The linear elimination rate constant (Ke), volume of the central compartment (V2), and maximum target-mediated rate of elimination (Vmax) decreased (and hence exposure increased) with decrease in body weight in patients with PN (Study POH0779).

Table 6. Mean (SD)[CV%] observed steady-state exposures of dupilumab in patients with PN by weight category

Weight categories	Observed at Week 12		Observed at Week 24	
	N (median weight)	$C_{trough,ss}$ (mg/L)	N (median weight)	$C_{trough,ss}$ (mg/L)
<60 kg	31 (55.0 kg)	93.7 (31.2) [33.3%]	29 (55.0 kg)	96.1 (34.8) [36.3%]
60 -< 90 kg	84 (73.9 kg)	59.3 (25.4) [42.8%]	79 (73.8 kg)	62.4 (30.8) [49.4%]
≥ 90 kg	26 (101 kg)	35.8 (14.9) [41.6%]	24 (101 kg)	33.1 (17.7) [53.6%]
All	141 (72.8 kg)	62.5 (31.4) [50.2%]	132 (72.8 kg)	64.5 (35.9) [55.6%]

Abbreviation: CV: coefficient of variation; $C_{trough,ss}$: minimum concentration at steady state; N: subject number; SD: standard deviation.

Age

There were 40 of elderly patients (≥65 years, n=33; ≥75 years, n=7); representing 23.1% and 4.9% of total patients in the Pop PK dataset. The respective Pop PK analyses of dupilumab concentration data obtained from the different age groups of adults showed comparable PK parameters of dupilumab. Due to the lack of age effect on PK in adults and as there are no clinically significant differences in efficacy and safety across age subgroups, no dose adjustment for age is recommended in patients with PN.

Gender

There are no differences in the dupilumab concentrations between female and male patients with PN in Studies EFC16459 and EFC16460. The post hoc assessment (Study POH0779) of data from 96 (67.1%) female and 47 (32.9%) male subjects showed that gender had no impact on dupilumab PK, similar to previous findings in patients with AD, asthma, and CRSwNP. Due to the lack of an effect of gender on PK and, as there are no clinically significant differences in efficacy and safety across gender subgroups, no dose adjustment is recommended for gender.

Race/ethnicity

The post hoc assessment (Study POH0779) of the data from patients with PN in Studies EFC16459 and EFC16460 consisting of Caucasian (N=81, 56.6%), Asian (N=46, 32.2%), Black (N=11, 7.7%), and other races (N=5, 3.5%) showed that race had no impact on dupilumab PK, consistent with the previous findings in patients with AD, asthma, and CRSwNP.

The higher mean exposure (observed C_{trough} and post hoc estimate of steady-state exposure) in Asians versus non-Asians is mainly the result of differences in body weight (median weight of 67.1 kg in Asians versus 78.8 kg in non-Asians).

The lower mean exposure in Black population versus other races is mainly the result of differences in body weight (median weight of 94.3 kg in Blacks versus 67.1-76.8 kg in other races).

Similarly, when data from a subset of the Japanese population (patients from Japan) are considered, the higher mean exposure in this subset of Japanese patients versus the rest of the population (non-Japanese) is mainly the result of differences in body weight (median weight of 60.0 kg in Japanese versus 75.8 kg in non-Japanese).

As the small differences in PK by race/ethnicity are explained by body weight differences and as there are no clinically significant differences in efficacy and safety across race groups or ethnic groups, no dose adjustment is recommended for race or ethnicity.

Other laboratory parameters

The comparison of Pop PK model predicted post hoc estimates (Study POH0779) showed that albumin had no impact on dupilumab PK in patients with PN, similar to previous findings in patients with AD, asthma, and CRSwNP.

Baseline biomarkers and disease markers

Based on the comparison of Pop PK model-predicted post hoc estimates (Study POH0779), baseline IgE and baseline disease characteristics (baseline WI-NRS score and baseline IGA score) did not significantly affect the PK of dupilumab in patients with PN.

Disease populations

The comparison of Pop PK model predicted post hoc estimates (Study POH0779) showed that history of atopy (ie, atopic or non-atopic) had no impact on dupilumab PK in patients with PN.

The observed dupilumab steady state C_{trough} in patients with PN are similar to those with AD, asthma and CRSwNP and also shown by Pop PK analysis via MAP Bayesian approach, which is consistent with the previously reported similarity of PK in patients across the disease populations.

2.4.3. Pharmacodynamics

Mechanism of action

Blocking of the IL 4Rα receptor subunit with dupilumab inhibits IL 4 and IL 13 (type 2) cytokine-induced responses, including the release of pro-inflammatory cytokines, chemokines, and IgE through this pathway. Total IgE, as a biomarker of type 2 inflammation, was assessed in serum in study EFC16460 and EFC16459 to further characterize the mode of action of dupilumab.

Primary and secondary pharmacology

Total IgE in serum

Total IgE in serum at baseline were generally similar in both studies, with higher numerical median values in the dupilumab group compared to the placebo group but with considerable overlap in ranges. In the pooled ITT population, median baseline total IgE levels in serum were elevated compared to the normal reference range (0-119 IU/mL) with the median value of 261.0 IU/mL (Q1-Q3 ranges: 64.1-1050.0 IU/mL) and 146.0 IU/mL (Q1 Q3 ranges: 36.3-971.5 IU/mL) in the dupilumab and placebo groups, respectively. Median values of baseline total IgE levels in serum were numerically higher in participants with comorbid atopic history compared to those without with considerable overlap in ranges.

Table 7. Summary of biomarker data at baseline - ITT population from EFC16460 and EFC16459 and Pooled ITT population

	EFC16460			EFC16459			Pooled Data		
	Placebo (N=82)	Dupilumab 300 mg Q2W (N=78)	All (N=160)	Placebo (N=76)	Dupilumab 300 mg Q2W (N=75)	All (N=151)	Placebo (N=158)	Dupilumab 300 mg Q2W (N=153)	All (N=311)
Total IgE in serum (IU/mL)									
Number	79	76	155	73	74	147	152	150	302
Mean (SD)	1469.1 (3714.0)	900.0 (1490.3)	1190.1 (2854.7)	1770.7 (10217.1)	1004.9 (2404.4)	1385.2 (7383.6)	1614.0 (7544.7)	951.7 (1988.3)	1285.0 (5533.8)
Median	109.0	367.0	202.0	169.0	243.5	209.0	146.0	261.0	205.0
Q1 ; Q3	28.6 ; 898.0	72.9 ; 1155.0	40.6 ; 1030.0	47.3 ; 997.0	57.7 ; 924.0	49.0 ; 997.0	36.3 ; 971.5	64.1 ; 1050.0	47.3 ; 997.0
Min ; Max	1 ; 18183	1 ; 10140	1 ; 18183	3 ; 87589	3 ; 17171	3 ; 87589	1 ; 87589	1 ; 17171	1 ; 87589

Table 8. Summary of biomarker data at baseline by history of atopy - Pooled ITT population

	Atopic			Non-Atopic			Pooled Data		
	Placebo (N=68)	Dupilumab 300 mg Q2W (N=67)	All (N=135)	Placebo (N=90)	Dupilumab 300 mg Q2W (N=86)	All (N=176)	Placebo (N=158)	Dupilumab 300 mg Q2W (N=153)	All (N=311)
Total IgE in serum (IU/mL)									
Number	64	64	128	88	86	174	152	150	302
Mean (SD)	1746.1 (3936.3)	1066.7 (1652.0)	1406.4 (3026.0)	1517.9 (9357.1)	866.2 (2211.3)	1195.8 (6822.0)	1614.0 (7544.7)	951.7 (1988.3)	1285.0 (5533.8)
Median	172.5	395.0	223.0	110.0	251.5	161.5	146.0	261.0	205.0
Q1 ; Q3	48.3 ; 1058.0	87.8 ; 1443.0	66.7 ; 1080.5	30.4 ; 630.0	48.2 ; 729.0	39.0 ; 729.0	36.3 ; 971.5	64.1 ; 1050.0	47.3 ; 997.0
Min ; Max	4 ; 18183	6 ; 10140	4 ; 18183	1 ; 87589	1 ; 17171	1 ; 87589	1 ; 87589	1 ; 17171	1 ; 87589

Concentrations of total IgE in serum showed a continuous decline throughout the dupilumab-treatment period, in contrast to participants receiving placebo with no apparent difference observed between Studies EFC16459 and EFC16460. The median percent reduction from baseline in total IgE concentrations with dupilumab treatment was -60.86% at Week 24. Total serum IgE percent change over time was similar in participants with and without history of atopy. The decline in total IgE, a marker specific for type 2 immunity, is consistent with effective IL-4 and IL-13 signaling blockade. The IgE profiles showed a similar median magnitude of effect over time in PN, AD, asthma, and CRSwNP patient populations.

Figure 5. Median percent change in total IgE in serum over time following dupilumab 300 mg Q2W or placebo in adults with PN

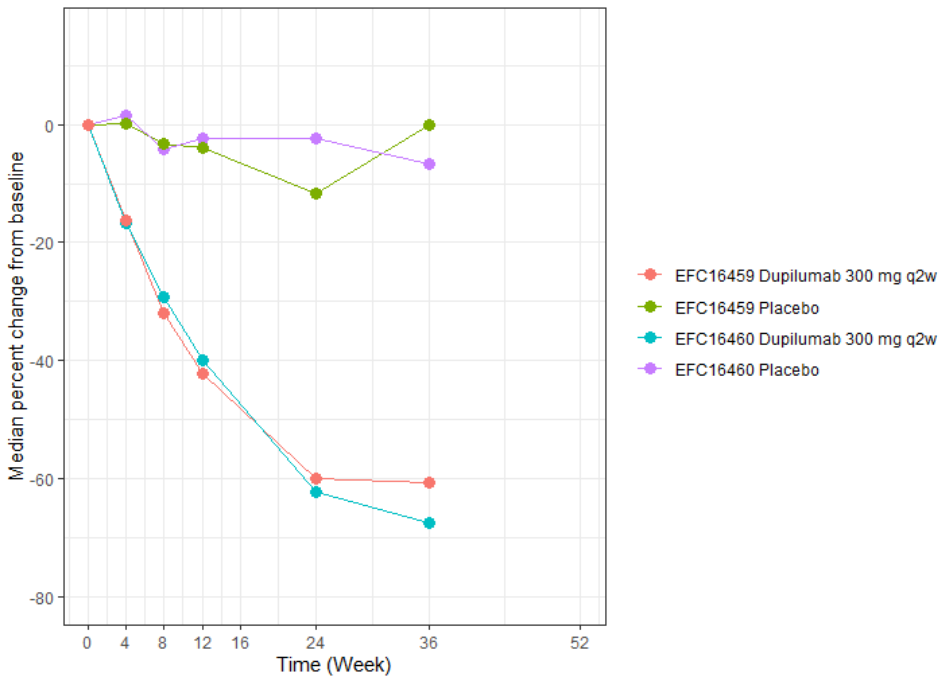
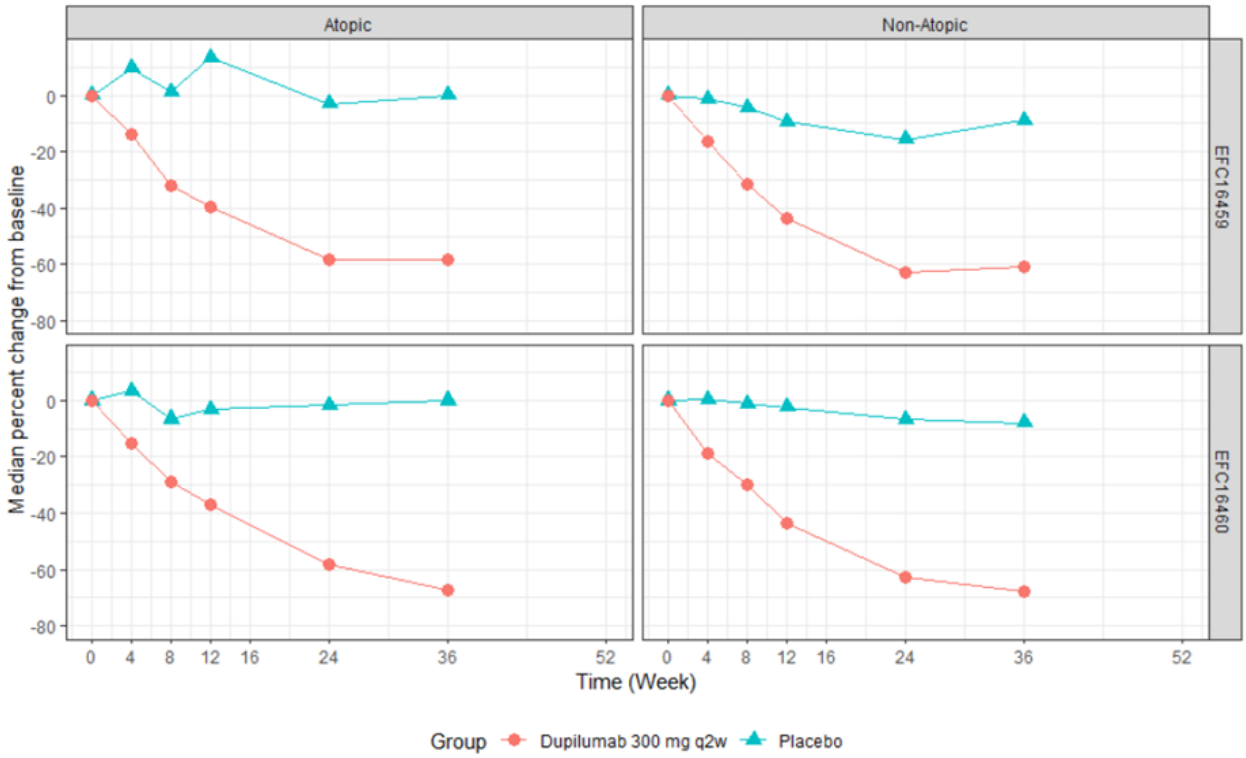


Figure 6. Median percent change in total IgE in serum over time following dupilumab 300 mg Q2W or placebo in adults with PN by patient subgroups with and without a history of atopy



Immunogenicity Data

The incidence of treatment-emergent ADAs was 7.7% (11 participants) in the dupilumab 300 mg Q2W group compared to 2.0% (3 participants) in the placebo group. Persistent ADA responses were observed in 1.4% of participants receiving dupilumab 300 mg Q2W compared to 0% for placebo. Most of these treatment-emergent ADA responses were low titer. High titer ADA response (>10 000) was not observed. A total of 2.8% of participants receiving dupilumab 300 mg Q2W were classified as NAb-positive compared to 1.4% of participants in the placebo group.

Table 9. Anti-drug antibody incidence in Phase 3 studies in patients with PN (EFC16459 and EFC16460)

Anti-dupilumab antibodies N (%)	Pooled		EFC16459		EFC16460	
	Placebo (N=147)	300 mg Q2W (N=143)	Placebo (N=67)	300 mg Q2W (N=68)	Placebo (N=80)	300 mg Q2W (N=75)
Pre-existing ADA[a]	2 (1.4%)	3 (2.1%)	1 (1.5%)	3 (4.4%)	1 (1.3%)	0
Treatment-emergent response[b]	3 (2.0%)	11 (7.7%)	3 (4.5%)	7 (10.3%)	0	4 (5.3%)
Persistent response[c]	0	2 (1.4%)	0	2 (2.9%)	0	0
Indeterminate response[d]	1 (0.7%)	7 (4.9%)	1 (1.5%)	4 (.5.9%)	0	3 (4.0%)
Transient response[e]	2 (1.4%)	2 (1.4%)	2 (3.0%)	1 (1.5%)	0	1 (1.3%)
Peak post-baseline titer						
Low (<1,000)	3 (2.0%)	8 (5.6%)	3 (4.5%)	4 (5.9%)	0	4 (5.3%)
Moderate (1,000-10,000)	0	3 (2.1%)	0	3 (4.4%)	0	0
High (>10,000)	0	0	0	0	0	0

Treatment-boosted response[f]	0	0	0	0	0	0
Neutralizing antibodies	2 (1.4%)	4 (2.8%)	2 (3.0%)	4 (5.9%)	0	0

a Either an ADA positive response in the ADA assay at baseline with all post first dose ADA results negative, OR a positive response at baseline in the ADA assay with all post first dose ADA results less than 4-fold baseline titer levels.

b A positive response in the ADA assay post first dose when baseline results are negative or missing.

c Treatment-emergent ADA positive response with two or more consecutive ADA positive sampling time points separated by greater than 12-week period (greater than 84 days), with no ADA negative samples in between.

d Treatment-emergent response with only the last collected sample positive in the ADA assay.

e Treatment-emergent ADA positive response that is not considered persistent or indeterminate.

f A positive response in the ADA assay post first dose that is greater than or equal to 4-fold over baseline titer levels, when baseline results are positive.

ADA: anti-drug antibody; N: number of patients; Q2W: every 2 weeks

Source: 5.3.5.1 Studies EFC16459 and EFC16460, Appendix 16.2.5 [16.2.5.4.1.2.2] and [16.2.5.4.1.2.6]

Comparing the immunogenicity of dupilumab across different populations, the ADA incidence was generally similar across the AD, asthma, CRSwNP, and PN populations with respect to treatment-emergent positive ADA response (5.1-7.7%), persistent ADA response (1.4-2.1%), and NAb response (1.0-3.4%) after 24 or 52 weeks of treatment with dupilumab 300 mg Q2W with or without a loading dose.

The association between the treatment-emergent ADA response and the clinical response was investigated in participants using the measures of improvement (reduction) in WI NRS by ≥4 points from baseline to Week 12 and Week 24, the percentage of participants with IGA PN S 0 ("clear") or 1 ("almost clear") score at Week 24, and the percentage of participants with both an improvement (reduction) in WI NRS by ≥4 points from baseline to Week 24 and IGA PN S 0 or 1 score at Week 24. Overall, the efficacy of dupilumab was within the range observed for ADA negative participants for efficacy endpoints used in study EFC16460 and EFC 16459.

2.4.4. PK/PD modelling

This section summarizes the Pop PK and PK/PD analyses in patients with PN as shown in the table below.

Table 10. Summary of clinical studies in patients with PN included in the population pharmacokinetic (Study POH0779) and empirical pharmacokinetic/pharmacodynamic (Study CTS0084) analyses

Phase	Study identifier	Dupilumab dose regimens	Population	Analyses
3	EFC16460	A loading dose on Day 1 of 600 mg (2 SC injections of 300 mg) or matching placebo followed by 300 mg or matching placebo Q2W for 24 weeks	Adult patients with PN	Pop PK in PN (POH0779)[a], PK/PD (CTS0084)[b]
3	EFC16459	A loading dose on Day 1 of 600 mg (2 SC injections of 300 mg) or matching placebo followed by 300 mg or matching placebo Q2W for 24 weeks	Adult patients with PN	Pop PK in PN (POH0779)[a], PK/PD (CTS0084)[b]

a PK data cut-off date of 27 October 2021 for Study EFC16459 and 11 August 2021 for Study EFC16460

b Clinical data cut-off date of 12 November 2021 for Study EFC16459 and 30 August 2021 for Study EFC16460

PD: pharmacodynamic; PK: pharmacokinetic; PN: prurigo nodularis; Pop PK: population PK; Q2W: every 2 weeks; SC: subcutaneous

Study POH0779

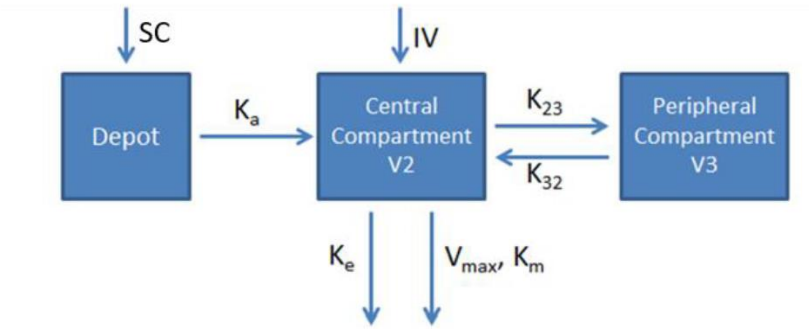
Population pharmacokinetic analysis of dupilumab using pooled data from 2 Phase 3 studies in patients with prurigo nodularis

Objective and methods: The main objectives of this study were to characterize the PK of dupilumab in patients with PN based on a previously developed Pop PK model for dupilumab (i.e., external validation) and to assess the influence of intrinsic and extrinsic factors on dupilumab PK in patients with PN via post hoc assessment.

Data from Studies EFC16459 and EFC16460 in patients with PN were pooled for this analysis. At the PK data cut-off dates of 27 October 2021 for Study EFC16459 and of 11 August 2021 for Study EFC16460 (prior to clinical database lock), PK data up to Week 24 were available for 87% of participants in Study EFC16459 (N=65 [87%]) and Study EFC16460 (N=67 [87%]). Also included in the dataset were PK data at Week 36 (after 12 weeks off-treatment) from 48 (64%) and 34 (44%) participants from Study EFC16459 and Study EFC16460, respectively. The final dataset included 143 patients with PN with a total of 568 dupilumab concentrations.

The global base model previously developed using dupilumab data pooled from Phase 1 to Phase 3 studies in healthy subjects (adults), patients with AD (adults) and patients with asthma (adults and adolescents) in Study POH0668 (in the CRSwNP submission) was used in the analysis. Taking into account the similarity in the observed dupilumab PK profiles across different populations, the previously developed global Pop PK base model (study POH0668) based on pooled data from HV, patients with AD and asthma was utilized in the Pop PK analysis in patients with PN. As shown in the figure below, the global Pop PK base model was a two-compartment model with a first order absorption, and parallel linear and nonlinear elimination.

Figure 7. Schematic structure of dupilumab global PK base model

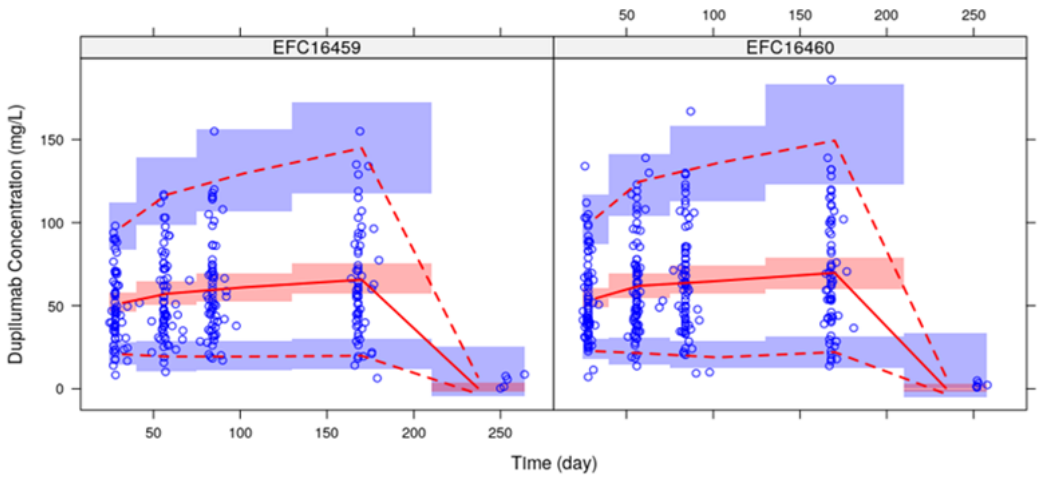


Abbreviation: IV: intravenous; K_a : absorption rate constant; V_2 : central compartment volume; V_3 : peripheral compartment volume; K_{23}, K_{32} : inter-compartmental rate constants; K_e : elimination rate constant; SC: subcutaneous; V_{max} : maximum target-mediated rate of elimination; k_m : Michaelis constant.

Data from Studies EFC16459 and EFC16460 were not included in the global Pop PK model development but were evaluated through a MAP Bayesian approach in which all Pop PK model parameters were fixed to the values of the global PK model and individual concentrations were generated by MAP probability Bayesian estimation for patients with PN.

Results: The PK of dupilumab in patients with PN was adequately described by the global Pop PK base model, which is a 2 compartment model with parallel linear and nonlinear elimination, with body weight included as a covariate in the base model. Results of the external visual predictive check of observed dupilumab concentrations in Studies EFC16459 and EFC16460 and concentrations predicted by the global Pop PK base model are presented below. The visual predictive check, along with diagnostic plots and quality criteria, confirmed dupilumab PK similarity across the disease populations and justified the application of the previously developed model for covariate assessment.

Figure 8. Visual predictive check of Studies EFC16459 and EFC16460 (POH0779)



Legend: blue dots: observations; red solid and dashed lines: the median and bounds (5th and 95th percentiles) of predicted concentrations at each time bin; pink and light blue areas: confidence intervals of median and centiles of predicted concentrations at each time bin.

Study CTS0084

Empirical exposure-response analysis of WI-NRS and IGA PN-S for dupilumab prurigo nodularis Phase 3 studies

Objectives and methods: The objectives of the empirical PK/PD analyses in this study were to understand dupilumab E-R relationships in patients with PN with regard to the 2 key efficacy endpoints, and to identify covariates influencing E-R relationships. Efficacy endpoints assessed were improvement (reduction) in WI-NRS by ≥4 points from baseline at Week 24 and achievement of IGA PN-S score of 0 or 1 at Week 24. Observed C_{trough} at Week 24 was used as the dupilumab exposure parameter. The E-R relationships between the observed Week 24 C_{trough} and the probability of patients achieving response at Week 24 for either WI-NRS or IGA PN-S was evaluated using the logistic regression. The analyses included pooled data from Studies EFC16459 and EFC16460. Three base models of the E-R relationship, linear, log linear, and maximum drug-induced effect (E_{max}), with appropriate covariates, were compared to select the best model by a goodness of fit criterion (the Akaike information criterion with sample size correction).

Any missing observed C_{trough} at Week 24 was imputed using last observation carried forward from Week 12. The same approach of handling missing efficacy data in the primary and key secondary efficacy endpoint analyses was applied in the E-R relationship analyses assessments for WI-NRS and IGA PN-S. Participants taking prohibited medications/procedures and/or rescue medications prior to Week 24 or having missing data at Week 24 are considered non responders.

In addition, the E-R relationship for an improvement (reduction) in WI-NRS by ≥4 points from baseline at Week 12, IGA PN-S score of 0 or 1 at Week 12, and the multicomponent endpoint was explored using univariate descriptive analyses.

Results: The relationship between WI-NRS response (≥4 points from baseline at Week 24) and functional dupilumab Ctrough at Week 24 was best described by a log linear model. Age is a significant covariate for the treatment response. Older patients were predicted to have modestly higher response.

Table 11. Observed and pharmacokinetic/pharmacodynamic model-predicted WI-NRS responses versus trough concentration at Week 24 (Study CTS0084)

Comparison versus placebo	Observed proportion of responders (95% CI)[a]	Model-predicted proportion of responders (95% CI)[b]	Median C_{trough} at Week 24 (mg/L)
Placebo	19.0% (13.2%, 26.0%)	16.9% (11.7%, 23.8%)	BLQ[c]
Dupilumab	61.3% (52.7%, 69.3%)	65.6% (56.7%, 73.6%)	59.9

a Observed proportion of responders (95% CI) in pooled data of Studies EFC16459 and EFC16460

b Predicted proportion of responders (95% CI) at median C_{trough} from PK/PD model for dupilumab 300 mg Q2W

c BLQ is replaced by half of the LLOQ (0.039 mg/L) as a concentration was analyzed on the log scale

BLQ: below the limit of quantitation (0.078 mg/L); CI: confidence interval; C_{trough}: trough concentration; LLOQ: lower limit of quantitation; WI-NRS: worst-itch numeric rating scale

Source: 5.3.3.5 [Study CTS0084]

The relationship between IGA PN S response (IGA PN-S score of 0 or 1 at Week 24) and functional dupilumab C_{trough} at Week 24 was best described by a log linear model. The use of TCS/TCI and baseline IGA PN-S score are significant covariates for the treatment response. Patients using TCS/TCI as well as patients with higher baseline IGA PN S scores were predicted to have higher response (the odds ratio of dupilumab versus placebo) to dupilumab treatment. The differences were contributed by a lower placebo responder rate in those participants who used TCS/TCI or those participants who had higher IGA PN S scores. The results of descriptive quartile analysis for the multicomponent endpoint at Week 24 were consistent to WI-NRS response and IGA PN-S response at Week 24, showing a generally flat E-R relationship.

Table 12. Observed and pharmacokinetic/pharmacodynamic model-predicted IGA PN-S responses versus trough concentration at Week 24 (Study CTS0084)

Comparison versus placebo	Observed proportion of responders (95% CI)[a]	Model-predicted proportion of responders (95% CI)[b]	Median C_{trough} at Week 24 (mg/L)
Placebo	17.1% (11.6%, 23.9%)	22.8% (15.5%, 32.3%)	BLQ[c]
Dupilumab	48.6% (40.1%, 57.1%)	49.7% (39.1%, 60.3%)	59.9

a Observed proportion of responders (95% CI) in pooled data of Studies EFC16459 and EFC16460

b Predicted proportion of responders (95% CI) at median C_{trough} from PK/PD model for dupilumab 300 mg Q2W. Covariates set to median values in placebo arm for placebo predictions; covariates set to median values in dupilumab arm for dupilumab predictions

c BLQ was replaced by half of the LLOQ (0.039 mg/L) as a concentration was analyzed on the log scale

BLQ: below the limit of quantitation (0.078 mg/L); CI: confidence interval; C_{trough}: trough concentration; IGA PN-S: Investigator's Global Assessent for prurigo nodularis-Stage; LLOQ: lower limit of quantitation; PD: pharmacodynamic; PK: pharmacokinetic; Q2W: every 2 weeks

Source: 5.3.3.5 [Study CTS0084]

Descriptive quartile analysis for WI-NRS at Week 24

The proportion of patients with WI NRS response (≥4 points improvement from baseline) by observed Ctrough quartiles at Week 24 from Studies EFC16459 and EFC16460 were calculated and show no clear relationship within the range of dupilumab concentrations in the study. The baseline values of WI-NRS, baseline values of IGA PN-S, and history of atopy (%) were in general balanced in each exposure quartile, while the distributions of TCS/TCI use, and baseline antidepressant use showed numerical differences by exposure quartile. The unbalanced distributions of baseline values in each exposure quartile likely contributed to the difference observed in each quartile as the potential

influence of confounding factors. Additionally, the distributions of baseline value of body weight showed higher body weight in the patients in the lowest exposure quartile, which is expected since body weight is the main source of PK variability.

Empirical model for WI-NRS

Model-based analysis showed a greater increase of WI-NRS response with increasing dupilumab C_{trough} at Week 24 from the first to second quartile (Q1 - Q2) and thereafter a shallow increase that appeared to plateau. Older patients were predicted to have modestly greater treatment response. Body weight, race, and history of atopy were not found to be significant covariates for the treatment response.

Table 13. WI-NRS response (% achieving at least a 4-point improvement) by quartiles of observed trough concentration at Week 24 in patients with PN in pooled data of Studies EFC16459 and EFC16460 (Study CTS0084)

Treatment	C_{trough} quartile	N	WI-NRS response %	C_{trough} mean (mg/L)	C_{trough} standard error	WI-NRS BL Mean	IGA PN-S BL Mean	TCS/TCI use	BL anti-depressant Use	History of atopy (%)	BL weight (kg)
Placebo	-	158	18.99%	BLQ	0	8.40	3.35	57.6%	10.8%	40.5%	73.29
Dupilumab	1	35	45.71%	21.16	2.01	8.54	3.33	43.5%	13.0%	30.4%	86.20
	2	36	80.56%	50.03	1.09	8.88	3.36	69.4%	13.9%	38.9%	77.27
	3	35	57.14%	69.88	1.22	8.58	3.29	74.3%	5.7%	54.3%	69.33
	4	36	61.11%	112.9	3.55	8.36	3.33	58.3%	8.3%	38.9%	61.93

C_{trough} quartiles: Q1 (<39.9 mg/L), Q2 (39.9-<59.85 mg/L), Q3 (59.85-<86.2 mg/L), Q4 (86.2-186 mg/L).
BL: baseline; BLQ: below the limit of quantitation (0.078 mg/L); C_{trough}: trough concentration; IGA PN-S: Investigator's Global Assessment for prurigo nodularis-Stage; Q: Quartile; TCI: topical calcineurin inhibitors; TCS: topical corticosteroids; WI-NRS: worst-itch numeric rating scale
Source: 5.3.3.5 Study CTS0084

Descriptive quartile analysis for IGA PN-S at Week 24

The IGA PN-S response is summarized by observed C_{trough} quartiles in the table below. The results appeared to show a generally flat relationship within the range of dupilumab concentrations in the study. The baseline values of IGA PN-S, baseline values of WI-NRS, and history of atopy (%) were in general balanced in each exposure quartile, while the distributions of TCS/TCI use and baseline antidepressant use showed numerical differences by exposure quartile. The baseline values were potentially confounding factors as they were unbalanced across quartiles, thus contributing to the observed difference by quartile. The lowest exposure quartile had higher baseline body weight, which is expected since body weight is the main source of PK variability.

Empirical model for IGA PN-S

Model-based analysis showed a greater increase of IGA PN-S response increasing dupilumab C_{trough} at Week 24 from the first to second quartile (Q1 - Q2) and thereafter a shallow increase that appeared to plateau. Patients using TCS/TCI and with higher baseline IGA PN-S were predicted to have higher response (the odds ratio of dupilumab versus placebo). A lower placebo responder rate in those participants who used TCS/TCI or those participants who had higher IGA PN-S, rather than a difference in dupilumab exposure, contributed to this difference in response. Body weight, race, and history of atopy were not found to be significant covariates for the treatment response.

Table 14. IGA PN-S response (%) by quartiles of observed trough concentration at Week 24 in patients with PN in pooled data from Studies EFC16459 and EFC16460 (Study CTS0084)

Treatment	C_{trough} quartile	N	IGA PN-S response %	C_{trough} mean (mg/L)	C_{trough} standard error	WI-NRS BL Mean	IGA PN-S BL Mean	TCS/ TCI use	BL anti-depressant use	History of atopy (%)	BL weight (kg)
Placebo	-	158	17.09%	BLQ	0	8.40	3.35	57.6%	10.8%	40.5%	73.29
Dupilumab	1	35	45.71%	21.16	2.01	8.54	3.33	43.5%	13.0%	30.4%	86.20
	2	36	58.33%	50.03	1.09	8.88	3.36	69.4%	13.9%	38.9%	77.27
	3	35	45.71%	69.88	1.22	8.58	3.29	74.3%	5.7%	54.3%	69.33
	4	36	44.44%	112.9	3.55	8.36	3.33	58.3%	8.3%	38.9%	61.93

C_{trough} quartiles: Q1 (<39.9 mg/L), Q2 (39.9-<59.85 mg/L), Q3 (59.85-<86.2 mg/L), Q4 (86.2-186 mg/L).
BL: baseline; BLQ: below the limit of quantitation (0.078 mg/L); C_{trough}: trough concentration; IGA PN-S: Investigator's Global Assessment for prurigo nodularis-Stage; Q: Quartile; TCI: topical calcineurin inhibitors; TCS: topical corticosteroids; WI-NRS: worst-itch numeric rating scale
Source: 5.3.3.5 Study CTS0084

2.4.5. Discussion on clinical pharmacology

The PK and PD profiles of dupilumab were evaluated in studies EFC16460 and EFC16459 including adult patients with PN whose disease was inadequately controlled on topical prescription therapies or when those therapies were not advisable. Efficacy and the main safety data for this application were also derived from these studies. In EFC16460 and EFC16459, dupilumab was administered for 24 weeks with the same dose regimen (300mg, Q2W) as for the already approved indications: AD, asthma and CRSwNP. As for AD, an initial loading dose of 600mg (2 injection with 300mg) was used. Considering the pathophysiological similarities between PN and AD and the already demonstrated itch reduction in the AD studies, this approach is reasonable. Bioanalytical methods for the PK and PD analysis include assays for quantitation of functional dupilumab, quantitative and functional assays for anti-drug antibodies, and an assay to determine total IgE concentrations.

In studies EFC16460 and EFC16459, the mean C_{trough} of functional dupilumab reached steady state by Week 12, and remained on this level until the end of the treatment period (Week 24). Steady-state exposures at 300mg, Q2W were overall similar between both individual studies. At Week 12 and Week 24, the mean (SD) trough concentration of dupilumab was 65.3 (32.7) and 68.6 (36.7) mg/L in study EFC16460 and 59.8 (29.5) and 60.2 (34.7) mg/L in study EFC16459, respectively. After discontinuation dupilumab concentrations declined to 0.460 (1.10) and 1.94 (6.12) within the 12-Week follow-up period. Similar to adult patients with AD, asthma and CRSwNP, the distribution of dupilumab can be described as primarily within the vascular compartment with a non-linear target-mediated elimination.

Comparing the observed dupilumab concentrations in PN across other indications, for which dupilumab is already approved, an overall similar PK profile is apparent. In particular, the mean observed steady state exposures of dupilumab are comparable to adult patients with AD or asthma were the same dosing regimen (including a loading dose) was used. The time profile of observed through concentrations appears also very similar as compared to the other approved adult indications.

A previously developed dupilumab global Pop PK base model (study POH0668) which was also assessed in the CRSwNP application was used in the current Pop PK analysis for patients with PN (study POH0779). This global Pop PK base model is based on pooled data from 6 studies in healthy subjects, 10 studies in adult AD patients and 4 studies in asthma with adult and adolescent patients and was a two-compartment model with a first order absorption and parallel linear and nonlinear

elimination, with body weight as covariate. Data from Studies EFC16459 and EFC16460 were not included in the global Pop PK model development, but were evaluated using the MAP Bayesian approach. The predicted dupilumab typical concentration-time profile at 300 mg Q2W in adult patients with PN is very similar to the observed trough concentration-time profiles in studies EFC16460 and EFC1645 and also comparable to the other indications: AD, asthma and CRSwNP.

As within the other indications, body weight was identified as the primary factor responsible for dupilumab PK variability which however does not significantly impair the efficacy of dupilumab. Overall, the PK variability of dupilumab is considered similar in PN, CRSwNP, asthma, and AD patient populations. No relevant effect on the dupilumab PK is apparent considering intrinsic factors analysed including age, gender, race/ethnicity, albumin, laboratory parameters and baseline disease markers and disease characteristics. No dose adjustment with respect to PK covariates is proposed by the MAH in the PN population which is endorsed by the CHMP.

A base PK/PD model was used to evaluate the exposure/response form within linear, log-linear and E_{max} models. The fitted model with stable coefficient estimates and lowest goodness of fit criterion AICc was used. The AUC of the ROC curve was provided indicating an overall good fit of the model and predicted response rates for WI-NRS and PN-S were similar to the observed responses. Bar plots by the concentration quartiles, placebo and corresponding summary statistics were calculated for WI-NRS and IGA PN-S response rates at Week 24 (and also Week 12). Overall, no clear relationship within the range of dupilumab concentrations is apparent from the descriptive analysis of percentages of WI-NRS and PN-S responders by C_{trough} quartiles at Week 24.

In studies EFC16460 and EFC164569, the incidence of treatment emergent ADAs was 2.0% (n=2) and 7.7% (n=11) for the placebo and dupilumab group, respectively, which is comparable to the incidences observed in the other indications AD, asthma and CRSwNP. No relevant impact of ADA-formation on efficacy and safety is apparent which is further described in Section 2.5 and Section 2.6.

Total IgE in serum was used as a main PD biomarker in studies EFC16460 and EFC16459 to further characterize the mode of action of dupilumab. Treatment with dupilumab led to a pronounced reduction (median percent reduction from baseline: 60.86%) of total IgE at the end of the treatment period at Week 24 indicating inhibition of IL-4 and IL-13 signaling. The extent and the kinetics of total IgE-reduction are comparable to what has been already observed in the other indications AD, asthma and CRSwNP. Total serum IgE percent change over time was similar in participants with and without history of atopy.

Overall, the PK profile of dupilumab 300mg Q2W in patients with PN appears to be similar to the observed PK profiles in adults with in the other indications AD, asthma, and CRSwNP.

2.4.6. Conclusions on clinical pharmacology

Results of the PK/PD analyses are consistent with the efficacy evaluation in patients with PN. The PK profile of dupilumab is very similar to adult patients with AD, asthma and CRSwNP with regard to absorption, distribution and elimination, steady state exposures and pharmacokinetic variability.

As within the other indications, body weight was identified as the primary factor responsible for dupilumab PK variability which however does not significantly impair the efficacy of dupilumab. No dose adjustment with respect to these PK covariates is proposed by the MAH in the PN population which is endorsed.

Descriptive and model-based analysis showed no relevant relationship with individual dupilumab exposure ranges. The ADA response in PN patients is consistent with ADAs observed for AD, asthma

and CRSwNP patients. As within other indications, treatment with dupilumab led to a pronounced reduction of total IgE used as PD marker for IL-4/IL 13 signalling inhibition.

In conclusion, the proposed dose regimen for dupilumab 300 mg Q2W with a loading dose of 600 mg in adults with PN is endorsed from a pharmacological point of view. The following dose recommendation for PN patients is therefore added in section 4.2 of the SmPC: *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.*

2.5. Clinical efficacy

2.5.1. Dose response study

No dose response study was performed.

2.5.2. Main studies

Study EFC16460 (LIBERTY-PN PRIME2) and EFC16459 (LIBERTY-PN PRIME): Randomized, double-blind, placebo-controlled, parallel study to assess the efficacy and safety of a 24 week treatment period with Dupilumab 300mg Q2W in adult participants with moderate to severe PN with or without the use of topical prescription therapies

Data for clinical efficacy is based on two replicate phase 3 studies **EFC16459** (LIBERTY-PN PRIME) and **EFC16460** (LIBERTY-PN PRIME2). Both studies are randomized, double blind, placebo controlled, parallel group studies to assess the efficacy and safety of a 24 week treatment period with dupilumab 300 mg Q2W in adult participants with moderate to severe PN with or without the use of topical prescription therapies. Both studies were in general identical in design except for the timing of the primary endpoint in study EFC16459 that was moved from Week 12 to Week 24 during study conduct per protocol amendment.

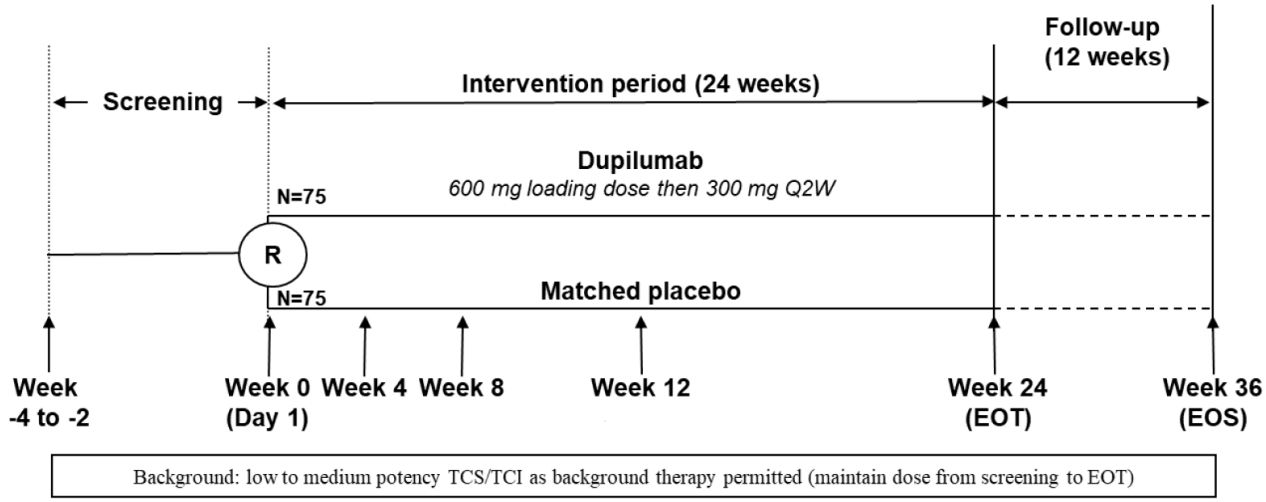
Methods

Both studies had the same design consisting of the following 3 periods (see also Figure below):

- Screening period (2 to 4 weeks)
- Randomized study intervention period (24 weeks):
- Follow-up period (12 weeks).

Both studies were initiated with evaluation of the primary endpoint at Week 12. However, in study EFC16459 the timing for the primary endpoint in study was later moved from Week 12 to Week 24 per protocol amendment.

Figure 9. Overview on the study design for study EFC16460 and EFC16459
Primary Endpoint: EFC16460 (Week 12); EFC16459 (Week 24)



EOS: end of study; EOT: end of treatment; N: number of patients; PN: prurigo nodularis; Q2W: every 2 weeks; R: randomization; SC: subcutaneous; TCI: topical calcineurin inhibitors; TCS: topical corticosteroid

Study participants

For both studies, the **key inclusion criteria** were:

- Aged 18 to 80 years, at the time of signing the informed consent
- Diagnosed with PN by a dermatologist for at least 3 months before the Screening visit
- An average score of ≥7 on the WI-NRS (range: 0 to 10) in the 7 days prior to Day 1
- A minimum of 20 PN lesions in total on both legs, and/or both arms, and/or trunk, at Screening visit and on Day 1
- History of failing a 2 week course of medium-to-superpotent TCS or when TCS were not medically advisable
- Having applied a stable dose of topical emollient (moisturizer) once or twice daily for at least 5 out of 7 consecutive days immediately before Day 1

For both studies, the **key exclusion criteria** were:

- Presence of skin morbidities other than PN and mild AD 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
- Participants with a documented AD severity of moderate-to-severe within 6 months before the Screening visit, or documented diagnosis of moderate-to-severe AD from Screening visit to Randomization visit
- Initiation of treatment with TCS/TCI (any potency) during the screening period or treatment with high potency or superpotent TCS/TCI during the screening period.

- For participants who were on a stable regimen of TCS/TCI (maintain same medicine, same dose from 2 weeks prior to screening visit) at the screening visit:
- Application of TCS/TCI on fewer than 6 days during the 7 days immediately preceding randomization.
- Application of TCS/TCI of incorrect potency within 7 days before Day 1 according to the requirements of Section 6.1.1, ie, low potency if on low potency at screening visit and medium potency if on medium or higher potency at screening visit.
- Severe concomitant illness(es) under poor control that, in the Investigator's judgement, would adversely affect the patient's participation in the study
- Active chronic or acute infection (except HIV infection) requiring treatment with systemic antibiotics, antivirals, antiprotozoals, or antifungals within 2 weeks before screening visit or during the screening period

Treatment failure with medium-to-superpotent TCS was defined as patients who are unable to achieve and/or maintain remission and low disease activity despite treatment with a daily regimen of medium-to-superpotent TCS (±TCI as appropriate), applied for at least 14 days, or for the maximum duration recommended by the product prescribing information, whichever is shorter.

A cap was integrated such that no more than 60% of enrolled PN participants could have a history of atopy. Up to 10% of the enrolled atopic participants were allowed to have active mild AD while participants with moderate-to-severe AD were excluded to minimize confounding of the pruritus endpoints. Participants with systemic medical or psychological conditions were excluded unless these conditions were well controlled.

Treatments

The following study treatments were used:

Dupilumab
Dupilumab 300 mg Q2W after an initial loading dose of 600 mg (2 injections of 300 mg) on Day 1, administered subcutaneously.

Placebo
Matching placebo Q2W after an initial loading dose (2 injections of placebo) on Day 1.

Background Medication
Participants were required to apply moisturizers (emollients) once or twice daily for at least 5 out of 7 consecutive days immediately before Day 1 and to continue throughout the study duration until Week 36. Participants on a stable regimen of low to medium potency TCS or TCI at screening could continue their TCS or TCI application once daily without tapering from screening to Week 24. Stable regimen for TCS is 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 maintaining the same medicine of TCI and the treatment frequency (once or twice daily) used from 2 weeks prior to screening. If specific lesions resolved, the participant could stop applying steroids to those sites but was permitted to continue applying to persistent lesions. Participants on stable regimens of high potency or superpotent steroids at screening were to decrease potency to medium potency TCS and continue to apply daily from screening to Week 24. Occlusion was not allowed from Screening to Week 24.

Rescue Therapy
Participants were allowed to use high potency or superpotent TCS/TCI as rescue therapy as needed throughout the study. Participants with use of rescue medications were considered non-responders with regard to the primary efficacy analysis.

Objectives

Primary objective:

- To demonstrate the efficacy of dupilumab on itch response in participants with PN, inadequately controlled on topical prescription therapies or when those therapies are not advisable.

Secondary objective:

- To demonstrate the efficacy of dupilumab on additional itch endpoints in participants with PN, inadequately controlled on topical prescription therapies or when those therapies are not advisable.
- To demonstrate efficacy of dupilumab on skin lesions of PN.
- To demonstrate efficacy of dupilumab on both itch as well as skin lesions within the same participant.
- To demonstrate the improvement in health-related quality of life (HRQoL).
- To evaluate safety outcome measures.
- To evaluate immunogenicity of dupilumab.

Tertiary/exploratory:

- To demonstrate a reduction in the use of rescue medication and systemic immunosuppressant
- To evaluate exploratory outcome measures
- To evaluate the efficacy of dupilumab on skin lesions using a modified PAS 5-item questionnaire
- To evaluate the efficacy of dupilumab on other PN endpoints

PK:

- To evaluate pharmacokinetic (PK) and pharmacodynamic (PD) outcome measures

Outcomes/endpoints

Both studies had the same objectives and endpoints except for the timing for the primary endpoint of study EFC16459 which was moved during the study conduct from Week 12 to Week 24 as per protocol amendment. The key secondary endpoint (the proportion of participants with IGA PN-S at Week 24) was added for both studies per protocol amendment.

Primary endpoint:
EFC16460:

- Proportion of participants with improvement (reduction) in worst-itch numeric rating scale (WI-NRS) by ≥4 from baseline to Week 12

EFC16459:

- Proportion of participants with improvement (reduction) in worst-itch numeric rating scale (WI-NRS) by ≥4 from baseline to Week 24
  (timing moved from Week 12 to Week 24 with protocol amendment 03)

Key Secondary endpoints:

EFC16460 & EFC16459:

- Proportion of participants with Investigator's Global Assessment 0 or 1 score for PN-Stage (IGA PN-S) at Week 24
  (added for both studies with protocol amendment 01)

EFC16460:

- Proportion of participants with improvement (reduction) in WI-NRS by ≥4 from baseline to Week 24

Other Secondary endpoints (summary)

EFC16460 & EFC16459:

- Time to onset of effect on pruritus as measured by proportion of participants with an improvement (reduction) in WI-NRS by ≥4 from baseline during the 24-week treatment period
- Change from baseline in WI-NRS at Week 24
- Change from baseline in WI-NRS at Week 12
- Percent change from baseline in WI-NRS at Week 24
- until Week 24
- Proportion of participants with WI-NRS reduction ≥4 over time until Week 24
- Proportion of participants with IGA PN-S 0 or 1 score at Week 12.
- Change from baseline in IGA PN-S score at Week 24.
- Change from baseline in IGA PN-S score at Week 12.
- Proportion of participants with Investigator's Global Assessment 0 or 1 score for PN-Activity (IGA PN-A) at Week 24.
- Proportion of participants with IGA PN-A 0 or 1 score at Week 12.
- Change from baseline in HRQoL, as measured by Dermatology Life Quality Index (DLQI) to Week 24.

Sample size

The primary endpoint is the proportion of participants with WI-NRS reduction of ≥4 from baseline to Week 12. By assuming the response rate is 11% and 39% in placebo and dupilumab respectively, 56 participants/arm will provide 90% power to detect the difference of 28% between dupilumab and placebo with Fisher exact test at 2-sided level of 0.05. Assuming 15% drop out during the 12 weeks of treatment, the target is to randomize 75 participants/arm with a cap of up to 10% of participants in the atopic population having active mild AD. Both the atopic and the non-atopic PN population will be capped at 60% of the total enrolled population.

In study EFC 16459, the endpoint was changed (from week 12 to week 24) but the sample size calculation was not amended.

Randomisation

Participants in studies EFC16460 and EFC16459 were planned to be randomized to dupilumab or placebo in 1:1 ratio with stratification factors of documented history of atopy (atopic or non-atopic), stable use of TCS/TCI (yes or no), and country/territory code.

Blinding (masking)

Dupilumab 300 mg and placebo matching dupilumab 300 mg is provided in identically matched 2 mL pre-filled syringes that are visually indistinguishable. Syringes and box will be labelled with a treatment kit number.

Statistical methods

EFC16460 (PRIME2)

The primary estimand was defined in the SAP (version 2, 08-Aug-2021) as follows:

Endpoint Category	Estimands			
	Endpoint(s)[a]	Population	Intercurrent event(s) strategy and missing data handling	Population-level summary
Primary objective: To demonstrate the efficacy of dupilumab on itch response in participants with PN, inadequately controlled on topical prescription therapies or when those therapies are not advisable.				
Primary endpoint	Proportion of participants with improvement (reduction) in worst-itch numeric rating scale (WI-NRS) by ≥4 from baseline to Week 12	ITT	The intercurrent events will be handled as follows: • Discontinuation of study treatment before Week 12: Off-study treatment data up to Week 12 will be included in the analysis (treatment policy strategy). • Taking the prohibited medications/procedures and/or rescue medications[b] prior to Week 12: Participants will be considered as non-responders (composite strategy). In addition, the missing data imputation rules are as follows: • Having missing data at Week 12: Participants will be considered as non-responders.	CMH test adjusted by documented history of atopy (atopic or non-atopic), stable use of TCS/TCI (yes or no), region (countries combined), and baseline antidepressant use (yes or no).

The following description of the methods is based on the study protocol:

The efficacy population was planned to be the ITT population, defined as all randomized participants analyzed according to the treatment group allocated by randomization regardless if treatment kit is used or not.

The primary outcome variable was planned to be the Proportion of participants with improvement (reduction) in WI-NRS by ≥4 from baseline to Week 12.

The primary analysis was planned to be conducted by using CMH test stratifying by stratification factors (documented history of atopy [atopic or non-atopic], stable use of TCS/TCI [yes or no], and region [countries combined]) and covariate of baseline anti-depressant use (yes or no).

For participants discontinuing the study treatment before Week 12, their off-study treatment values measured up to Week 12 were planned to be included in the analysis.

Participants taking selected prohibited medications and/or rescue medications prior to Week 12 or having missing data at Week 12 were planned to be considered non-responders.

In a sensitivity analysis, the data collected after taking selected prohibited medications and/or rescue medications was planned not to be censored and included to evaluate the robustness of the primary analysis results with respect to the method of handling data while taking selected prohibited medications.

Subgroup analyses were prespecified for documented history of atopy (atopic or non-atopic), age group, gender, region. A subgroup analysis was planned to be performed excluding participants with a current diagnosis of AD.

A study-level multiplicity procedure was planned to be used to control the overall type I error rate for testing the primary, key secondary, and selected other endpoints at a 2-sided significance level of 0.05. The hierarchy was defined in the SAP only, and different hierarchies were defined for different regions. For EU and EU reference countries, the following hierarchy was defined in the SAP:

1. Proportion of participants with improvement (reduction) in WI-NRS by ≥4 from baseline to Week 24
2. Proportion of participants with IGA PN-S 0 or 1 score at Week 24
3. Percent change from baseline in WI-NRS at Week 24
4. Change from baseline in HRQoL, as measured by Dermatology Life Quality Index (DLQI) to Week 24
5. Change from baseline in skin Pain-NRS to Week 24
6. Change from baseline in Hospital Anxiety and Depression Scale (HADS) total score to Week 24.

No interim analysis was planned.

A primary database lock was planned to be performed when all randomized participants in this study have completed their 24-week treatment phase. Final analyses in the CSR were planned to be based on this database.

EFC16459 (PRIME)

The primary estimand was defined in the SAP (version 4, 11-Nov-2021) as follows:

Endpoint Category	Estimands			
	Endpoint(s)[a]	Population	Intercurrent event(s) strategy and missing data handling	Population-level summary
Primary objective: To demonstrate the efficacy of dupilumab on itch response in participants with PN, inadequately controlled on topical prescription therapies or when those therapies are not advisable.				
Primary endpoint	Proportion of participants with improvement (reduction) in worst-itch numeric rating scale (WI NRS) by ≥4 from baseline to Week 24	ITT	The intercurrent events will be handled as follows: • Discontinuation of study treatment before Week 24: Off-study treatment data up to Week 24 will be included in the analysis (treatment policy strategy). • Taking the prohibited medications/procedures and/or rescue medications[b] prior to Week 24: Participants will be considered as non-responders (composite strategy). In addition, the missing data imputation rules are as follows: • Having missing data at Week 24: Participants will be considered as non-responders	CMH test adjusted by documented history of atopy (atopic or non-atopic), stable use of TCS/TCI (yes or no), region (countries combined), and baseline antidepressant use (yes or no).

The following description of the methods is based on the study protocol.

The efficacy population was planned to be the ITT population, defined as all randomized participants analyzed according to the treatment group allocated by randomization regardless if treatment kit is used or not.

The primary outcome variable was planned to be the Proportion of participants with improvement (reduction) in WI-NRS by ≥4 from baseline to Week 24.

The primary analysis was planned to be conducted by using CMH test stratifying by stratification factors (documented history of atopy [atopic or non-atopic], stable use of TCS/TCI [yes or no], and region [countries combined]) and covariate of baseline anti-depressant use (yes or no).

For participants discontinuing the study treatment before Week 24, their off-study treatment values measured up to Week 24 were planned to be included in the analysis.

Participants taking selected prohibited medications and/or rescue medications prior to Week 24 or having missing data at Week 24 were planned to be considered non-responders.

In a sensitivity analysis, the data collected after taking selected prohibited medications and/or rescue medications was planned not to be censored and included to evaluate the robustness of the primary analysis results with respect to the method of handling data while taking selected prohibited medications.

Subgroup analyses were prespecified for documented history of atopy (atopic or non-atopic), age group, gender, region. A subgroup analysis was planned to be performed excluding participants with a current diagnosis of AD.

A study-level multiplicity procedure was planned to be used to control the overall type I error rate for testing the primary, key secondary, and selected other endpoints at a 2-sided significance level of 0.05. The hierarchy was defined in the SAP only, and different hierarchies were defined for different regions. For EU and EU reference countries, the following hierarchy was defined in the SAP:

1. Proportion of participants with improvement (reduction) in WI-NRS by ≥4 from baseline to Week 12.
2. Proportion of participants with improvement (reduction) in WI-NRS by ≥4 from baseline to Week 24
3. Proportion of participants with IGA PN-S 0 or 1 score at Week 24
4. Percent change from baseline in WI-NRS at Week 24
5. Proportion of participants with IGA PN-S 0 or 1 score at Week 12
6. Change from baseline in HRQoL, as measured by Dermatology Life Quality Index (DLQI) to Week 24
7. Change from baseline in skin Pain-NRS to Week 24

8. Change from baseline in Sleep-NRS to Week 24
9. Change from baseline in Hospital Anxiety and Depression Scale (HADS) total score to Week 24

No interim analysis was planned.

A primary database lock was planned to be performed when all randomized participants in this study have completed their 24-week treatment phase. Final analyses in the CSR were planned to be based on this database.

Results

Participant flow

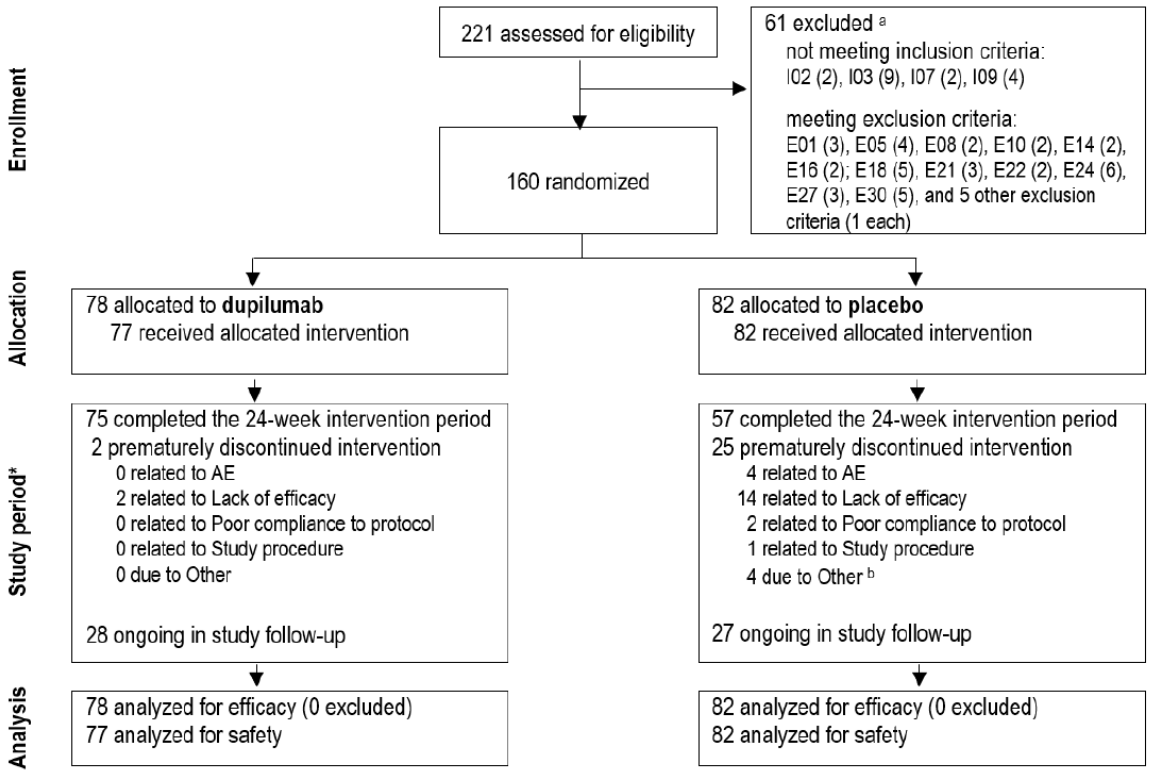
EFC16460 (PRIME2)
Out of the 221 participants screened for study eligibility, 61 (27.6%) were screen failures. The main reason for screen failure was not meeting inclusion criterion I03 (i.e., participants must have an average worst itch score of ≥7 in the 7 days prior to Day 1 [4.1% of all screened participants]).

A total of 160 participants with PN were randomized to study intervention, 78 in the dupilumab group and 82 in the placebo group.

132 (82.5%) participants completed the 24 week study intervention period, 27 (16.9%) permanently discontinued study intervention prior to Week 24. The most frequently reported reason for permanent study intervention discontinuation prior to Week 24 was lack of efficacy, either reported as the main reason by the Investigator or as the reason for withdrawal by the subject (2 [2.6%] participants in the dupilumab group and 14 [17.1%] in the placebo group). Of all participants who permanently discontinued study intervention due to lack of efficacy, 6 participants (1 in the dupilumab group and 5 in the placebo group) started prohibited medications and permanently discontinued the study intervention.

As of the cut-off date for study EFC16460 (30 August 2021), 76 (47.5%) participants had completed the study, while 55 (34.4%) participants were still ongoing in the study follow-up period and 29 (18.1%) participants had discontinued from the study (of which 2 participants in the placebo group who discontinued the study due to an AE [PTs: HIV infection and neurodermatitis]).

Figure 10. Patient Disposition Study EFC16460 (Flow Diagram)



Source: Table 5 and Appendix 16-2-1-disposition [16.2.1.1], [16.2.1.2], [16.2.1.3], and [16.2.1.5]

* Study period = study intervention period + post-intervention follow-up period

a A full description of the inclusion and exclusion criteria is provided in the protocol (16-1-1-protocol [5.1] and [5.2]).

b None of the "other" reasons for permanent study intervention discontinuation were related to safety or lack of efficacy. All were reported as reason for withdrawal by subject.

EFC16459 (PRIME)

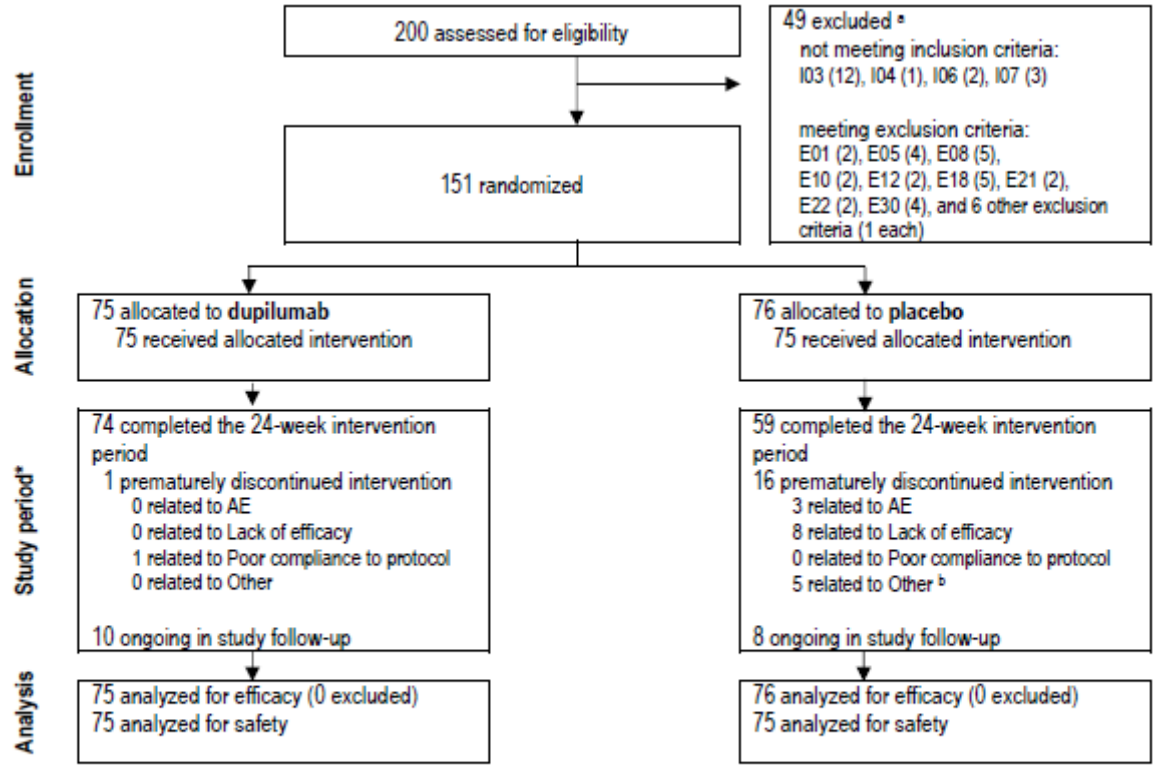
Out of the 200 participants screened for study eligibility, 49 (24.5%) were screen failures. The main reason for screen failure was not meeting inclusion criterion I03 (participants must have an average worst itch score of ≥7 in the 7 days prior to Day 1, [6.0%] of all screened participants).

A total of 151 participants were randomized to study intervention: 75 in the dupilumab group and 76 in the placebo group. There was 1 (1.3%) participant in the placebo group who was randomized but not exposed to study intervention due to participant's decision (fear of being exposed to COVID-19). There were no participants who were exposed to study intervention but not randomized.

133 (88.1%) participants completed the 24-week study intervention period as planned. The percentage of participants permanently discontinuing study intervention was lower in the dupilumab group compared to the placebo group (1 [1.3%] versus 16 [21.1%], respectively). Of all participants who permanently discontinued study intervention due to lack of efficacy, 4 participants in the placebo group started prohibited medications and had to permanently discontinue study intervention.

As of the cut-off date for study EFC16459 (12 November 2021), 119 (78.8%) participants had completed the study, while 18 (11.9%) participants were ongoing in the study follow-up period and 14 (9.3%) participants had discontinued from the study (of which 1 participant in the placebo group discontinued the study due to AE [PT: Inflammatory bowel disease]).

Figure 11. Patient Disposition Study EFC16459 (Flow Diagram)



Source: Table 5 and Appendix 16-2-1-disposition [16.2.1.1], [16.2.1.2], [16.2.1.3], [16.2.1.5], and [16.2.1.6]
* Study period = study intervention period + post-intervention follow-up period
a A full description of the inclusion and exclusion criteria is provided in the protocol (16-1-1-protocol [5.1] and [5.2]).
b None of the "other" reasons for permanent study intervention discontinuation were related to safety or lack of efficacy. All were reported as reason for withdrawal by subject.

Recruitment

EFC16460 (PRIME2):

First participant enrolled:	16 January 2020
Last participant (end of treatment visit):	30 August 2021
The primary analysis data cut-off:	27 September 2021

EFC16459 (PRIME):

First participant enrolled:	12 December 2019
Last participant (end of treatment visit):	12 November 2021
The primary analysis data cut-off:	09 December 2021

Conduct of the study

Changes to the conduct of the study

There was 1 amendment to the protocol of study EFC16460 and 3 amendments to the protocol of study EFC16459. Amendment 01 (20-May-2020) for study EFC 16460 and EFC 16459 included a new lesion-related key secondary endpoint (the proportion of participants with IGA PN-S at Week 24). Amendment 02 (14-Apr-2021) for study EFC16459 was not implemented in any country. Of note, within amendment 03 (21-Oct-2021) the timing for the primary endpoint of study EFC16459 was moved from Week 12 to Week 24 based on the efficacy data observed within study EFC16460.

Changes to the Planned Analyses

Protocol deviations
Critical or major protocol deviation occurred in 11 (14.1%) and 13 (17.3%) participants in the dupilumab group and in 22 (26.8%) and 17 (22.4%) participants in the placebo group within study EFC16460 and EFC16459, respectively. Most deviations were related to the informed consent procedures (EFC16460: 7; EFC16459: 7), inclusion/exclusion criteria (EFC16460: 11; EFC16459: 4), assessment procedures (EFC16460: 7; EFC16459: 10) and concomitant therapy (EFC16460: 8; EFC16459: 4).

Baseline data

Demographics

EFC16460:
The mean age of the randomized population was 48.8 years (range: 18 to 80 years). The proportion of participants aged 65 years or older was higher in the dupilumab group compared to the placebo group (24.4% versus 11.0%, respectively). 35.6% of participants were male and 64.4% were female, 60.0% were White, 32.5% Asian and 5.0% Black or African American. The median BMI was 26.04 kg/m2, with 38 (24.1%) participants having a BMI of ≥30 kg/m2. Out of the 4 regions included in the study (Western Countries, Asia, Latin America, and East Europe), the majority of enrolled participants were from Western Countries (57.5%) followed by Asia (26.9%), Latin America (8.8%), and East Europe (6.9%).

EFC16459:
The mean age of the randomized population was 50.1 years (range: 18 to 80 years). Approximately 22% of participants were 65 years or older. Overall, 33.8% of participants were male and 66.2% were female, and 53.0% were White with 35.8% Asian and 7.3% Black or African American. The median BMI was 26.08 kg/m^2, with 42 (28.0%) participants having a BMI of ≥30 kg/m2. Enrolled participants were from Asia (33.1%), Latin America (27.2%), Western Countries (25.2%), and East Europe (14.6%).

Baseline Disease Characteristics

EFC16460:
The mean age at onset of PN was 46.1 years in the dupilumab group and 41.7 years in the placebo group. Mean duration of PN was 5.42 years. The proportion of atopic participants was 43.6% in the dupilumab group, including 2.6% of participants with active mild AD, and 48.8% in the placebo group, including 6.1% of participants with active mild AD. Overall, 56.3% of participants were on a stable regimen of TCS/TCI at baseline.

Mean (SD) WI-NRS score at baseline was 8.5 (1.0). Mean IGA PN-S score was 3.4 (0.5) with 61.6% and 38.4% of the participants having an IGA PN-S score of 3 ("moderate") or 4 ("severe"), respectively. Mean (SD) IGA PN-A score at baseline was 3.4 (0.6) with 41.5% of all the participants having an IGA PN-A score of 4 ("severe"). The majority of participants (157 [98.1%]) classified their disease severity as "moderate" or "severe" at baseline, as measured by PGIS.

EFC16459:
The mean age at onset of PN was 45.0 years and the mean duration of PN was 5.70 years. The proportion of atopic participants was 44.0% in the dupilumab group (including 5.3% of participants with active mild AD) and 36.8% in the placebo group (including 2.6% of participants with active mild

AD), which was consistent with the prespecified cap in enrollment of atopic participants. Overall, 60.9% of participants were on a stable regimen of TCS/TCI at baseline.

Mean (SD) WI-NRS score at baseline was 8.5 (1.0) (scale range: 0 to 10, with 10 indicating worst imaginable itch) and a mean (SD) IGA PN-S score of 3.3 (0.5) (scale range: 0 to 4, with 4 indicating severe disease stage), with 28.7% of all randomized participants having an IGA PN-S score 4 ("severe"). The overall mean (SD) IGA PN-A score at baseline was 3.3 (0.6) (scale range: 0 to 4, with 4 indicating severe disease activity), with 39.3% of all randomized participants having at least an IGA PN-A score of 4 ("severe").

Numbers analysed

Study EFC16460 (PRIME2)

The actual number of participants analysed per analysis population is as follows:

- Randomized population: 151 (dupilumab: 75; placebo: 76)
- Efficacy population (intent-to-treat [ITT]): 151 (dupilumab: 75; placebo: 76)
- Safety population: 150 (dupilumab: 75; placebo: 75)
- Anti-drug antibody (ADA) population: 135 (dupilumab: 68; placebo: 67)

Study EFC16459 (PRIME)

The actual number of participants analysed per analysis population is as follows:

- Randomized population: 160 (dupilumab: 78; placebo: 82)
- Efficacy population (intent-to-treat [ITT]): 160 (dupilumab: 78; placebo: 82)
- Safety population: 159 (dupilumab: 77; placebo: 82)
- Anti-drug antibody (ADA) population: 155 (dupilumab: 75; placebo: 80)

Outcomes and estimation

Study EFC16460 (PRIME2)

Primary efficacy endpoint

The proportion of participants with an improvement (reduction) in weekly average WI NRS by ≥4 points from baseline to Week 12 was higher in the dupilumab group as compared to the placebo group (37.2% versus 22.0%; p=0.0216).

Table 15. Proportion of participants with an improvement (reduction) in WI-NRS by ≥4 points from baseline at Week 12 - ITT population (EFC16460)

	Placebo (N=82) n (%)	Dupilumab 300 mg Q2W (N=78) n (%)
Weekly average WI-NRS improvement ≥ 4 points at Week 12 from baseline		
Responder	18 (22.0)	29 (37.2)
Non-responder	64 (78.0)	49 (62.8)
Imputed non-responder	19 (23.2)	7 (9.0)
OR, 95% CI vs. placebo[a]		2.3 (1.08, 5.00)
P-value vs. placebo[b]		0.0216
RRD (%), 95% CI vs. placebo[a]		16.8 (2.34, 31.16)

CMH: Cochran-Mantel Haenszel; WI-NRS: worst-itch numeric rating scale; CI: confidence interval.

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

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

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

PGM=PRODOPS/SAR231893/EFC16460/CSR/REPORT/PGM/eff_resp_i_t.sas
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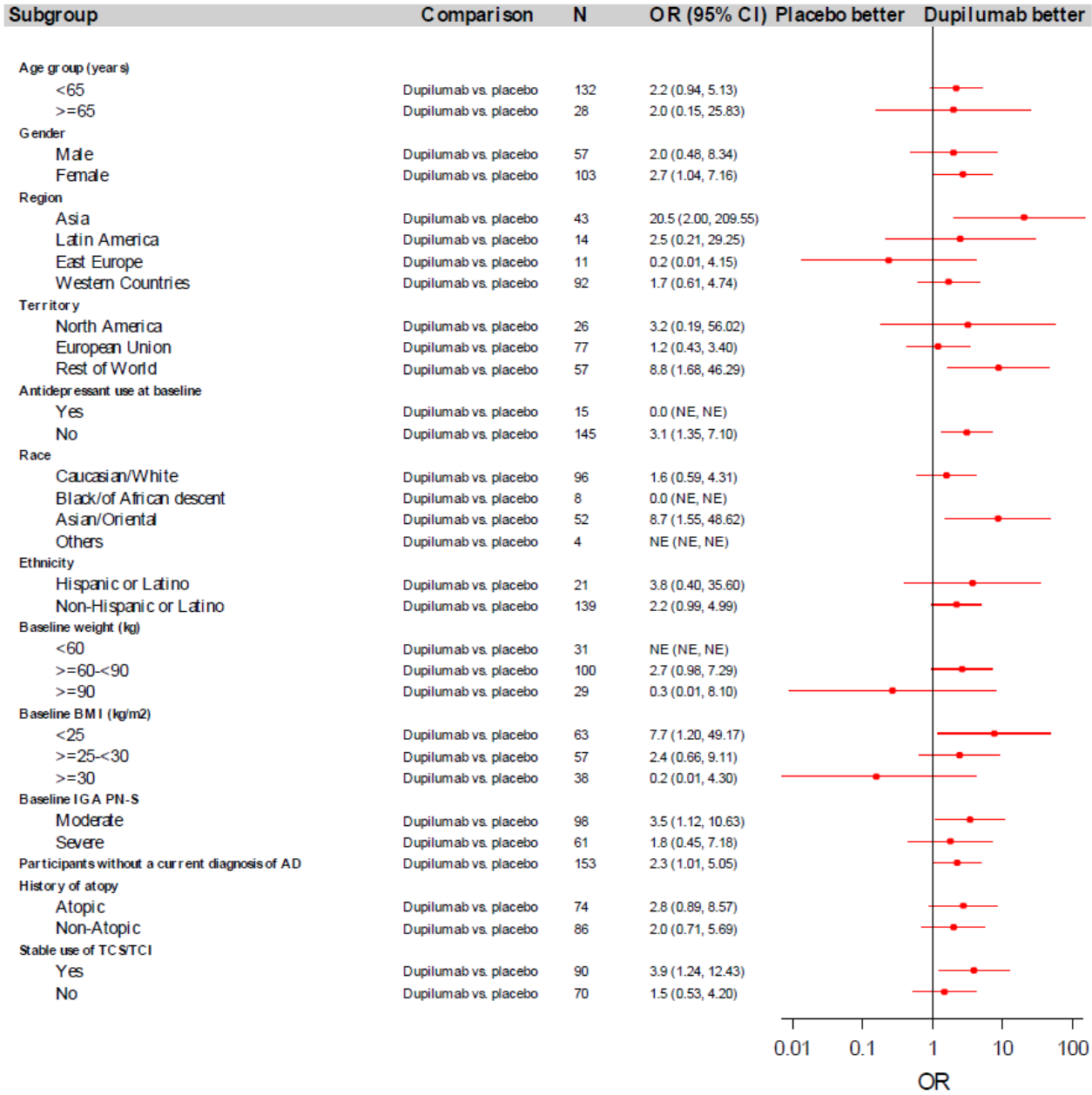
Subgroup analyses at Week 12 by demographics and baseline disease characteristics (EFC16460)

Subgroup analyses by demographics and baseline disease characteristics are shown below. The treatment benefit of dupilumab versus placebo was still observed after excluding participants with active mild AD. There was a comparable dupilumab treatment benefit between atopic and non-atopic participants, and between participants with a baseline IGA PN-S score of 3 (“moderate”) and 4 (“severe”).

Most subgroups showed improvement with dupilumab with the exception of East European participants and participants with baseline body weight ≥90 kg and BMI ≥30 kg/m2.

Figure 12. Proportion of participants with an improvement (reduction) in WI-NRS by ≥4 points from baseline at Week 12 by subgroup - ITT population (EFC16460)



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OUT=REPORT/OUTPUT/eff_resp_sub_winrs_w12_i_g_i.rtf (28OCT2021 8:02)

Key Secondary endpoint

The proportion of participants with an improvement (reduction) in weekly average WI-NRS by ≥4 points from baseline to Week 24 was higher in the dupilumab group compared to the placebo group (57.7% versus 19.5%). The difference was clinically meaningful and statistically significant ($p<0.0001$). The magnitude of the itch response observed in the dupilumab group as compared to the placebo group at Week 24 was greater than it had been at Week 12.

Table 16. Proportion of participants with an improvement (reduction) in WI-NRS by ≥4 points from baseline at Week 24 - ITT population (EFC16460)

	Placebo (N=82) n (%)	Dupilumab 300 mg Q2W (N=78) n (%)
Weekly average WI-NRS improvement ≥ 4 points at Week 24 from baseline		
Responder	16 (19.5)	45 (57.7)
Non-responder	66 (80.5)	33 (42.3)
Imputed non-responder	33 (40.2)	12 (15.4)
OR, 95% CI vs. placebo[a]		9.0 (3.56, 22.66)
P-value vs. placebo[b]		<.0001
RRD (%), 95% CI vs. placebo[a]		42.6 (29.06, 56.08)

CMH: Cochran-Mantel Haenszel; WI-NRS: worst-itch numeric rating scale; CI: confidence interval.

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

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

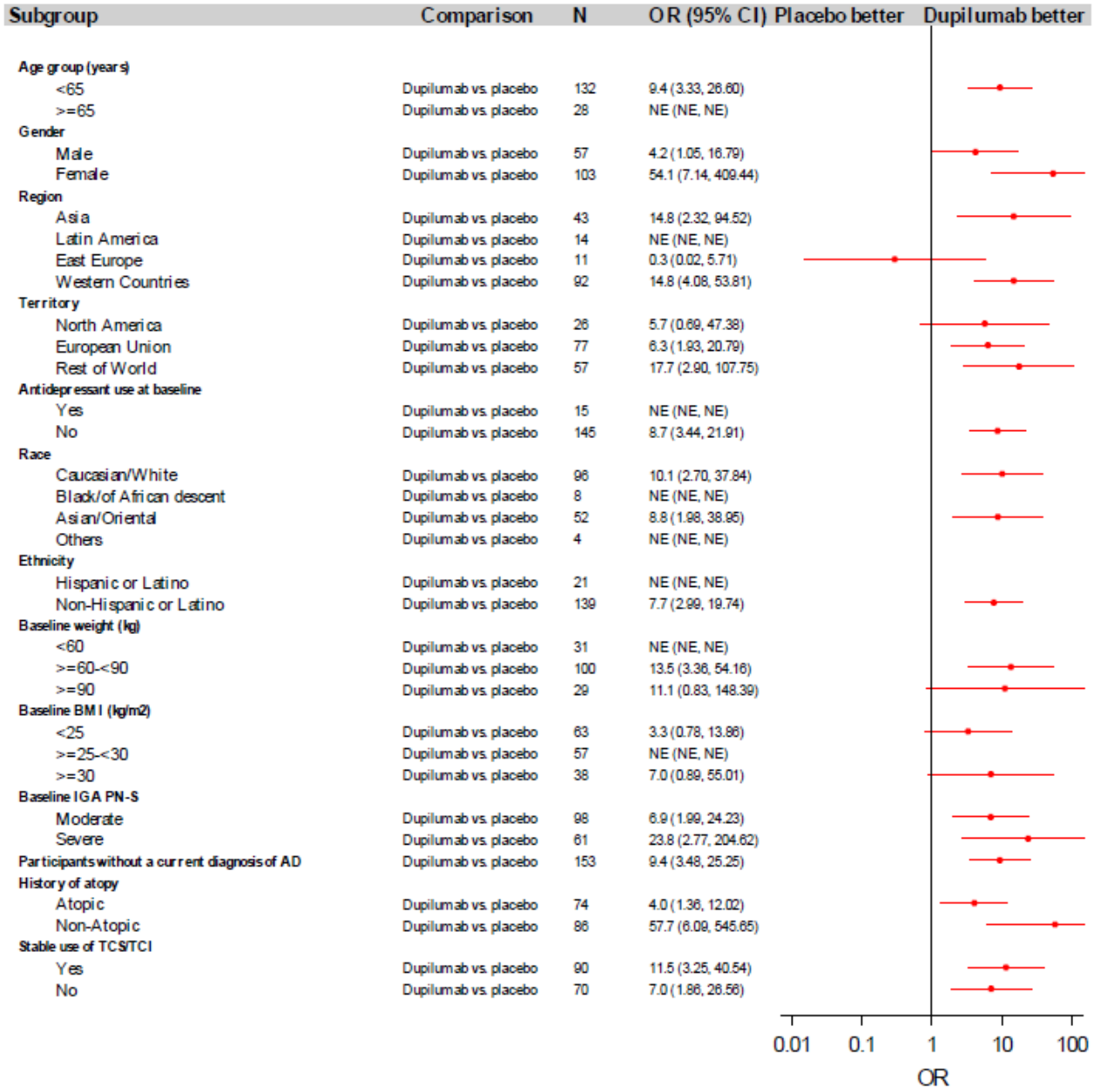
Note: Participants who received the prohibited medications/procedures and/or rescue medications that impacted efficacy before Week 24 were considered as non-responders, and missing data at Week 24 were considered as non-responders.

PGM=PRODOPS/SAR231893/EFC16460/CSR/REPORT/PGM/eff_resp_i_t.sas
OUT=REPORT/OUTPUT/eff_resp_winrs_w24_i_t_i.rtf (28OCT2021 8:03)

Subgroup analyses at Week 24 by demographics and baseline disease characteristics (EFC16460)

Subgroup analyses by demographics and baseline disease characteristics are shown below. No significant treatment-by-subgroup interactions were observed. The treatment benefit of dupilumab versus placebo was still observed after excluding participants with active mild AD. There was a comparable dupilumab treatment benefit between the atopic and non-atopic subgroups, and between participants with a baseline IGA PN-S score of 3 ("moderate") and 4 ("severe"). Subgroups showed a trend of dupilumab treatment benefit, with the exception of East Europe which showed a trend toward lower efficacy. The numerically lower dupilumab treatment effect observed at Week 12 in participants with baseline body weight ≥90 kg and in participants with baseline BMI ≥30 kg/m2 was no longer observed at Week 24.

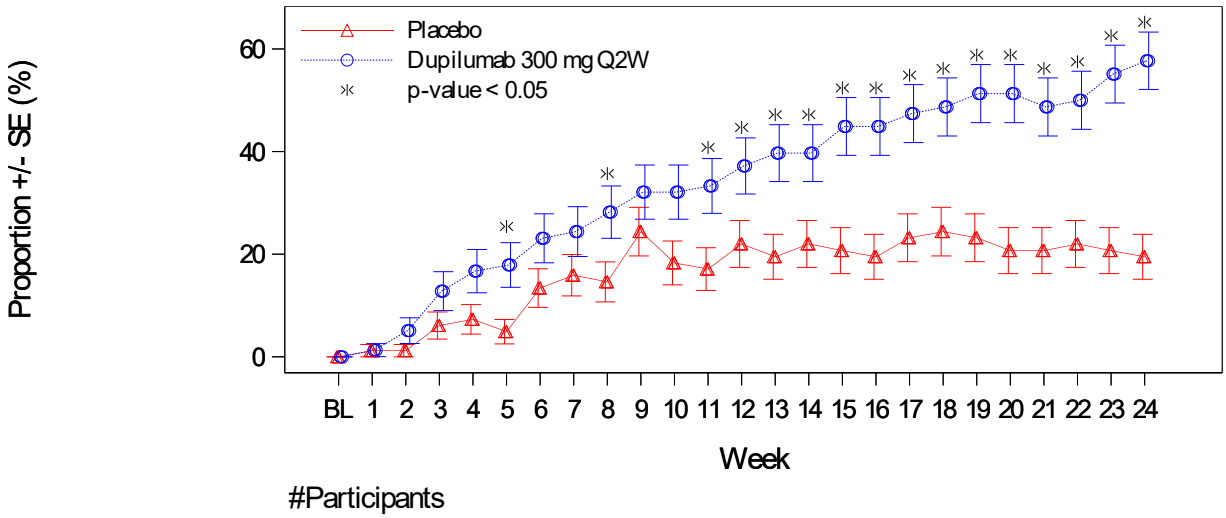
Figure 13. Proportion of participants with an improvement (reduction) in WI-NRS by ≥4 points from baseline at Week 24 by subgroup - ITT population (EFC16460)



Proportion of participants with improvement (reduction) in WI-NRS by ≥4 points over time up to Week 24 (EFC16460)

The treatment group difference progressively increased over time with the largest difference observed at Week 24.

Figure 14. Proportion of participants with an improvement (reduction) in WI-NRS by ≥4 points from baseline over time up to Week 24 - ITT population (EFC16460)



#Participants

Placebo	82 82 82 82 82 82 82 82 82 82 82 82 82 82 82 82 82 82 82 82 82 82 82 82 82
Dupilumab 300 mg Q2W	78 78 78 78 78 78 78 78 78 78 78 78 78 78 78 78 78 78 78 78 78 78 78 78 78

Proportion of participants with an IGA PN-S 0 or 1 score at Week 24 (EFC16460)

The proportion of participants with an IGA PN-S 0 ("clear") or 1 ("almost clear") score at Week 24 was higher in the dupilumab group as compared to the placebo group (44.9% versus 15.9%; p<0.0001).

Table 17. Proportion of participants with an IGA PN-S 0 or 1 score at Week 24 - ITT population (EFC16460)

	Placebo (N=82) n (%)	Dupilumab 300 mg Q2W (N=78) n (%)
IGA PN-S 0 or 1 score		
Responder	13 (15.9)	35 (44.9)
Non-responder	69 (84.1)	43 (55.1)
Imputed non-responder	33 (40.2)	10 (12.8)
OR, 95% CI vs. placebo[a]		4.4 (2.02, 9.55)
P-value vs. placebo[b]		<.0001
RRD (%), 95% CI vs. placebo[a]		30.8 (16.37, 45.22)

CMH: Cochran-Mantel Haenszel; CI: confidence interval.

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

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

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.

PGM=PRODOPS/SAR231893/EFC16460/CSR/REPORT/PGM/eff_resp_i_t.sas
OUT=REPORT/OUTPUT/eff_resp_igapns_w24_i_t_i.rtf (28OCT2021 8:03)

Subgroup analyses by demographics and baseline disease characteristics at Week 24 (EFC16460)

Subgroup analyses by demographics and baseline disease characteristics showed a trend of dupilumab treatment benefit in the proportion of participants with an IGA PN-S 0 ("clear") or 1 ("almost clear") score at Week 24 across the majority of subgroups. No significant treatment-by-subgroup interactions were observed. The treatment benefit of dupilumab versus placebo was still observed after excluding participants with active mild AD. There was a comparable dupilumab treatment benefit between the

atopic and non-atopic subgroups, and between participants with a baseline IGA PN-S score of 3 ("moderate") and 4 ("severe"). Responder rates grouped by body weight were 9/13 (69.2%) vs. 2/16 (12.5%) for participants with baseline body weight ≥90 kg, 19/47 (40.4%) vs. 9/53 (17.0%) for participants with baseline body weight ≥60-<90 kg, and 7/18 (38.9%) vs. 2/13 (15.4%) for participants with baseline body weight <60 kg. A trend toward lower efficacy was observed in the subgroup of participants who were using antidepressants at baseline was observed.

Study EFC16459 (PRIME)

Primary efficacy endpoint

The proportion of participants with an improvement (reduction) in weekly average WI-NRS by ≥4 points from baseline to Week 24 was higher in the dupilumab group compared to the placebo group (60.0% versus 18.4%; p<0.0001).

Table 18. Proportion of participants with an improvement (reduction) in WI-NRS by ≥4 points from baseline at Week 24 - ITT population (EFC16459)

	Placebo (N=76) n (%)	Dupilumab 300 mg Q2W (N=75) n (%)
Weekly average WI-NRS improvement ≥ 4 points at Week 24 from baseline		
Responder	14 (18.4)	45 (60.0)
Non-responder	62 (81.6)	30 (40.0)
Imputed non-responder	32 (42.1)	8 (10.7)
OR, 95% CI vs. placebo[a]		6.5 (2.78, 15.41)
P-value vs. placebo[b]		<.0001
RRD (%), 95% CI vs. placebo[a]		42.7 (27.76, 57.72)

CMH: Cochran-Mantel Haenszel; WI-NRS: worst-itch numeric rating scale; CI: confidence interval.

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

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

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.

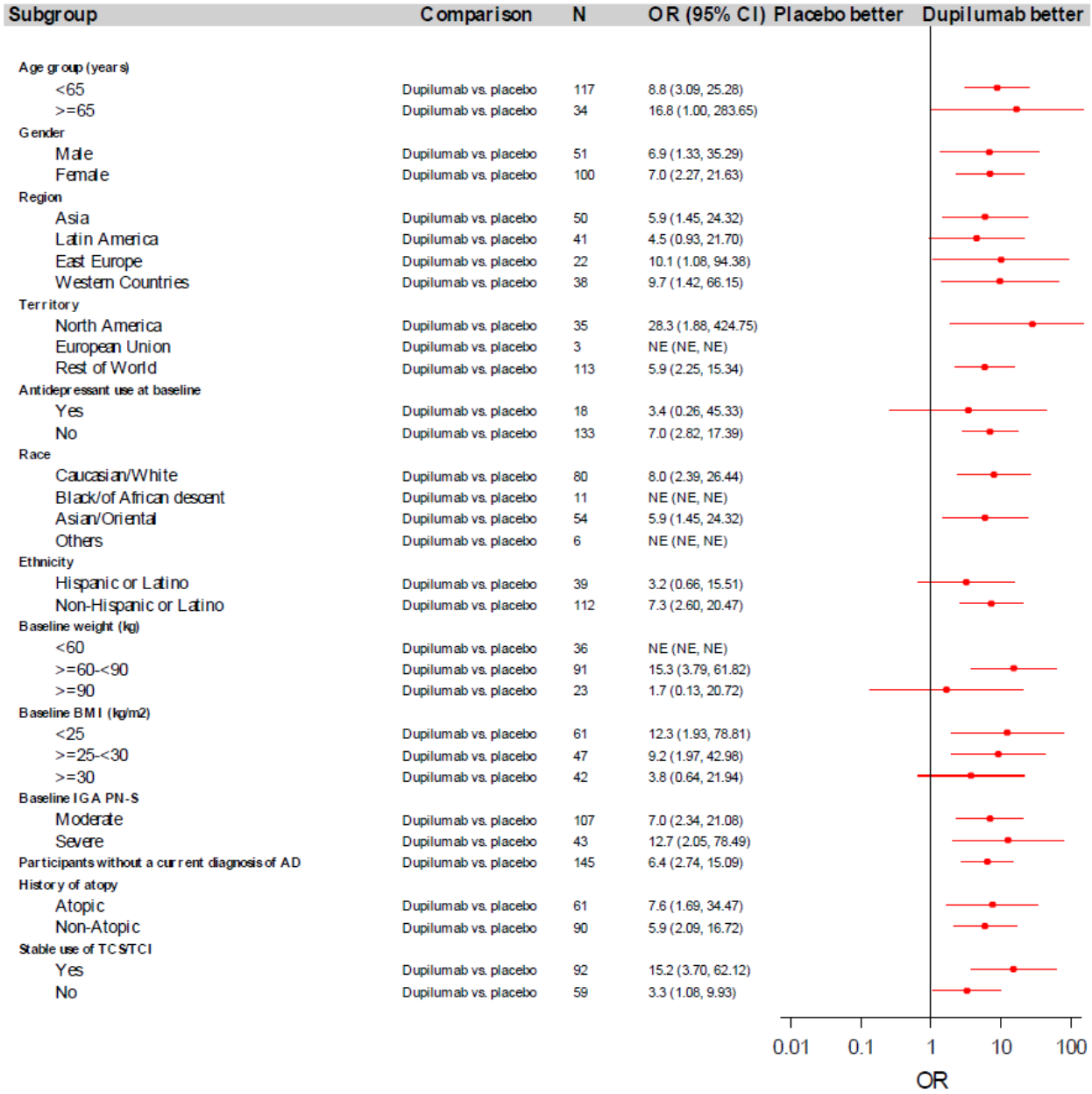
PGM=PRODOPS/SAR231893/EFC16459/CSR/REPORT/PGM/eff_resp_i_t.sas OUT=REPORT/OUTPUT/eff_resp_winrs_w24_i_t_i.rtf (04FEB2022 4:46)

Subgroup analyses at Week 24 by demographics and baseline disease characteristics (EFC16459)

Subgroup analyses by demographics and baseline disease characteristics are shown below. The treatment effect of dupilumab versus placebo was still observed after excluding participants with active mild AD. There was a comparable dupilumab treatment benefit between atopic and non-atopic participants, and between participants with baseline IGA PN-S score of 3 ("moderate") and 4 ("severe").

Regarding body weight, the magnitude of the treatment effect was greater in the subgroup of participants with baseline body weight ≥60 to <90 kg (dupilumab: 33/46 (71.7%) vs. placebo: 6/45 (13.3%)) as to participants with baseline body weight ≥90 kg (dupilumab: 5/14 (35.7%) vs. placebo: 3/9 (33.3%)) and participants with baseline body weight <60 kg (dupilumab: 7/15 (46.7%) vs. placebo: 5/21 (23.8%)).

Figure 15. Proportion of participants with WI-NRS improvement (reduction) from baseline ≥4 points at Week 24 by subgroup - ITT population (EFC16459)

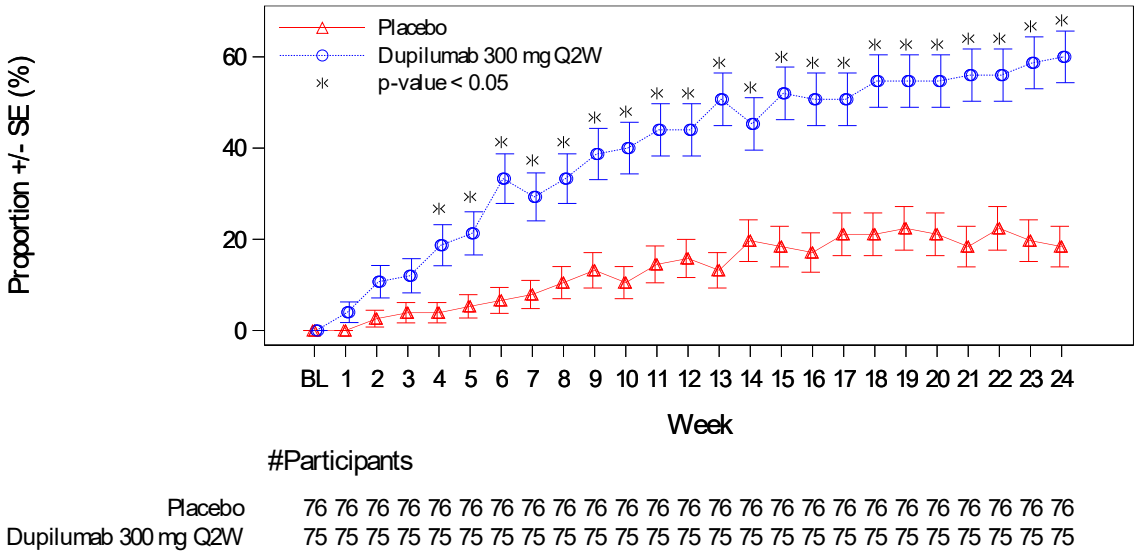


PGM=PRODOPS/SAR231893/EFC16459/CSR/REPORT/PGM/eff resp sub i g.sas
OUT=REPORT/OUTPUT/eff_resp_sub_winrs_w24_i_g_i.rtf (11JAN2022 6:35)

Proportion of participants with improvement (reduction) in WI-NRS by ≥4 points over time up to Week 24 (EFC16459)

The treatment group difference progressively increased over time with the largest difference observed at Week 24.

Figure 16. Proportion of participants with an improvement (reduction) in WI-NRS by ≥4 points from baseline over time up to Week 24 - ITT population (EFC16459)



#Participants

Placebo	76 76 76 76 76 76 76 76 76 76 76 76 76 76 76 76 76 76 76 76 76 76 76 76 76
Dupilumab 300 mg Q2W	75 75 75 75 75 75 75 75 75 75 75 75 75 75 75 75 75 75 75 75 75 75 75 75 75

Key Secondary endpoint

Proportion of participants with an IGA PN-S 0 or 1 score at Week 24 (EFC16459)

The proportion of participants with an IGA PN-S 0 ("clear") or 1 ("almost clear") score at Week 24 was higher in the dupilumab group as compared to the placebo group (48.0% versus 18.4%; p=0.0004).

Table 19. Proportion of participants with an IGA PN-S 0 or 1 score at Week 24 - ITT population (EFC16459)

	Placebo (N=76) n (%)	Dupilumab 300 mg Q2W (N=75) n (%)
IGA PN-S 0 or 1 score		
Responder	14 (18.4)	36 (48.0)
Non-responder	62 (81.6)	39 (52.0)
Imputed non-responder	29 (38.2)	8 (10.7)
OR, 95% CI vs. placebo[a]		4.0 (1.81, 8.98)
P-value vs. placebo[b]		0.0004
RRD (%), 95% CI vs. placebo[a]		28.3 (13.41, 43.16)

CMH: Cochran-Mantel Haenszel; CI: confidence interval.

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

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

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.

PGM=PRODOPS/SAR231893/EFC16459/CSR/REPORT/PGM/eff_resp_i_t.sas OUT=REPORT/OUTPUT/eff_resp_igapns_w24_i_t_i.rtf (04FEB2022 4:46)

Subgroup analyses by demographics and baseline disease characteristics at Week 24 (EFC16459)

A trend of dupilumab treatment benefit in the proportion of participants with an IGA PN-S 0 ("clear") or 1 ("almost clear") score at Week 24 across subgroups can be observed. The treatment effect of dupilumab versus placebo was still observed after excluding participants with active mild AD, and there was a comparable dupilumab treatment benefit between the atopic and non-atopic subgroups and between participants with baseline IGA PN-S score of 3 ("moderate") and 4 ("severe"). A significant

quantitative treatment-by-subgroup interaction was detected with regard to stable use of TCS/TCI at baseline (nominal p=0.0327). Both subgroups of participants showed a similar trend of dupilumab treatment benefit; however, the magnitude of the treatment effect was greater in the subgroup of participants with a stable use of TCS/TCI at baseline (53.2% versus 11.1% in the dupilumab and placebo groups, respectively) as compared to the subgroup of participants with no use of TCS/TCI at baseline (39.3% versus 29.0%, respectively).

Summary of main studies

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 20. Summary of Efficacy for trial EFC16460 (LIBERTY-PN PRIME2)

Title: A randomized, double-blind, placebo-controlled, multicenter, parallel-group study to evaluate the efficacy and safety of dupilumab in patients with prurigo nodularis who are inadequately controlled on topical prescription therapies or when those therapies are not advisable (LIBERTY-PN PRIME2)			
Short title: Study of dupilumab for the treatment of patients with prurigo nodularis, inadequately controlled on topical prescription therapies or when those therapies are not advisable			
Study identifier	EFC16460		
Design	Study EFC16460 is a randomized, multi-center, double-blind, placebo-controlled, parallel-group, study to evaluate the efficacy and safety of 24-week treatment with dupilumab 300 mg Q2W in participants with PN whose disease was is inadequately controlled on topical prescription therapies or when those therapies were not advisable. The study assessed the effect of dupilumab on itch improvement as well as its effect on PN lesions, HRQoL, anxiety and depression, skin pain and sleep quality, and overall health status. After 2-4 weeks of screening, participants were randomized (1:1) to dupilumab 300 mg Q2W or matching placebo. Randomization was stratified by documented history of atopy (atopic or non-atopic), stable use of TCS/TCI (yes or no), and country/territory code.		
	Duration of main phase		40 weeks
Hypothesis	Superiority		
Treatments groups	Dupilumab		Dupilumab 300 mg Q2W after an initial loading dose of 600 mg (2 injections of 300 mg) on Day 1, 24-week treatment period, 78 randomized participants
	Placebo		Matching placebo Q2W after an initial loading dose (2 injections) on Day 1, 24-week treatment period, 82 randomized participants
Endpoints and definitions	Primary endpoint	WI-NRS at Week 12	Proportion of participants with an improvement (reduction) in WI-NRS by ≥4 points from baseline to Week 12

	Key secondary endpoints	WI-NRS at Week 24	Proportion of participants with an improvement (reduction) in WI-NRS by ≥4 points from baseline to Week 24
	Key secondary endpoints	IGA PN-S at Week 24	Proportion of participants with an IGA PN-S 0 ("clear") or 1 ("almost clear") score at Week 24
	Key secondary endpoints	Composite	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 (for US and US reference countries only)
Core database lock	27 Sep 2021		
Results and Analysis			
Analysis description	**Primary analysis**		
Analysis population and timepoint description	ITT population defined as all randomized participants 12 weeks from baseline		
Descriptive statistics and estimate variability	Treatment group	Placebo	Dupilumab 300 mg Q2W
	Number of participants	82	78
	WI-NRS at Week 12	18 (22.0)	29 (37.2)
	Imputed non-responders	19 (23.2)	7 (9.0)
Effect estimate per comparison	WI-NRS at Week 12	Comparison groups	Dupilumab 300 mg Q2W vs. placebo
		OR (95% CI)	2.3 (1.08, 5.00)
		Response rate difference (%) (95% CI)	16.8 (2.34, 31.16)
		p-value (CMH)	0.0216
Analysis description	**Key secondary analysis**		
Analysis population and timepoint description	ITT population defined as all randomized patients 24 weeks from baseline		
Descriptive statistics and estimate variability	Treatment group	Placebo	Dupilumab 300 mg Q2W
	Number of participants	82	78
	WI-NRS at Week 24 Responder n (%)	16 (19.5)	45 (57.7)
	IGA PN-S at Week 24	13 (15.9)	35 (44.9)
	Composite Responder n (%)	7 (8.5)	25 (32.1)
Effect estimate per comparison	WI-NRS at Week 24	Comparison groups	Dupilumab 300 mg Q2W vs. placebo
		OR (95% CI)	9.0 (3.56, 22.66)

		Response rate difference (%) (95% CI)	42.6 (29.06, 56.08)
		p-value (CMH)	<0.0001
	IGA PN-S at Week 24	OR (95% CI)	4.4 (2.02, 9.55)
		Response rate difference (%) (95% CI)	30.8 (16.37, 45.22)
		p-value (CMH)	<0.0001
	Composite	OR (95% CI)	6.1 (2.03, 18.11)
		Response rate difference (%) (95% CI)	25.5 (13.09, 37.86)
		p-value (CMH)	0.0001

Table 21. Summary of Efficacy for trial EFC16459 (LIBERTY-PN PRIME)

Title: A randomized, double-blind, placebo-controlled, multicenter, parallel-group study to evaluate the efficacy and safety of dupilumab in patients with prurigo nodularis who are inadequately controlled on topical prescription therapies or when those therapies are not advisable (LIBERTY-PN PRIME)		
Short title: Study of dupilumab for the treatment of patients with prurigo nodularis, inadequately controlled on topical prescription therapies or when those therapies are not advisable		
Study identifier	EFC16459	
Design	Study EFC16459 is a randomized, multi-center, double-blind, placebo-controlled, parallel-group, study to evaluate the efficacy and safety of 24-week treatment with dupilumab 300 mg Q2W in participants with PN whose disease was inadequately controlled on topical prescription therapies or when those therapies were not advisable. The study assessed the effect of dupilumab on itch improvement as well as its effect on PN lesions, HRQoL, anxiety and depression, skin pain and sleep quality, and overall health status. After 2-4 weeks of screening, participants were randomized (1:1) to dupilumab 300 mg Q2W or matching placebo. Randomization was stratified by documented history of atopy (atopic or non-atopic), stable use of TCS/TCI (yes or no), and country/territory code.	
	Duration of main phase	40 weeks
Hypothesis	Superiority	
Treatments groups	Dupilumab	Dupilumab 300 mg Q2W after an initial loading dose of 600 mg (2 injections of 300 mg) on Day 1, 24-week treatment period, 75 randomized participants
	Placebo	Matching placebo Q2W after an initial loading dose (2 injections) on Day 1, 24-week treatment period, 76 randomized participants

Endpoints and definitions	Primary endpoint	WI-NRS at Week 24	Proportion of participants with an improvement (reduction) in WI-NRS by ≥4 points from baseline to Week 24	
	Key secondary endpoints	IGA PN-S at Week 24	Proportion of participants with an IGA PN-S 0 ("clear") or 1 ("almost clear") score at Week 24	
	Key secondary endpoints	Composite	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 (for US and US reference countries only)	
Core database lock	09 Dec 2021			
Results and Analysis				
Analysis description	**Primary analysis**			
Analysis population and timepoint description	ITT population defined as all randomized participants 24 weeks from baseline			
Descriptive statistics and estimate variability	Treatment group		Placebo	Dupilumab 300 mg Q2W
	Number of participants		76	75
	WI-NRS at Week 24 Responder n (%)		14 (18.4)	45 (60.0)
	Imputed non-responders		32 (42.1)	8 (10.7)
Effect estimate per comparison	WI-NRS at Week 24	Comparison groups		Dupilumab 300 mg Q2W vs placebo
		OR (95% CI)		6.5 (2.78, 15.41)
		Response rate difference (%) (95% CI)		42.7 (27.76, 57.72)
		p-value (CMH)		<0.0001
Analysis description	**Key secondary analysis**			
Analysis population and timepoint description	ITT population defined as all randomized participants 24 weeks from baseline			
Descriptive statistics and estimate variability	Treatment group		Placebo	Dupilumab 300 mg Q2W
	Number of participants		76	75
	IGA PN-S at Week 24 Responder n (%)		14 (18.4)	36 (48.0)
	Composite Responder n (%)		7 (9.2)	29 (38.7)
Effect estimate per comparison	IGA PN-S at Week 24	Comparison groups		Dupilumab 300 mg Q2W vs placebo
		Odds ratio (95% CI)		4.0 (1.81, 8.98)

		Response rate difference (%) (95% CI)	28.3 (13.41, 43.16)
		p-value (CMH)	0.0004
	Composite	Odds ratio, 95% CI	6.9 (2.49, 19.05)
		Response rate difference (%), 95% CI	29.6 (16.42, 42.81)
		p-value (CMH)	<0.0001

Analysis performed across trials

Efficacy data from the two pivotal phase 3 studies EFC16460 (PRIME2) and EFC16459 (PRIME) were pooled, including all data up to the data cut-off dates of 30 August 2021 for EFC16460 and 12 November 2021 for EFC16459. Results from the pooled analysis are described below.

Participant flow

Disposition of study participants

A total of 311 pooled participants were randomized to study intervention, 153 in the dupilumab group and 158 in the placebo group. There were 2 (0.6%) participants (1 [0.7%] in the dupilumab group and 1 [0.6%] in the placebo group) who were randomized but not exposed to study intervention due to the participants' decision.

In the randomized and exposed population, 265 (85.2%) participants completed the 24 week study intervention period. The percentage of participants permanently discontinuing study intervention was lower in the dupilumab group (3 [2.0%]) compared to the placebo group (41 [25.9%]).

As of the time of the data cut-off, 73 (23.5%) participants were still ongoing in the study follow-up period, 195 (62.7%) participants had completed the study period (ie, entire study intervention and post-intervention follow-up periods), and 43 (13.8%) participants had permanently discontinued from the studies.

Table 22. Participant disposition - Pooled ITT population

n (%)	Placebo (N=158)	Dupilumab 300 mg Q2W (N=153)	All (N=311)
Randomized and not exposed	1 (0.6)	1 (0.7)	2 (0.6)
Randomized and exposed	157 (99.4)	152 (99.3)	309 (99.4)
Completed the 12-week study intervention period	133 (84.2)	149 (97.4)	282 (90.7)
Did not complete the 12-week study intervention period	24 (15.2)	3 (2.0)	27 (8.7)
Completed the 24-week study intervention period	116 (73.4)	149 (97.4)	265 (85.2)
Did not complete the 24-week study intervention period	41 (25.9)	3 (2.0)	44 (14.1)
Reason for permanent study intervention withdrawal prior to Week 24			
Adverse event	5 (3.2)	0	5 (1.6)
Related to COVID-19	0	0	0
Not related to COVID-19	5 (3.2)	0	5 (1.6)
Lack of efficacy	16 (10.1)	1 (0.7)	17 (5.5)

n (%)	Placebo (N=158)	Dupilumab 300 mg Q2W (N=153)	All (N=311)
Poor compliance to protocol	2 (1.3)	1 (0.7)	3 (1.0)
Withdrawal by Subject	18 (11.4)	1 (0.7)	19 (6.1)
Other	0	0	0
Related to COVID-19	0	0	0
Not related to COVID-19	0	0	0
Reason for permanent study intervention withdrawal prior to Week 12			
Adverse event	4 (2.5)	0	4 (1.3)
Related to COVID-19	0	0	0
Not related to COVID-19	4 (2.5)	0	4 (1.3)
Lack of efficacy	9 (5.7)	1 (0.7)	10 (3.2)
Poor compliance to protocol	1 (0.6)	1 (0.7)	2 (0.6)
Withdrawal by Subject	10 (6.3)	1 (0.7)	11 (3.5)
Other	0	0	0
Related to COVID-19	0	0	0
Not related to COVID-19	0	0	0
Reason for permanent study intervention withdrawal from Weeks 12-24			
Adverse event	1 (0.6)	0	1 (0.3)
Related to COVID-19	0	0	0
Not related to COVID-19	1 (0.6)	0	1 (0.3)
Lack of efficacy	7 (4.4)	0	7 (2.3)
Poor compliance to protocol	1 (0.6)	0	1 (0.3)
Withdrawal by Subject	8 (5.1)	0	8 (2.6)
Other	0	0	0
Related to COVID-19	0	0	0
Not related to COVID-19	0	0	0
Reason for study intervention withdrawal by subject prior to Week 24[a]			
Adverse event	2 (1.3)	0	2 (0.6)
Related to COVID-19	0	0	0
Not related to COVID-19	2 (1.3)	0	2 (0.6)
Study procedure	1 (0.6)	0	1 (0.3)
Lack of efficacy	6 (3.8)	1 (0.7)	7 (2.3)
Other	9 (5.7)	0	9 (2.9)
Related to COVID-19	0	0	0
Not related to COVID-19	9 (5.7)	0	9 (2.9)
Completed the study period	88 (55.7)	107 (69.9)	195 (62.7)
Did not complete the study period	35 (22.2)	8 (5.2)	43 (13.8)
Ongoing during the study period	35 (22.2)	38 (24.8)	73 (23.5)
Reason for study discontinuation			
Adverse event	3 (1.9)	0	3 (1.0)
Poor compliance to protocol	1 (0.6)	0	1 (0.3)
Withdrawal by Subject	31 (19.6)	8 (5.2)	39 (12.5)
Site terminated by sponsor	0	0	0
Study terminated by sponsor	0	0	0
Other	0	0	0
Related to COVID-19	0	0	0
Not related to COVID-19	0	0	0
Status at last contact			

n (%)	Placebo (N=158)	Dupilumab 300 mg Q2W (N=153)	All (N=311)
Alive	122 (77.2)	114 (74.5)	236 (75.9)
Dead	0	0	0

a This is a further breakdown of the reasons for withdrawal by participant reported above, as collected in the standard CRF form.

Percentages are calculated using the number of participants randomized as denominator

Note: One participant (ID: 016460-826-0001-30003) in dupilumab group was alive at the status of last contact on 10SEP2021, but was not counted in this table due to data cutoff by 30AUG2021. One participant (ID: 016459-032-0003-10001) in placebo group was alive at the status of last contact on 24NOV2021, but was not counted in this table due to data cutoff by 12NOV2021.
For the status of last contact, ongoing participants were excluded as the corresponding CRF page was not collected.
Study period = study intervention period + post-intervention follow-up period.

Baseline Data

Demographics

The mean age of the study participants was 49.5 years (median: 51 years with a range of 18 to 80 years). A total of 62 (19.9%) participants were aged 65 years or older; of them, 38 participants were treated with dupilumab. Female participants represented 65.3% of the population. The mean (SD) weight was 73.90 (17.92) kg and 26.0% of the population had a BMI ≥30 kg/m2. Studies EFC16460 and EFC16459 were conducted globally with regional representation including Asia, Latin America, Eastern Europe, and Western Countries; race representation included White (56.6%), Asian (34.1%), Black or African American (6.1%), and other races (3.2%). Of the 44 participants enrolled in both studies from the US, 16 (36.4%) were Black or African American.

Table 23. Demographics and participant characteristics at baseline - ITT population from EFC16460 and EFC16459 and Pooled ITT population

	EFC16460			EFC16459			Pooled Data		
	Placebo (N=82)	Dupilumab 300 mg Q2W (N=78)	All (N=160)	Placebo (N=76)	Dupilumab 300 mg Q2W (N=75)	All (N=151)	Placebo (N=158)	Dupilumab 300 mg Q2W (N=153)	All (N=311)
Age (years)									
Number	82	78	160	76	75	151	158	153	311
Mean (SD)	46.7 (15.2)	51.0 (15.8)	48.8 (15.6)	51.1 (15.8)	49.2 (17.4)	50.1 (16.6)	48.8 (15.6)	50.1 (16.6)	49.5 (16.1)
Median	49.0	52.5	50.0	52.0	49.0	51.0	50.0	52.0	51.0
Q1 ; Q3	33.0 ; 59.0	42.0 ; 64.0	38.5 ; 60.0	38.0 ; 62.0	35.0 ; 66.0	36.0 ; 62.0	36.0 ; 60.0	40.0 ; 64.0	37.0 ; 61.0
Min ; Max	20 ; 79	18 ; 80	18 ; 80	21 ; 80	18 ; 79	18 ; 80	20 ; 80	18 ; 80	18 ; 80
Age group [n (%)]									
Number	82	78	160	76	75	151	158	153	311
18-39	28 (34.1)	15 (19.2)	43 (26.9)	20 (26.3)	22 (29.3)	42 (27.8)	48 (30.4)	37 (24.2)	85 (27.3)
40-64	45 (54.9)	44 (56.4)	89 (55.6)	41 (53.9)	34 (45.3)	75 (49.7)	86 (54.4)	78 (51.0)	164 (52.7)
65-74	7 (8.5)	16 (20.5)	23 (14.4)	10 (13.2)	14 (18.7)	24 (15.9)	17 (10.8)	30 (19.6)	47 (15.1)
≥75	2 (2.4)	3 (3.8)	5 (3.1)	5 (6.6)	5 (6.7)	10 (6.6)	7 (4.4)	8 (5.2)	15 (4.8)
Region[a] [n (%)]									
Number	82	78	160	76	75	151	158	153	311
Asia	23 (28.0)	20 (25.6)	43 (26.9)	23 (30.3)	27 (36.0)	50 (33.1)	46 (29.1)	47 (30.7)	93 (29.9)
Latin America	8 (9.8)	6 (7.7)	14 (8.8)	22 (28.9)	19 (25.3)	41 (27.2)	30 (19.0)	25 (16.3)	55 (17.7)
East Europe	5 (6.1)	6 (7.7)	11 (6.9)	11 (14.5)	11 (14.7)	22 (14.6)	16 (10.1)	17 (11.1)	33 (10.6)
Western Countries	46 (56.1)	46 (59.0)	92 (57.5)	20 (26.3)	18 (24.0)	38 (25.2)	66 (41.8)	64 (41.8)	130 (41.8)
Territory[b] [n (%)]									

	EFC16460			EFC16459			Pooled Data		
	Placebo (N=82)	Dupilumab 300 mg Q2W (N=78)	All (N=160)	Placebo (N=76)	Dupilumab 300 mg Q2W (N=75)	All (N=151)	Placebo (N=158)	Dupilumab 300 mg Q2W (N=153)	All (N=311)
Number	82	78	160	76	75	151	158	153	311
North America	14 (17.1)	12 (15.4)	26 (16.3)	18 (23.7)	17 (22.7)	35 (23.2)	32 (20.3)	29 (19.0)	61 (19.6)
European Union	37 (45.1)	40 (51.3)	77 (48.1)	2 (2.6)	1 (1.3)	3 (2.0)	39 (24.7)	41 (26.8)	80 (25.7)
Rest of World	31 (37.8)	26 (33.3)	57 (35.6)	56 (73.7)	57 (76.0)	113 (74.8)	87 (55.1)	83 (54.2)	170 (54.7)
Sex [n (%)]									
Number	82	78	160	76	75	151	158	153	311
Male	31 (37.8)	26 (33.3)	57 (35.6)	28 (36.8)	23 (30.7)	51 (33.8)	59 (37.3)	49 (32.0)	108 (34.7)
Female	51 (62.2)	52 (66.7)	103 (64.4)	48 (63.2)	52 (69.3)	100 (66.2)	99 (62.7)	104 (68.0)	203 (65.3)
Race [n (%)]									
Number	82	78	160	76	75	151	158	153	311
White	48 (58.5)	48 (61.5)	96 (60.0)	45 (59.2)	35 (46.7)	80 (53.0)	93 (58.9)	83 (54.2)	176 (56.6)
Black or African American	5 (6.1)	3 (3.8)	8 (5.0)	3 (3.9)	8 (10.7)	11 (7.3)	8 (5.1)	11 (7.2)	19 (6.1)
Asian	27 (32.9)	25 (32.1)	52 (32.5)	25 (32.9)	29 (38.7)	54 (35.8)	52 (32.9)	54 (35.3)	106 (34.1)
Japanese	0	0	0	8 (10.5)	8 (10.7)	16 (10.6)	8 (5.1)	8 (5.2)	16 (5.1)
Native Hawaiian or Other Pacific Islander	0	1 (1.3)	1 (0.6)	0	0	0	0	1 (0.7)	1 (0.3)
American Indian or Alaska Native	1 (1.2)	0	1 (0.6)	2 (2.6)	3 (4.0)	5 (3.3)	3 (1.9)	3 (2.0)	6 (1.9)
Multiple	0	1 (1.3)	1 (0.6)	0	0	0	0	1 (0.7)	1 (0.3)
Unknown	0	0	0	0	0	0	0	0	0
Not reported	1 (1.2)	0	1 (0.6)	1 (1.3)	0	1 (0.7)	2 (1.3)	0	2 (0.6)
Ethnicity [n (%)]									
Number	82	78	160	76	75	151	158	153	311
Hispanic or Latino	11 (13.4)	10 (12.8)	21 (13.1)	21 (27.6)	18 (24.0)	39 (25.8)	32 (20.3)	28 (18.3)	60 (19.3)
Not Hispanic or Latino	71 (86.6)	68 (87.2)	139 (86.9)	55 (72.4)	57 (76.0)	112 (74.2)	126 (79.7)	125 (81.7)	251 (80.7)
Weight (kg)									
Number	82	78	160	75	75	150	157	153	310
Mean (SD)	75.04 (19.73)	73.86 (17.50)	74.47 (18.63)	71.37 (16.97)	75.22 (17.26)	73.30 (17.17)	73.29 (18.50)	74.53 (17.34)	73.90 (17.92)
Median	70.35	72.40	72.15	69.00	72.80	71.00	70.00	72.70	71.25
Q1 ; Q3	62.00 ; 85.00	60.30 ; 82.00	61.53 ; 84.20	59.00 ; 81.00	62.50 ; 85.70	60.50 ; 84.60	60.50 ; 84.10	62.30 ; 84.30	61.00 ; 84.30
Min ; Max	43.0 ; 154.0	43.9 ; 127.0	43.0 ; 154.0	38.8 ; 125.8	44.5 ; 124.0	38.8 ; 125.8	38.8 ; 154.0	43.9 ; 127.0	38.8 ; 154.0
Weight group (kg) [n (%)]									
Number	82	78	160	75	75	150	157	153	310
<60	13 (15.9)	18 (23.1)	31 (19.4)	21 (28.0)	15 (20.0)	36 (24.0)	34 (21.7)	33 (21.6)	67 (21.6)
≥60-<90	53 (64.6)	47 (60.3)	100 (62.5)	45 (60.0)	46 (61.3)	91 (60.7)	98 (62.4)	93 (60.8)	191 (61.6)
≥90	16 (19.5)	13 (16.7)	29 (18.1)	9 (12.0)	14 (18.7)	23 (15.3)	25 (15.9)	27 (17.6)	52 (16.8)
BMI (kg/m^2)									
Number	80	78	158	75	75	150	155	153	308
Mean (SD)	26.98 (5.89)	26.88 (5.86)	26.93 (5.86)	26.43 (5.78)	28.08 (6.26)	27.26 (6.07)	26.71 (5.83)	27.47 (6.07)	27.09 (5.95)
Median	26.06	26.02	26.04	25.22	27.45	26.08	25.54	26.30	26.06

	EFC16460			EFC16459			Pooled Data		
	Placebo (N=82)	Dupilumab 300 mg Q2W (N=78)	All (N=160)	Placebo (N=76)	Dupilumab 300 mg Q2W (N=75)	All (N=151)	Placebo (N=158)	Dupilumab 300 mg Q2W (N=153)	All (N=311)
Q1 ; Q3	22.23 ; 29.98	23.11 ; 30.02	22.59 ; 29.98	22.64 ; 28.44	23.74 ; 31.01	23.02 ; 30.35	22.41 ; 29.78	23.42 ; 30.79	22.94 ; 30.10
Min ; Max	16.1 ; 50.3	18.0 ; 45.0	16.1 ; 50.3	16.5 ; 45.0	17.5 ; 42.7	16.5 ; 45.0	16.1 ; 50.3	17.5 ; 45.0	16.1 ; 50.3
BMI group (kg/m^2) [n (%)]									
Number	80	78	158	75	75	150	155	153	308
<25	33 (41.3)	30 (38.5)	63 (39.9)	37 (49.3)	24 (32.0)	61 (40.7)	70 (45.2)	54 (35.3)	124 (40.3)
25-<30	29 (36.3)	28 (35.9)	57 (36.1)	22 (29.3)	25 (33.3)	47 (31.3)	51 (32.9)	53 (34.6)	104 (33.8)
≥30	18 (22.5)	20 (25.6)	38 (24.1)	16 (21.3)	26 (34.7)	42 (28.0)	34 (21.9)	46 (30.1)	80 (26.0)

BMI: Body mass index, ITT: Intent-to-treat

a Asia: Japan, China, South Korea, Taiwan; East Europe: Hungary, Russia; Latin America: Argentina, Mexico, Chile; Western Countries: USA, Canada, France, Italy, Portugal, Spain, and UK.

b North America: USA, Canada; European Union: France, Italy, Hungary, Portugal, Spain, and UK; Rest of World: Russia, Japan, China, Taiwan, South Korea, Argentina, Chile, and Mexico.

Baseline Disease Characteristics

The mean WI-NRS score was 8.5 (scale range 0-10, with 10 indicating worst imaginable itch), mean IGA PN-S score was 3.3 (scale range 0-4, with 4 indicating severe disease stage), and a mean IGA PN-A score was 3.4. Overall, 66.3% and 33.7% of participants had an IGA PN S score of 3 ("moderate", 20-100 nodules) or 4 ("severe", >100 nodules), respectively, and 55.0% and 40.5% of participants had an IGA PN A score of 3 ("moderate") or 4 ("severe"), respectively. In total 99.0% of participants had a WI NRS score ≥7 at baseline and 100% of participants had at least 20 PN skin lesions, with a mean duration of PN disease of 5.6 years.

The HRQoL of the enrolled participants as measured by DLQI, was 17.5 (scale range 0-30, with 30 indicating the largest impact on quality of life, and 11-20 indicating a very large impact on quality of life). Mental health of the enrolled participants as measured by HADS, with a mean score of 15.2 (scale range 0-42, with a high score indicative of an abnormal anxiety and/or depression level) and a high proportion of participants meeting the cut-off score for anxiety with HADS-A ≥8 (58.9%) or depression with HADS D ≥8 (37.2%). Participants also had a high Skin Pain-NRS score (mean score 7.2, score range 0-10, with 10 indicating the worst possible pain) and a low Sleep Quality NRS score (mean score 4.3, score range 0-10, with 0 indicating the worst possible sleep) at baseline.

Overall, 43.4% of the participants in the pooled ITT population had a history or current diagnosis of atopy, consistent with the prespecified cap (60%) in enrolment of atopic participants, and of these atopic participants, 9.6% had active mild AD, consistent with the cap instituted (10% of the atopic population). In addition, 56.9% of participants had other comorbid conditions associated with PN; hypertension, type 2 diabetes mellitus, and hypothyroidism were the most frequent ones.

Table 24. Disease and other characteristics at baseline - ITT population from EFC16460 and EFC16459 and Pooled ITT population

	EFC16460			EFC16459			Pooled Data		
	Placebo (N=82)	Dupilumab 300 mg Q2W (N=78)	All (N=160)	Placebo (N=76)	Dupilumab 300 mg Q2W (N=75)	All (N=151)	Placebo (N=158)	Dupilumab 300 mg Q2W (N=153)	All (N=311)
Age at onset of PN (years)									
Number	82	78	160	76	75	151	158	153	311

	EFC16460			EFC16459			Pooled Data		
	Placebo (N=82)	Dupilumab 300 mg Q2W (N=78)	All (N=160)	Placebo (N=76)	Dupilumab 300 mg Q2W (N=75)	All (N=151)	Placebo (N=158)	Dupilumab 300 mg Q2W (N=153)	All (N=311)
Mean (SD)	41.7 (15.3)	46.1 (16.5)	43.9 (16.0)	46.2 (16.2)	43.9 (18.2)	45.0 (17.2)	43.9 (15.8)	45.0 (17.4)	44.4 (16.6)
Median	41.0	47.0	45.0	48.5	43.0	46.0	44.0	46.0	45.0
Q1 ; Q3	29.0 ; 53.0	37.0 ; 57.0	32.5 ; 56.5	33.5 ; 57.5	29.0 ; 60.0	31.0 ; 59.0	32.0 ; 56.0	34.0 ; 57.0	32.0 ; 57.0
Min ; Max	15 ; 75	2 ; 80	2 ; 80	10 ; 79	4 ; 77	4 ; 79	10 ; 79	2 ; 80	2 ; 80
Duration of PN (year)[a]									
Number	82	78	160	76	75	151	158	153	311
Mean (SD)	5.48 (6.97)	5.36 (6.90)	5.42 (6.92)	5.40 (6.21)	6.01 (7.55)	5.70 (6.89)	5.44 (6.60)	5.68 (7.21)	5.56 (6.90)
Median	3.00	2.83	2.96	3.21	3.33	3.33	3.00	3.00	3.00
Q1 ; Q3	1.08 ; 7.00	0.83 ; 7.00	1.00 ; 7.00	1.04 ; 6.83	1.08 ; 8.00	1.08 ; 7.42	1.08 ; 7.00	1.00 ; 7.83	1.08 ; 7.17
Min ; Max	0.3 ; 40.0	0.3 ; 30.0	0.3 ; 40.0	0.3 ; 30.2	0.3 ; 45.0	0.3 ; 45.0	0.3 ; 40.0	0.3 ; 45.0	0.3 ; 45.0
Duration group of PN (year) [n (%)]									
Number	82	78	160	76	75	151	158	153	311
<3	40 (48.8)	40 (51.3)	80 (50.0)	37 (48.7)	32 (42.7)	69 (45.7)	77 (48.7)	72 (47.1)	149 (47.9)
≥3	42 (51.2)	38 (48.7)	80 (50.0)	39 (51.3)	43 (57.3)	82 (54.3)	81 (51.3)	81 (52.9)	162 (52.1)
History of atopy[b] [n (%)]									
Number	82	78	160	76	75	151	158	153	311
Atopic	40 (48.8)	34 (43.6)	74 (46.3)	28 (36.8)	33 (44.0)	61 (40.4)	68 (43.0)	67 (43.8)	135 (43.4)
Ongoing mild Atopic Dermatitis	5 (6.1)	2 (2.6)	7 (4.4)	2 (2.6)	4 (5.3)	6 (4.0)	7 (4.4)	6 (3.9)	13 (4.2)
Non-Atopic	42 (51.2)	44 (56.4)	86 (53.8)	48 (63.2)	42 (56.0)	90 (59.6)	90 (57.0)	86 (56.2)	176 (56.6)
Stable use of TCS/TCI[c] [n (%)]									
Number	82	78	160	76	75	151	158	153	311
Yes	46 (56.1)	44 (56.4)	90 (56.3)	45 (59.2)	47 (62.7)	92 (60.9)	91 (57.6)	91 (59.5)	182 (58.5)
No	36 (43.9)	34 (43.6)	70 (43.8)	31 (40.8)	28 (37.3)	59 (39.1)	67 (42.4)	62 (40.5)	129 (41.5)
Baseline WI-NRS score									
Number	82	78	160	76	75	151	158	153	311
Mean (SD)	8.5 (1.0)	8.5 (1.0)	8.5 (1.0)	8.3 (1.1)	8.6 (0.9)	8.5 (1.0)	8.4 (1.1)	8.6 (0.9)	8.5 (1.0)
Median	8.5	8.5	8.5	8.3	8.7	8.4	8.4	8.7	8.4
Q1 ; Q3	8.0 ; 9.2	7.7 ; 9.3	7.8 ; 9.3	7.8 ; 9.0	7.9 ; 9.3	7.9 ; 9.1	7.9 ; 9.1	7.9 ; 9.3	7.9 ; 9.1
Min ; Max	3 ; 10	7 ; 10	3 ; 10	2 ; 10	7 ; 10	2 ; 10	2 ; 10	7 ; 10	2 ; 10
Baseline IGA PN-S score									
Number	81	78	159	75	75	150	156	153	309
Mean (SD)	3.4 (0.5)	3.4 (0.5)	3.4 (0.5)	3.3 (0.5)	3.3 (0.5)	3.3 (0.5)	3.3 (0.5)	3.3 (0.5)	3.3 (0.5)
Median	3.0	3.0	3.0	3.0	3.0	3.0	3.0	3.0	3.0
Q1 ; Q3	3.0 ; 4.0	3.0 ; 4.0	3.0 ; 4.0	3.0 ; 4.0	3.0 ; 4.0	3.0 ; 4.0	3.0 ; 4.0	3.0 ; 4.0	3.0 ; 4.0
Min ; Max	3 ; 4	3 ; 4	3 ; 4	3 ; 4	3 ; 4	3 ; 4	3 ; 4	3 ; 4	3 ; 4
Baseline IGA PN-S categorical score [n (%)]									
Number	81	78	159	75	75	150	156	153	309
0 (clear)	0	0	0	0	0	0	0	0	0
1 (almost clear)	0	0	0	0	0	0	0	0	0
2 (mild)	0	0	0	0	0	0	0	0	0
3 (moderate)	49 (60.5)	49 (62.8)	98 (61.6)	53 (70.7)	54 (72.0)	107 (71.3)	102 (65.4)	103 (67.3)	205 (66.3)
4 (severe)	32 (39.5)	29 (37.2)	61 (38.4)	22 (29.3)	21 (28.0)	43 (28.7)	54 (34.6)	50 (32.7)	104 (33.7)

	EFC16460			EFC16459			Pooled Data		
	Placebo (N=82)	Dupilumab 300 mg Q2W (N=78)	All (N=160)	Placebo (N=76)	Dupilumab 300 mg Q2W (N=75)	All (N=151)	Placebo (N=158)	Dupilumab 300 mg Q2W (N=153)	All (N=311)
Baseline IGA PN-A score									
Number	81	78	159	75	75	150	156	153	309
Mean (SD)	3.4 (0.6)	3.4 (0.6)	3.4 (0.6)	3.3 (0.6)	3.3 (0.6)	3.3 (0.6)	3.4 (0.6)	3.4 (0.6)	3.4 (0.6)
Median	3.0	3.0	3.0	3.0	3.0	3.0	3.0	3.0	3.0
Q1 ; Q3	3.0 ; 4.0	3.0 ; 4.0	3.0 ; 4.0	3.0 ; 4.0	3.0 ; 4.0	3.0 ; 4.0	3.0 ; 4.0	3.0 ; 4.0	3.0 ; 4.0
Min ; Max	1 ; 4	2 ; 4	1 ; 4	1 ; 4	2 ; 4	1 ; 4	1 ; 4	2 ; 4	1 ; 4
Baseline IGA PN-A categorical score [n (%)]									
Number	81	78	159	75	75	150	156	153	309
0 (clear)	0	0	0	0	0	0	0	0	0
1 (almost clear)	1 (1.2)	0	1 (0.6)	1 (1.3)	0	1 (0.7)	2 (1.3)	0	2 (0.6)
2 (mild)	3 (3.7)	3 (3.8)	6 (3.8)	3 (4.0)	3 (4.0)	6 (4.0)	6 (3.8)	6 (3.9)	12 (3.9)
3 (moderate)	42 (51.9)	44 (56.4)	86 (54.1)	41 (54.7)	43 (57.3)	84 (56.0)	83 (53.2)	87 (56.9)	170 (55.0)
4 (severe)	35 (43.2)	31 (39.7)	66 (41.5)	30 (40.0)	29 (38.7)	59 (39.3)	65 (41.7)	60 (39.2)	125 (40.5)
Baseline Skin Pain-NRS score									
Number	82	78	160	76	75	151	158	153	311
Mean (SD)	7.1 (2.5)	7.3 (2.4)	7.2 (2.4)	7.2 (2.3)	7.2 (2.5)	7.2 (2.4)	7.2 (2.4)	7.2 (2.5)	7.2 (2.4)
Median	7.7	8.0	7.8	7.8	7.9	7.9	7.8	7.9	7.8
Q1 ; Q3	6.5 ; 8.7	6.7 ; 9.0	6.6 ; 8.8	6.6 ; 8.6	6.7 ; 8.9	6.7 ; 8.8	6.5 ; 8.7	6.7 ; 8.9	6.7 ; 8.8
Min ; Max	0 ; 10	0 ; 10	0 ; 10	0 ; 10	0 ; 10	0 ; 10	0 ; 10	0 ; 10	0 ; 10
Baseline Sleep-NRS score									
Number	82	78	160	76	75	151	158	153	311
Mean (SD)	4.2 (2.5)	4.4 (2.3)	4.3 (2.4)	4.3 (2.2)	4.4 (2.4)	4.3 (2.3)	4.2 (2.4)	4.4 (2.4)	4.3 (2.4)
Median	3.9	4.2	4.0	4.4	4.2	4.3	4.1	4.2	4.1
Q1 ; Q3	2.0 ; 6.0	2.7 ; 6.0	2.2 ; 6.0	2.5 ; 6.2	2.6 ; 6.4	2.5 ; 6.3	2.1 ; 6.1	2.6 ; 6.2	2.4 ; 6.1
Min ; Max	0 ; 10	0 ; 9	0 ; 10	0 ; 9	0 ; 9	0 ; 9	0 ; 10	0 ; 9	0 ; 10
Baseline PGIS score									
Number	82	78	160	76	75	151	158	153	311
Mean (SD)	3.7 (0.5)	3.7 (0.5)	3.7 (0.5)	3.6 (0.5)	3.7 (0.5)	3.6 (0.5)	3.7 (0.5)	3.7 (0.5)	3.7 (0.5)
Median	4.0	4.0	4.0	4.0	4.0	4.0	4.0	4.0	4.0
Q1 ; Q3	3.0 ; 4.0	4.0 ; 4.0	4.0 ; 4.0	3.0 ; 4.0	3.0 ; 4.0	3.0 ; 4.0	3.0 ; 4.0	3.0 ; 4.0	3.0 ; 4.0
Min ; Max	2 ; 4	1 ; 4	1 ; 4	3 ; 4	2 ; 4	2 ; 4	2 ; 4	1 ; 4	1 ; 4
Baseline PGIS categorical score [n (%)]									
Number	82	78	160	76	75	151	158	153	311
1 (none)	0	1 (1.3)	1 (0.6)	0	0	0	0	1 (0.7)	1 (0.3)
2 (mild)	1 (1.2)	1 (1.3)	2 (1.3)	0	1 (1.3)	1 (0.7)	1 (0.6)	2 (1.3)	3 (1.0)
3 (moderate)	21 (25.6)	15 (19.2)	36 (22.5)	32 (42.1)	23 (30.7)	55 (36.4)	53 (33.5)	38 (24.8)	91 (29.3)
4 (severe)	60 (73.2)	61 (78.2)	121 (75.6)	44 (57.9)	51 (68.0)	95 (62.9)	104 (65.8)	112 (73.2)	216 (69.5)
Baseline number of lesions from PAS [n (%)]									
Number	82	78	160	75	75	150	157	153	310
0	0	0	0	0	0	0	0	0	0
1-19	0	0	0	0	0	0	0	0	0
20-100	52 (63.4)	47 (60.3)	99 (61.9)	52 (69.3)	54 (72.0)	106 (70.7)	104 (66.2)	101 (66.0)	205 (66.1)
>100	30 (36.6)	31 (39.7)	61 (38.1)	23 (30.7)	21 (28.0)	44 (29.3)	53 (33.8)	52 (34.0)	105 (33.9)

	EFC16460			EFC16459			Pooled Data		
	Placebo (N=82)	Dupilumab 300 mg Q2W (N=78)	All (N=160)	Placebo (N=76)	Dupilumab 300 mg Q2W (N=75)	All (N=151)	Placebo (N=158)	Dupilumab 300 mg Q2W (N=153)	All (N=311)
Baseline exact number of lesions in representative area from PAS									
Number	82	78	160	75	75	150	157	153	310
Mean (SD)	26.4 (18.8)	25.6 (18.7)	26.0 (18.7)	25.1 (16.7)	27.0 (26.7)	26.1 (22.2)	25.8 (17.7)	26.3 (22.9)	26.0 (20.4)
Median	22.0	21.0	21.0	22.0	20.0	20.0	22.0	20.0	21.0
Q1 ; Q3	15.0 ; 33.0	10.0 ; 34.0	14.0 ; 33.5	14.0 ; 30.0	14.0 ; 32.0	14.0 ; 31.0	15.0 ; 31.0	13.0 ; 32.0	14.0 ; 32.0
Min ; Max	3 ; 100	3 ; 84	3 ; 100	4 ; 87	5 ; 183	4 ; 183	3 ; 100	3 ; 183	3 ; 183
Baseline healed lesions from PAS [n (%)]									
Number	82	78	160	75	75	150	157	153	310
0-24%	55 (67.1)	55 (70.5)	110 (68.8)	54 (72.0)	51 (68.0)	105 (70.0)	109 (69.4)	106 (69.3)	215 (69.4)
25-49%	13 (15.9)	18 (23.1)	31 (19.4)	13 (17.3)	15 (20.0)	28 (18.7)	26 (16.6)	33 (21.6)	59 (19.0)
50-74%	11 (13.4)	4 (5.1)	15 (9.4)	8 (10.7)	8 (10.7)	16 (10.7)	19 (12.1)	12 (7.8)	31 (10.0)
75-99%	3 (3.7)	1 (1.3)	4 (2.5)	0	1 (1.3)	1 (0.7)	3 (1.9)	2 (1.3)	5 (1.6)
100%	0	0	0	0	0	0	0	0	0
Baseline HADS total score									
Number	81	78	159	75	75	150	156	153	309
Mean (SD)	15.9 (8.4)	16.2 (7.7)	16.0 (8.0)	14.3 (8.0)	14.5 (8.2)	14.4 (8.1)	15.1 (8.2)	15.4 (7.9)	15.2 (8.1)
Median	16.0	16.0	16.0	15.0	14.0	15.0	15.0	15.0	15.0
Q1 ; Q3	9.0 ; 22.0	11.0 ; 20.0	9.0 ; 21.0	9.0 ; 19.0	8.0 ; 20.0	9.0 ; 20.0	9.0 ; 20.0	9.0 ; 20.0	9.0 ; 20.0
Min ; Max	1 ; 37	1 ; 34	1 ; 37	0 ; 34	0 ; 35	0 ; 35	0 ; 37	0 ; 35	0 ; 37
HADS-A subscale scores ≥8 at baseline									
Number	81	78	159	75	75	150	156	153	309
Yes	46 (56.8)	50 (64.1)	96 (60.4)	45 (60.0)	41 (54.7)	86 (57.3)	91 (58.3)	91 (59.5)	182 (58.9)
No	35 (43.2)	28 (35.9)	63 (39.6)	30 (40.0)	34 (45.3)	64 (42.7)	65 (41.7)	62 (40.5)	127 (41.1)
HADS-D subscale scores ≥8 at baseline									
Number	81	78	159	75	75	150	156	153	309
Yes	31 (38.3)	30 (38.5)	61 (38.4)	28 (37.3)	26 (34.7)	54 (36.0)	59 (37.8)	56 (36.6)	115 (37.2)
No	50 (61.7)	48 (61.5)	98 (61.6)	47 (62.7)	49 (65.3)	96 (64.0)	97 (62.2)	97 (63.4)	194 (62.8)
Baseline DLQI score									
Number	81	78	159	75	75	150	156	153	309
Mean (SD)	18.2 (7.0)	18.2 (6.5)	18.2 (6.7)	15.7 (7.3)	17.8 (7.1)	16.7 (7.2)	17.0 (7.2)	18.0 (6.7)	17.5 (7.0)
Median	19.0	19.0	19.0	15.0	19.0	16.0	17.0	19.0	18.0
Q1 ; Q3	14.0 ; 24.0	14.0 ; 22.0	14.0 ; 23.0	9.0 ; 21.0	12.0 ; 23.0	11.0 ; 22.0	12.0 ; 23.0	13.0 ; 23.0	13.0 ; 23.0
Min ; Max	1 ; 29	2 ; 30	1 ; 30	2 ; 30	2 ; 30	2 ; 30	1 ; 30	2 ; 30	1 ; 30
Baseline EQ-5D visual analog scale score									
Number	81	78	159	75	75	150	156	153	309
Mean (SD)	62.0 (23.0)	59.9 (24.7)	60.9 (23.8)	68.5 (19.7)	66.6 (23.5)	67.6 (21.7)	65.1 (21.7)	63.2 (24.3)	64.2 (23.0)
Median	66.0	70.0	68.0	74.0	73.0	73.5	70.0	70.0	70.0
Q1 ; Q3	50.0 ; 80.0	49.0 ; 80.0	50.0 ; 80.0	53.0 ; 80.0	50.0 ; 88.0	51.0 ; 82.0	50.0 ; 80.0	50.0 ; 80.0	50.0 ; 80.0
Min ; Max	0 ; 100	0 ; 100	0 ; 100	11 ; 100	10 ; 100	10 ; 100	0 ; 100	0 ; 100	0 ; 100
Antidepressant use at baseline									
Number	82	78	160	76	75	151	158	153	311
Yes	8 (9.8)	7 (9.0)	15 (9.4)	9 (11.8)	9 (12.0)	18 (11.9)	17 (10.8)	16 (10.5)	33 (10.6)

	EFC16460			EFC16459			Pooled Data		
	Placebo (N=82)	Dupilumab 300 mg Q2W (N=78)	All (N=160)	Placebo (N=76)	Dupilumab 300 mg Q2W (N=75)	All (N=151)	Placebo (N=158)	Dupilumab 300 mg Q2W (N=153)	All (N=311)
No	74 (90.2)	71 (91.0)	145 (90.6)	67 (88.2)	66 (88.0)	133 (88.1)	141 (89.2)	137 (89.5)	278 (89.4)

ITT: Intent-to-treat; WI-NRS: worst-itch numeric rating scale; IGA PN-S: Investigator's global assessment for prurigo nodularis - stage; IGA PN-A: Investigator's global assessment for prurigo nodularis - activity; DLQI: dermatology life quality index; PGIS: participant global impression of severity; PAS: prurigo activity score ; EQ-5D: Euroqol 5 dimensions; HADS: hospital anxiety and depression scale.

a Derived as (Year of randomization - Year of first diagnosis of PN) + (month of randomization - 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), Skin Pain-NRS (range 0-10), PGIS (range 1-4), DLQI (range 0-30), and HADS total score (range 0-42); A high score indicates good outcome for Sleep-NRS (range 0-10) and EQ-5D visual analog scale score (range 0-100).

Prior medications

99.7% participants had used topical medications for the treatment of PN before study entry (TCS: 98.4%; TCI: 11.3%) while 66.2% had used systemic medications (Antihistamines: 53.1%, non-steroidal immunosuppressants: 20.6%; systemic corticosteroids: 17.4%; antidepressants: 8.4%).

Concomitant medications

Almost all participants (99.3% in the dupilumab group and 99.4% in the placebo group) received concomitant medications during the study. Emollients were used by 94.3% and 90.2% of the participants in the dupilumab and placebo group, respectively. Dermatological preparations of corticosteroids were used by 69.6% and 66.7% of participants in the dupilumab and placebo group, respectively.

Compliance with study intervention

Mean compliance with administration of IMP was ≥98.68% in both intervention groups. Mean compliance with background intervention (moisturizers [emollients]) was 88.49% and 85.02% in the in the dupilumab and placebo group, respectively). In those participants who used stable doses of TCS/TCI, mean compliance with background treatment was 87.70% in the dupilumab group and 84.51% in the placebo group.

Results

A summary of the primary and key selected efficacy endpoints in studies EFC16460 and EFC16459 and the pooled ITT population is given below.

Table 25. Summary of the primary and key selected efficacy endpoints - ITT population from EFC16460 and EFC16459 and Pooled ITT population

Parameter	EFC16460				EFC16459				Pooled Data			
	Placebo[a] (N=82)	Dupilumab 300 mg Q2W[a] (N=78)	Difference (95% CI)[b] for Dupilumab vs. Placebo	P-value[c]	Placebo[a] (N=76)	Dupilumab 300 mg Q2W[a] (N=75)	Difference (95% CI)[b] for Dupilumab vs. Placebo	P-value[c]	Placebo[a] (N=158)	Dupilumab 300 mg Q2W[a] (N=153)	Difference (95% CI)[b]for Dupilumab vs. Placebo	P-value[d]
Proportion of participants with WI-NRS improvement (reduction) by ≥4 points from baseline to Week 24	16 (19.5%)	45 (57.7%)	42.6% (29.06%, 56.08%)	**<.0001**	14 (18.4%)	45 (60.0%)	42.7% (27.76%, 57.72%)	**<.0001**	30 (19.0%)	90 (58.8%)	42.7% (32.60%, 52.71%)	<.0001
Odds ratio			9.0 (3.56, 22.66)				6.5 (2.78, 15.41)				7.6 (4.03, 14.24)	
Proportion of participants with WI-NRS improvement (reduction) by ≥4 points from baseline to Week 12[e]	18 (22.0%)	29 (37.2%)	16.8% (2.34%, 31.16%)	**0.0216**	12 (15.8%)	33 (44.0%)	29.2% (14.49%, 43.81%)	0.0003	30 (19.0%)	62 (40.5%)	22.7% (12.40%, 33.08%)	<.0001
Odds ratio			2.3 (1.08, 5.00)				4.3 (1.86, 9.77)				3.1 (1.77, 5.43)	
Proportion of participants with IGA PN-S 0 or 1 score at Week 24	13 (15.9%)	35 (44.9%)	30.8% (16.37%, 45.22%)	**<.0001**	14 (18.4%)	36 (48.0%)	28.3% (13.41%, 43.16%)	**0.0004**	27 (17.1%)	71 (46.4%)	29.6% (19.22%, 39.94%)	<.0001
Odds ratio			4.4 (2.02, 9.55)				4.0 (1.81, 8.98)				4.2 (2.42, 7.37)	
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	7 (8.5%)	25 (32.1%)	25.5% (13.09%, 37.86%)	**0.0001**	7 (9.2%)	29 (38.7%)	29.6% (16.42%, 42.81%)	**<.0001**	14 (8.9%)	54 (35.3%)	27.5% (18.43%, 36.51%)	<.0001
Odds ratio			6.1 (2.03, 18.11)				6.9 (2.49, 19.05)				6.5 (3.05, 13.67)	
Proportion of participants with IGA PN-S 0 or 1 score at Week 12[e]	10 (12.2%)	20 (25.6%)	14.8% (2.64%, 26.99%)	**0.0194**	9 (11.8%)	24 (32.0%)	20.9% (7.80%, 33.99%)	0.0027	19 (12.0%)	44 (28.8%)	17.8% (8.81%, 26.69%)	0.0002
Odds ratio			2.9 (1.13, 7.52)				4.0 (1.54, 10.19)				3.4 (1.74, 6.63)	

Parameter	EFC16460				EFC16459				Pooled Data			
	Placebo[a] (N=82)	Dupilumab 300 mg Q2W[a] (N=78)	Difference (95% CI)[b] for Dupilumab vs. Placebo	P-value[c]	Placebo[a] (N=76)	Dupilumab 300 mg Q2W[a] (N=75)	Difference (95% CI)[b] for Dupilumab vs. Placebo	P-value[c]	Placebo[a] (N=158)	Dupilumab 300 mg Q2W[a] (N=153)	Difference (95% CI)[b]for Dupilumab vs. Placebo	P-value[d]
Percent change from baseline in WI-NRS at Week 24	-36.18 (6.21)	-59.34 (6.39)	-23.16 (-33.81, -12.51)	**<.0001**	-22.22 (5.74)	-48.89 (5.61)	-26.67 (-38.44, -14.90)	**<.0001**	-27.97 (4.23)	-53.44 (4.27)	-25.47 (-33.45, -17.48)	<.0001
Change from baseline in HRQoL measured by DLQI at Week 24	-6.77 (1.18)	-13.16 (1.21)	-6.39 (-8.42, -4.36)	**<.0001**	-5.77 (1.05)	-11.97 (1.02)	-6.19 (-8.34, -4.05)	**<.0001**	-6.27 (0.77)	-12.56 (0.77)	-6.29 (-7.75, -4.83)	<.0001
Change from baseline in Skin Pain-NRS at Week 24	-2.74 (0.51)	-4.35 (0.53)	-1.61 (-2.49, -0.73)	**0.0003**	-2.16 (0.44)	-4.33 (0.43)	-2.17 (-3.07, -1.28)	**<.0001**	-2.41 (0.33)	-4.28 (0.33)	-1.87 (-2.50, -1.25)	<.0001
Change from baseline in Sleep-NRS at Week 24[e]	0.76 (0.45)	1.30 (0.46)	0.54 (-0.22, 1.30)	0.1658	1.27 (0.34)	2.71 (0.33)	1.44 (0.75, 2.13)	<.0001	1.11 (0.27)	2.10 (0.28)	0.99 (0.47, 1.50)	0.0002
Change from baseline in HADS total score at Week 24[f]	-2.59 (1.03)	-5.55 (1.06)	-2.96 (-4.73, -1.19)	0.0010	-2.02 (0.94)	-4.62 (0.93)	-2.60 (-4.52, -0.67)	**0.0082**	-2.39 (0.70)	-5.04 (0.70)	-2.65 (-3.96, -1.34)	<.0001

WI-NRS: worst-itch numeric rating scale; IGA PN-S: Investigator's global assessment for prurigo nodularis - stage; HRQoL: health-related quality-of-life; DLQI: dermatology life quality index; HADS: hospital anxiety and depression scale; LS: least squares; CMH: Cochran-Mantel Haenszel; CI: confidence interval.

a Values presented are LS mean change from baseline with standard error for continuous variables and number and percent of responders for binary variables.

b Difference is LS mean difference for continuous variables and CMH response rate difference and odds ratio for binary variables.

c All values in bold font are statistically significant according to the hierarchical testing procedure.

d Nominal p-values. No hierarchical testing procedure for pooled data.

e Nominal p-value for study EFC16459 as not part of the hierarchical testing procedure.

f Nominal p value in Study EFC16460 as the statistical hierarchical testing procedure broke before this efficacy endpoint.

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), Skin Pain-NRS (range 0-10), DLQI (range 0-30), and HADS total score (range 0-42); A high score indicates good outcome for Sleep-NRS (range 0-10).

PGM=PRODOPS/SAR231893/OVERALL/ISE_PN_2021/REPORT/PGM/eff_sum_endpo_i_t.sas OUT=REPORT/OUTPUT/eff_sum_endpo_i_t_i.rtf (01MAR2022 2:36)

Itch-response (WI-NRS)

Proportion of participants with improvement (reduction) in WI-NRS by ≥4 points at week 12 and at week 24

The proportion of participants with an improvement (reduction) in weekly average WI-NRS by ≥4 points from baseline to Week 12 was higher in the dupilumab group as compared to the placebo group (40.5% versus 19.0%; p<0.0001).

The proportion of participants with an improvement (reduction) in weekly average WI NRS by ≥4 points from baseline to Week 24 was higher in the dupilumab group as compared to the placebo group (58.8% versus 19.0%; p<0.0001).

Table 26. Proportion of participants with an improvement (reduction) in WI-NRS by ≥4 points from baseline at Week 12 and Week 24 - ITT population from EFC16460 and EFC16459 and Pooled ITT population

	EFC16460		EFC16459		Pooled Data	
	Placebo (N=82) n (%)	Dupilumab 300 mg Q2W (N=78) n (%)	Placebo (N=76) n (%)	Dupilumab 300 mg Q2W (N=75) n (%)	Placebo (N=158) n (%)	Dupilumab 300 mg Q2W (N=153) n (%)
Weekly average WI-NRS improvement ≥4 points at Week 12 from baseline						
Responder	18 (22.0)	29 (37.2)	12 (15.8)	33 (44.0)	30 (19.0)	62 (40.5)
Non-responder	64 (78.0)	49 (62.8)	64 (84.2)	42 (56.0)	128 (81.0)	91 (59.5)
Imputed non-responder	19 (23.2)	7 (9.0)	20 (26.3)	4 (5.3)	39 (24.7)	11 (7.2)
OR, 95% CI vs. placebo[a]		2.3 (1.08, 5.00)		4.3 (1.86, 9.77)		3.1 (1.77, 5.43)
P-value vs. placebo[b]		0.0216		0.0003		<.0001
RRD (%), 95% CI vs. placebo[a]		16.8 (2.34, 31.16)		29.2 (14.49, 43.81)		22.7 (12.40, 33.08)

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

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

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

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

PGM=PRODOPS/SAR231893/OVERALL/ISE_PN_2021/REPORT/PGM/eff_resp_i_t.sas OUT=REPORT/OUTPUT/eff_resp_winrs_w12_i_t_i.rtf (28FEB2022 8:13)

	EFC16460		EFC16459		Pooled Data	
	Placebo (N=82) n (%)	Dupilumab 300 mg Q2W (N=78) n (%)	Placebo (N=76) n (%)	Dupilumab 300 mg Q2W (N=75) n (%)	Placebo (N=158) n (%)	Dupilumab 300 mg Q2W (N=153) n (%)
Weekly average WI-NRS improvement ≥4 points at Week 24 from baseline						
Responder	16 (19.5)	45 (57.7)	14 (18.4)	45 (60.0)	30 (19.0)	90 (58.8)
Non-responder	66 (80.5)	33 (42.3)	62 (81.6)	30 (40.0)	128 (81.0)	63 (41.2)
Imputed non-responder	33 (40.2)	12 (15.4)	32 (42.1)	8 (10.7)	65 (41.1)	20 (13.1)
OR, 95% CI vs. placebo[a]		9.0 (3.56, 22.66)		6.5 (2.78, 15.41)		7.6 (4.03, 14.24)
P-value vs. placebo[b]		<.0001		<.0001		<.0001
RRD (%), 95% CI vs. placebo[a]		42.6 (29.06, 56.08)		42.7 (27.76, 57.72)		42.7 (32.60, 52.71)

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

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

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

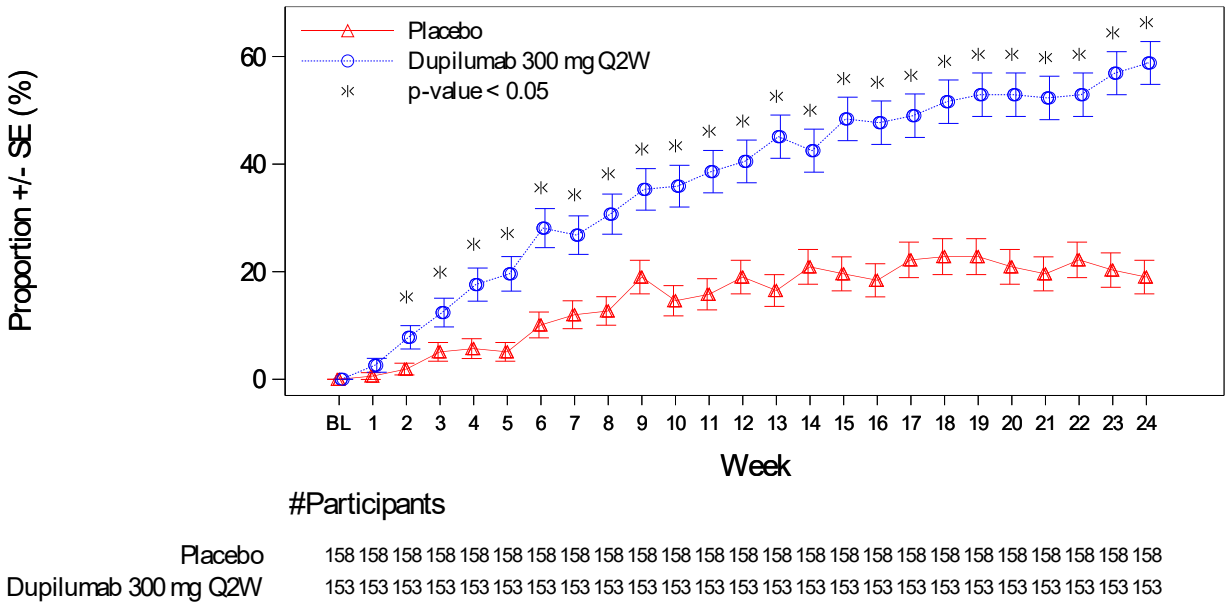
Note: Participants who received the prohibited medications/procedures and/or rescue medications that impacted efficacy before Week 24 were considered as non-responders, and participants with missing data at Week 24 were considered as non-responders.

PGM=PRODOPS/SAR231893/OVERALL/ISE_PN_2021/REPORT/PGM/eff_resp_i_t.sas OUT=REPORT/OUTPUT/eff_resp_winrs_w24_i_t_i.rtf (28FEB2022 8:13)

Proportion of participants with improvement (reduction) in WI-NRS by ≥4 points over time up to Week 24

The proportion of participants achieving an improvement (reduction) in WI-NRS of ≥4 points from baseline was higher in the dupilumab group compared to the placebo group, starting at Week 2. The treatment effect progressively increased through the rest of the 24-week intervention period and remained nominally significant at all subsequent weekly measurements, with the greatest treatment difference observed at Week 24.

Figure 17. Proportion of participants with an improvement (reduction) in WI-NRS by ≥4 points from baseline over time up to Week 24 - Pooled ITT population



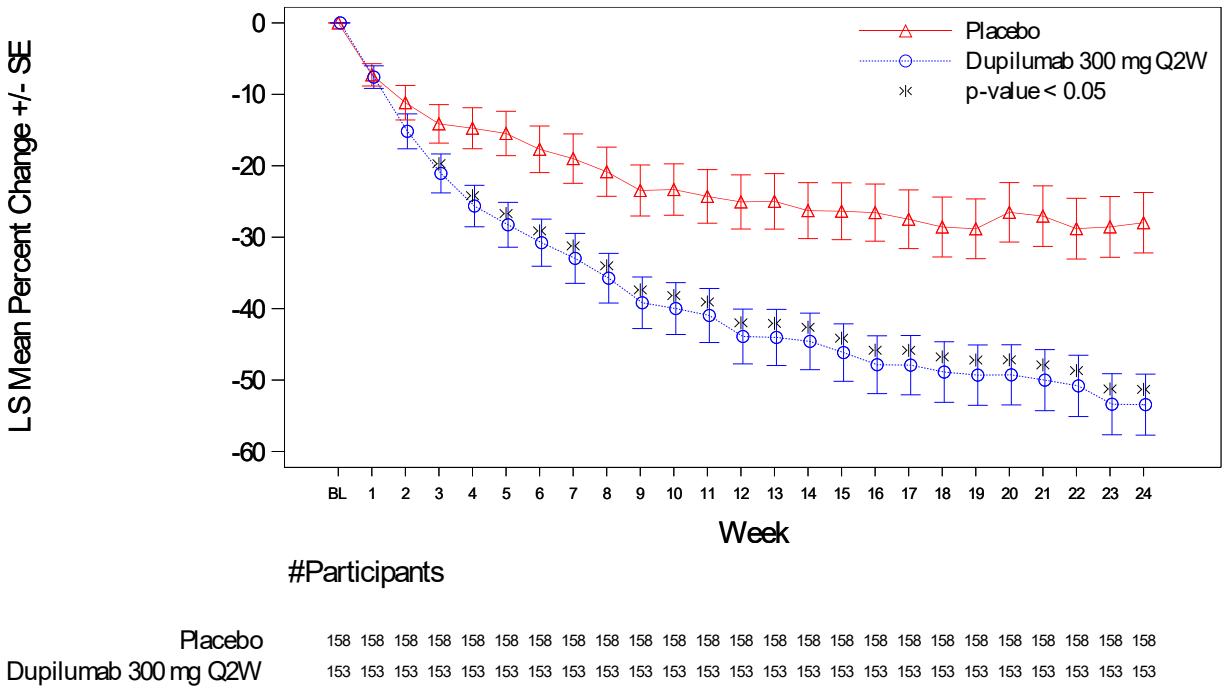
Time to onset analysis

In the pooled ITT population, dupilumab treatment reduced the time to first weekly average WI-NRS improvement (reduction) by ≥4 points from baseline as compared to placebo during the 24 week intervention period (HR [95% CI]: 2.341 [1.681, 3.261], nominal p<0.0001). The KM curves for first occurrence of weekly average WI-NRS improvement by ≥4 points from baseline for the dupilumab and placebo groups started to diverge as early as Week 4. The treatment effect progressively increased through the rest of the 24-week intervention period and remained nominally significant at all subsequent weekly measurements with the greatest treatment difference observed at Week 24.

Change from baseline in WI-NRS up to Week 24

In the pooled ITT population, the LS mean percent change from baseline to Week 12 and Week 24 in the weekly average WI NRS score was greater in the dupilumab group as compared to the placebo group (-43.90% versus -25.06% at Week 12; 53.44% versus 27.97% at Week 24). Mean values for dupilumab and placebo were 8.59 and 8.40 at baseline, 5.14 and 6.61 at Week 12 and 4.37 and 6.47 at Week 24.

Figure 18. LS mean percent change from baseline in WI-NRS over time up to Week 24 - Pooled ITT population



PN lesions (PN-S)

Proportion of participants with IGA PN-S 0 or 1 score at Week 24

In the pooled ITT population, the proportion of participants with an IGA PN S 0 ("clear") or 1 ("almost clear") score at Week 24 was higher in the dupilumab group compared to the placebo group (46.4% versus 17.1%; p<0.0001).

Table 27. Proportion of participants with IGA PN-S 0 or 1 score at Week 24 - ITT population from EFC16460 and EFC16459 and Pooled ITT population

	EFC16460		EFC16459		Pooled Data	
	Placebo (N=82) n (%)	Dupilumab 300 mg Q2W (N=78) n (%)	Placebo (N=76) n (%)	Dupilumab 300 mg Q2W (N=75) n (%)	Placebo (N=158) n (%)	Dupilumab 300 mg Q2W (N=153) n (%)
IGA PN-S 0 or 1 score						
Responder	13 (15.9)	35 (44.9)	14 (18.4)	36 (48.0)	27 (17.1)	71 (46.4)
Non-responder	69 (84.1)	43 (55.1)	62 (81.6)	39 (52.0)	131 (82.9)	82 (53.6)
Imputed non-responder	33 (40.2)	10 (12.8)	29 (38.2)	8 (10.7)	62 (39.2)	18 (11.8)
OR, 95% CI vs. placebo[a]		4.4 (2.02, 9.55)		4.0 (1.81, 8.98)		4.2 (2.42, 7.37)
P-value vs. placebo[b]		<.0001		0.0004		<.0001
RRD (%), 95% CI vs. placebo[a]		30.8 (16.37, 45.22)		28.3 (13.41, 43.16)		29.6 (19.22, 39.94)

CMH: Cochran-Mantel Haenszel; IGA PN-S: Investigator's Global Assessment 0 or 1 score for PN-Stage; CI: confidence interval. TCS: topical corticosteroids; TCI: topical calcineurin inhibitors.

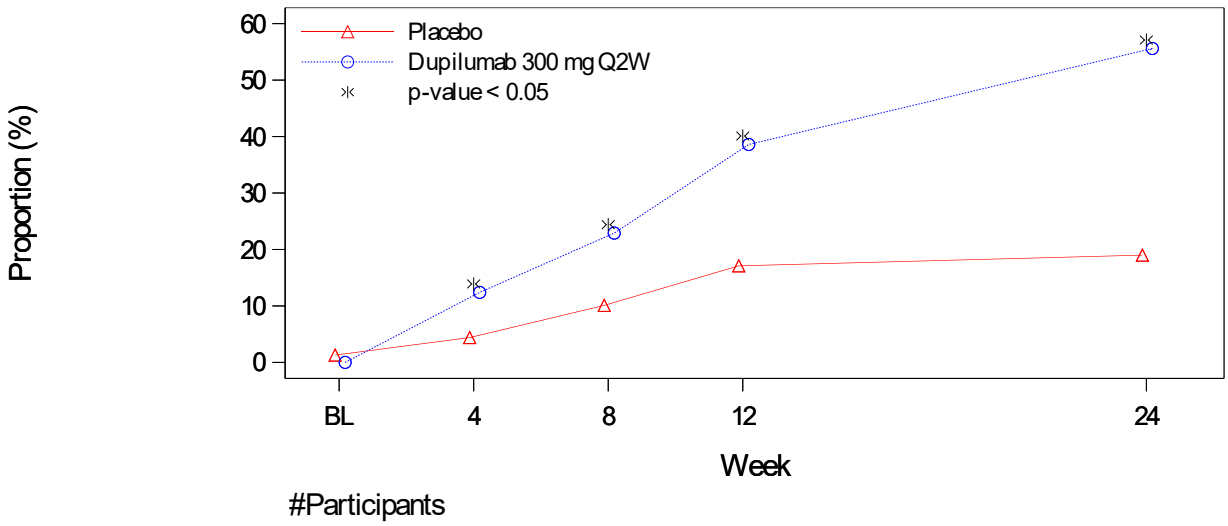
a OR: odds ratio; RRD: response rate difference; derived from the Mantel-Haenszel estimator.

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

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

PGM=PRODOPS/SAR231893/OVERALL/ISE_PN_2021/REPORT/PGM/eff_resp_i_t.sas OUT=REPORT/OUTPUT/eff_resp_igapns_w24_i_t_i.rtf (28FEB2022 8:13)

Figure 19. Proportion of participants with IGA PN-S 0 or 1 score by visit up to Week 24 - Pooled ITT population



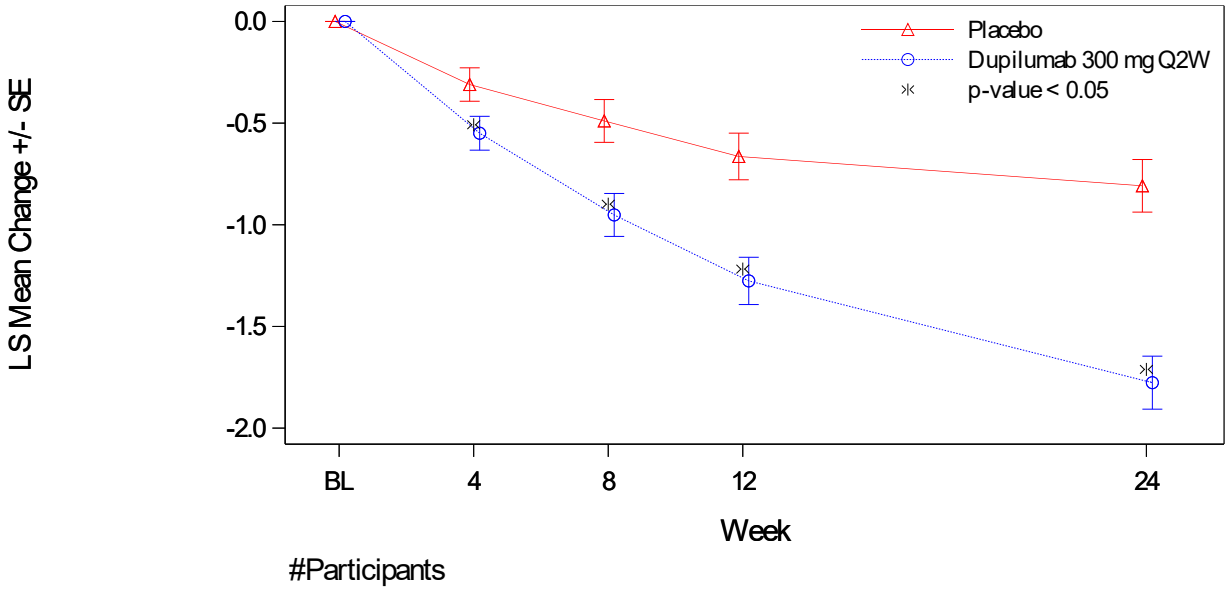
#Participants

Placebo	158	158	158	158	158
Dupilumab 300 mg Q2W	153	153	153	153	153

Change from baseline in IGA PN-S over time up to Week 24

The mean IGA PN S score decreased over time in the dupilumab group, with a nominally significant difference with placebo observed as early as Week 4 (LS mean difference versus placebo: -0.24 [95% CI: -0.39, -0.08], nominal p=0.0024). The treatment effect progressively increased through the rest of the 24-week intervention period and remained nominally significant at all subsequent measurements, with the greatest treatment difference observed at Week 24.

Figure 20. LS mean change from baseline in IGA PN-S by visit up to Week 24 - Pooled ITT population



#Participants

Placebo	156	156	156	156	156
Dupilumab 300 mg Q2W	153	153	153	153	153

Proportion of participants with IGA PN-S 0 or 1 <u>and</u> improvement (reduction) in WI-NRS by ≥4 points at week 24

The proportion of participants with both an improvement (reduction) in WI-NRS by ≥4 points from baseline to Week 24 and an IGA PN S score of 0 or 1 at Week 24 (multicomponent endpoint) was defined as an additional key secondary endpoint for the US and US reference countries' statistical hierarchy and was not part of the hierarchical testing procedure for the EU application. In the pooled ITT population, the proportion of participants with both an improvement in WI NRS by ≥4 points from baseline to Week 24 and achieving an IGA PN S score of 0 or 1 at Week 24 was greater in the dupilumab group as compared to the placebo group (35.3% versus 8.9%; nominal p<0.0001).

Change from baseline over time in exact number of lesions

Dupilumab treatment showed a nominally significant reduction in the exact number of lesions in the representative body area as measured by item 4 of the modified PAS, starting as early as Week 4. The treatment effect progressively increased through the rest of the 24-week intervention period with the greatest treatment difference observed at Week 24.

A greater reduction in the exact number of skin lesions in the representative body area in the dupilumab group compared to the placebo group was demonstrated starting as early as the first post baseline measurement at (Week 4) ([95% CI]: -4.06 [-6.52, -1.61], nominal p=0.0012). Reduction of lesions progressively increased through the rest of the 24 week intervention period. The greatest treatment difference was observed at Week 24 (LS mean difference in change from baseline versus placebo [95% CI]: -11.40 [15.05, 7.75], nominal p<0.0001). In the pooled ITT population, the proportion of participants with an improvement (reduction) in the exact number of lesions by ≥15 (defined as clinical meaningful threshold for item 4 of the modified PAS) from baseline to Week 24 was higher in the dupilumab group as compared to the placebo group (44.4% versus 20.3%, nominal p<0.0001).

Figure 21. LS mean change from baseline in exact number of lesions in representative area by visit up to Week 24 - Pooled ITT population

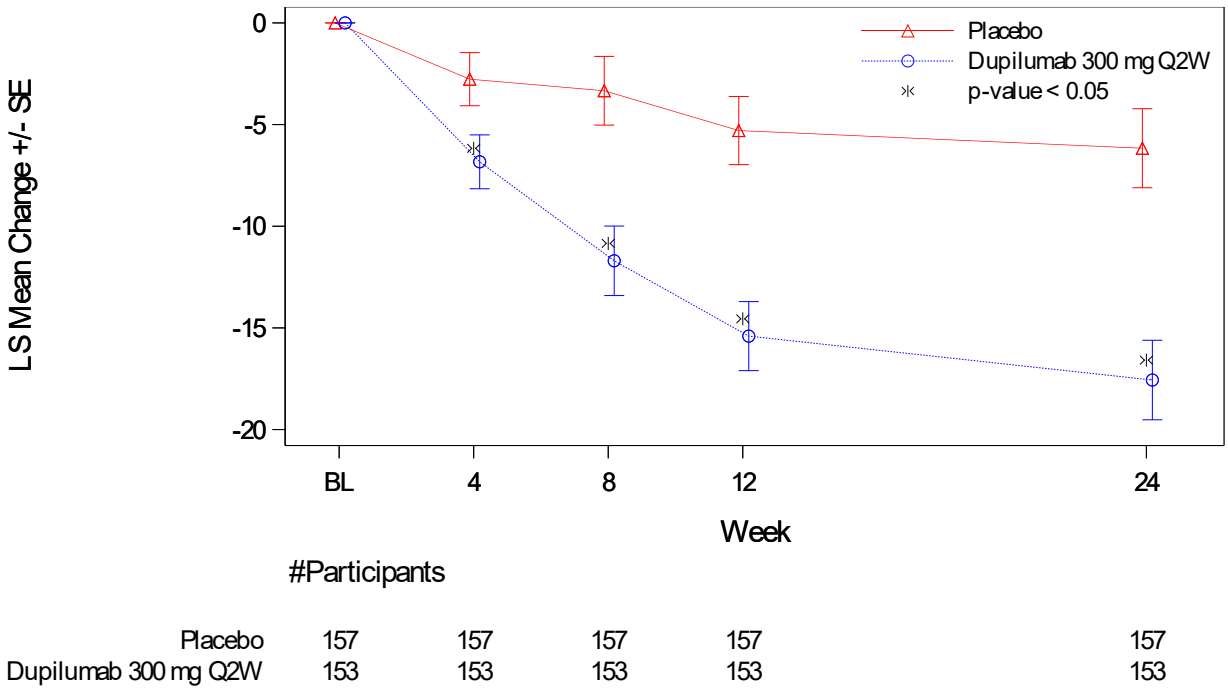


Table 28. Proportion of participants with a reduction in the exact number of lesions by ≥15 in representative area from baseline to Week 24 - ITT population from EFC16460 and EFC16459 and Pooled ITT population

	EFC16460		EFC16459		Pooled Data	
	Placebo (N=82) n (%)	Dupilumab 300 mg Q2W (N=78) n (%)	Placebo (N=76) n (%)	Dupilumab 300 mg Q2W (N=75) n (%)	Placebo (N=158) n (%)	Dupilumab 300 mg Q2W (N=153) n (%)
Exact number of lesions reduction by ≥15 in representative area from baseline to Week 24						
Responder	17 (20.7)	36 (46.2)	15 (19.7)	32 (42.7)	32 (20.3)	68 (44.4)
Non-responder	65 (79.3)	42 (53.8)	61 (80.3)	43 (57.3)	126 (79.7)	85 (55.6)
Imputed non-responder	31 (37.8)	10 (12.8)	29 (38.2)	8 (10.7)	60 (38.0)	18 (11.8)
OR, 95% CI vs. placebo		5.3 (2.29, 12.34)		3.2 (1.38, 7.50)		4.2 (2.29, 7.56)
P-value vs. placebo		<.0001		0.0052		<.0001
RRD (%), 95% CI vs. placebo		31.1 (17.48, 44.74)		20.7 (6.56, 34.75)		26.1 (16.22, 35.91)

CMH: Cochran-Mantel Haenszel; CI: confidence interval. TCS: topical corticosteroids; TCI: topical calcineurin inhibitors.

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

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

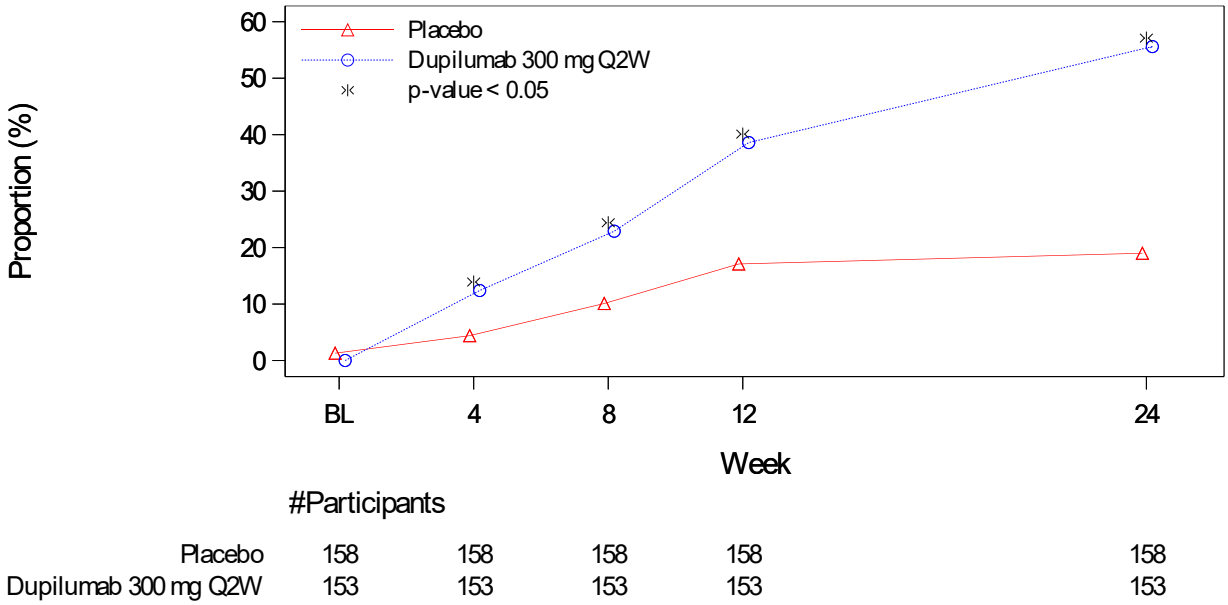
Note: The threshold value is based on minimum important difference (MID). Participants who received the prohibited medications/procedures and/or rescue medications that impacted efficacy before Week 24 were considered as non-responders, and participants with missing data at Week 24 were considered as non-responders.

Prurigo activity (PN-A)

Treatment effect on measures of prurigo activity

In the pooled ITT population, the proportion of participants with an IGA PN-A 0 ("clear") or 1 ("almost clear") score showed a clear separation between the dupilumab and placebo groups starting as early as Week 4 (12.4% versus 4.4%, nominal p=0.0293). The treatment effect progressively increased through the rest of the 24-week intervention period and remained nominally significant at all subsequent measurements, with the greatest treatment difference observed at Week 24 (55.6% versus 19.0%, nominal p<0.0001). Upon treatment, the proportion of participants who achieved ≥75% healed skin lesions was higher in the dupilumab group as compared to the placebo group, starting as early as Week 4 (14.4% versus 6.3%, nominal p=0.0294). The treatment effect progressively increased through the rest of the 24-week intervention period and remained nominally significant at Week 12 and Week 24, with the greatest treatment difference observed at Week 24 (56.2% versus 18.4%, nominal p<0.0001).

Figure 22. Proportion of participants with IGA PN-A 0 or 1 score by visit up to Week 24 - Pooled ITT population

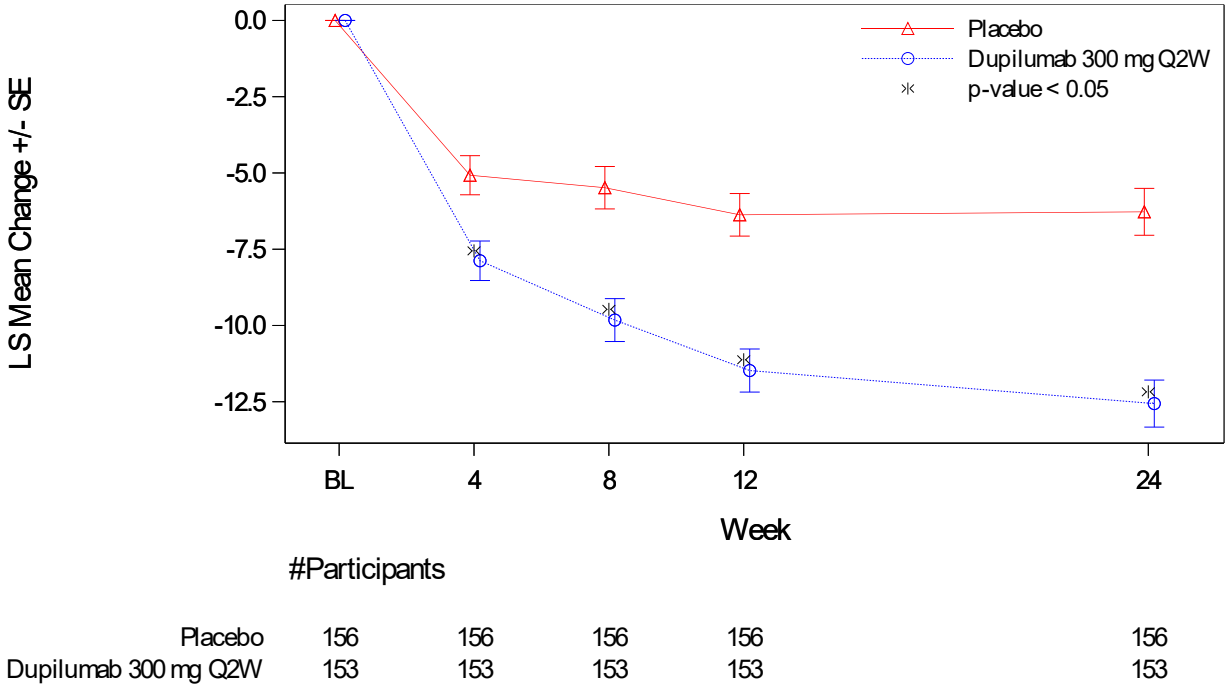


Quality of life / Skin Pain

Change from baseline over time up to Week 24 in DLQI

Dupilumab treatment improved HRQoL as measured by a decrease in Dermatology Life Quality Index (DLQI) from baseline to Week 12 and Week 24, compared to placebo. At Week 12, the LS mean difference in change from baseline versus placebo was 5.11 ([95% CI: 6.43, -3.78], nominal p<0.0001). At Week 24, the LS mean difference in change from baseline versus placebo was 6.29 ([95% CI: 7.75, -4.83], nominal p<0.0001). In the pooled ITT population, the proportion of participants with an improvement (reduction) in DLQI by ≥9 points from baseline to Week 24 was higher in the dupilumab group as compared to the placebo group (64.7% versus 22.8%, nominal p<0.0001).

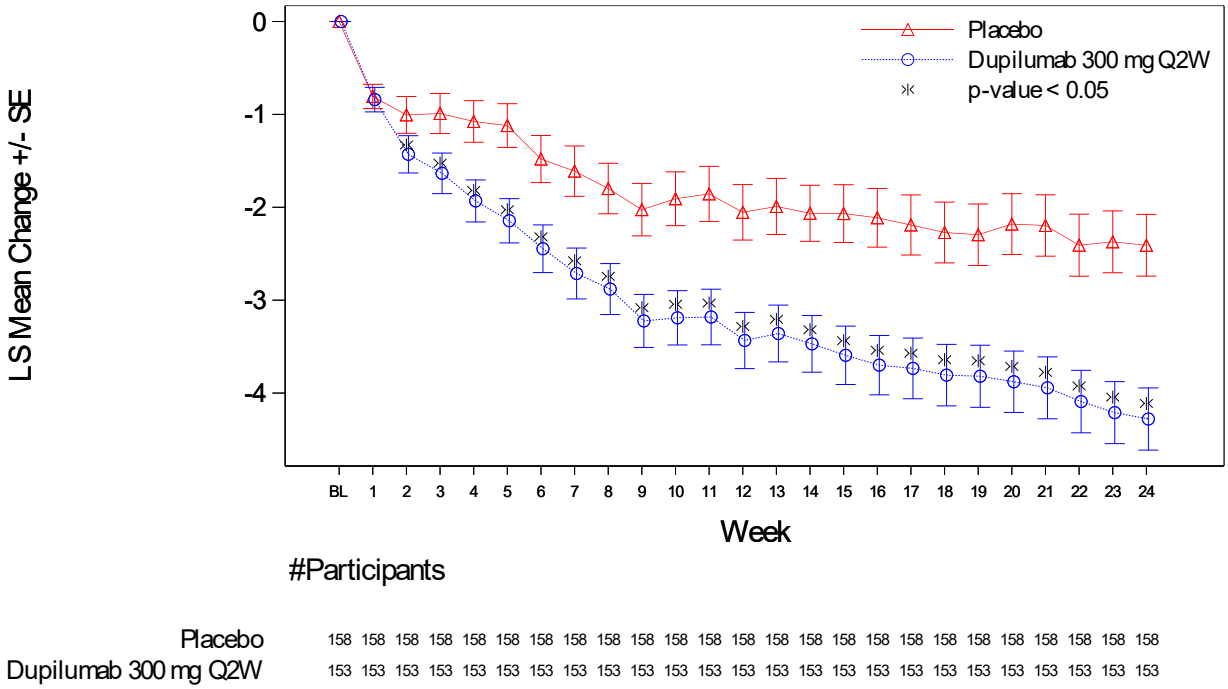
Figure 23. LS mean change from baseline in HRQoL as measured by DLQI by visit up to Week 24 - Pooled ITT population



Change in Skin Pain-NRS over time up to Week 24

In the pooled ITT population, dupilumab treatment demonstrated a decrease in the weekly average Skin Pain-NRS score over time as compared to the placebo group. The improvement in weekly average Skin Pain-NRS score observed in the dupilumab group compared to the placebo group was observed as early as Week 2 (LS mean difference in change from baseline versus placebo: 0.42 [95% CI: 0.80, 0.05], nominal p=0.0259). The treatment effect progressively increased through the rest of the 24-week intervention period and remained nominally significant at all subsequent weekly measurements with the greatest treatment difference observed at Week 24 (LS mean difference in change from baseline versus placebo: -1.87 [95% CI: 2.50, 1.25], nominal p<0.0001).

Figure 24. LS mean change from baseline in Skin Pain-NRS over time up to Week 24 - Pooled ITT population



Overall HRQoL endpoints (EQ-5D VAS and EQ-5D-5L Single Index score)

In the pooled ITT population, analysis of the EQ-5D-VAS, which presents the participant's self rated health status on a vertical scale from 0 ("worst imaginable health state") to 100 ("best imaginable health state"), showed a nominally significant improvement in the dupilumab group as compared to the placebo group at Week 12 (LS mean difference in change from baseline versus placebo at Week 12: 5.24 [95% CI: 1.84, 8.65], nominal p=0.0025) and at Week 24 (LS mean difference in change from baseline versus placebo at Week 24: 7.17 [95% CI: 3.53, 10.80], nominal p=0.0001).

Change from baseline to Week 24 in Sleep-NRS

A nominally significant increase (improvement) in weekly average Sleep-NRS score from baseline to Week 24 was observed in the dupilumab group compared to the placebo group (LS mean difference in change from baseline versus placebo: 0.99 ([95% CI: 0.47, 1.50], nominal p=0.0002). The difference did not reach the clinically meaningful threshold between groups of 1.0.

Change from baseline in HADS total score to Week 24

Dupilumab treatment demonstrated a nominally significant improvement (decrease) in total HADS score from baseline to Week 24 as compared to placebo, with an LS mean difference in change from baseline versus placebo of -2.65 ([95% CI: 3.96, 1.34], nominal p<0.0001). Both the anxiety (HADS-A) and depression (HADS D) subscores demonstrated a nominally significant improvement in the dupilumab group as compared to the placebo group. In the pooled ITT population, the proportion of participants with HADS-A subscale scores ≥8 at baseline who achieved HADS-A <8 was greater in the dupilumab group compared to the placebo group beginning at Week 12, with a larger treatment difference at Week 24 (51.6% versus 23.1%, nominal p=0.0001). The proportion of participants with HADS-D subscale scores ≥8 at baseline who achieved HADS D <8 was greater in the dupilumab group compared to the placebo group only at Week 24 (53.6% versus 25.4%, nominal p=0.0014).

Antidrug Antibodies

The pooled ADA population consisted of all participants in the safety pooled population who had at least 1 non-missing ADA result after the first dose of the study intervention.

The association between the treatment-emergent ADA response and the clinical response was investigated in participants using the measures of improvement (reduction) in WI NRS by ≥4 points from baseline to Week 12 and Week 24, the percentage of participants with IGA PN S 0 ("clear") or 1 ("almost clear") score at Week 24, and the percentage of participants with both an improvement (reduction) in WI NRS by ≥4 points from baseline to Week 24 and IGA PN S 0 or 1 score at Week 24.

Overall, in the dupilumab group:

- 4 of the 11 (36.4%) ADA-positive participants and 57 (43.2%) ADA-negative participants achieved an improvement (reduction) in weekly average WI-NRS by ≥4 points from baseline to Week 12.
- 6 of the 11 (54.5%) ADA-positive participants and 81 (61.4%) ADA-negative participants achieved an improvement (reduction) in weekly average WI-NRS by ≥4 points from baseline to Week 24.
- 4 of the 11 (36.4%) ADA-positive participants and 65 (49.2%) ADA-negative participants achieved an IGA PN-S score of 0 or 1 at Week 24.
- 3 of the 11 (27.3%) ADA-positive participants and 49 (37.1%) ADA-negative participants achieved 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.

Overall, in the dupilumab group:

- 1 of the 4 participants with a Nab positive response demonstrated an improvement in WI NRS by ≥4 points from baseline to Week 12.
- 3 of the 4 participants with a Nab positive response demonstrated an improvement in WI NRS by ≥4 points from baseline to Week 24.
- 1 of the 4 participants with a Nab positive response demonstrated an improvement in the proportion of participants with an IGA PN S 0 or 1 score at Week 24.
- 1 of the 4 participants with a Nab positive response demonstrated 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.

Subgroup analyses

In the pooled ITT population, the consistency of treatment effects in the primary, key secondary, and other selected efficacy endpoints (ie, percent change from baseline to Week 24 in WI-NRS and proportion of participants with IGA PN-S 0 or 1 score at Week 24) were assessed across various subgroups, including demographics and baseline characteristics, PN disease characteristics at baseline, atopic comorbidity history, and concomitant or background medications.

Subgroup analyses - Participants with an improvement (reduction) in WI-NRS by ≥4 points from baseline to Week 24

Results from subgroup analyses for the treatment effect of dupilumab on the proportion of participants with an improvement (reduction) in weekly average WI-NRS by ≥4 points from baseline to Week 24 are shown in the Figure below.

All 3 subgroups based on BMI showed a dupilumab treatment benefit; however, the magnitude of the treatment effect was greater in the subgroup of participants with baseline BMI ≥25 to <30 kg/m2 (75.5% in the dupilumab group versus 13.7% in the placebo group) as compared to the subgroup of

participants with baseline BMI <25 kg/m2 (50.0% versus 24.3%), or the subgroup of participants with baseline BMI ≥30 kg/m2 (50.0% versus 17.6%).

The odds ratio or 95% CI could not be calculated (ie, NE) in some specific subgroup categories:

Age: A higher responder rate was observed in the dupilumab group as compared to the placebo group in the subgroup of participants aged ≥65 to >75 years (19/30 [63.3%] versus 3/17 [17.6%]) and in the subgroup of participants aged ≥75 years (3/8 [37.5%] versus 1/7 [14.3%]).

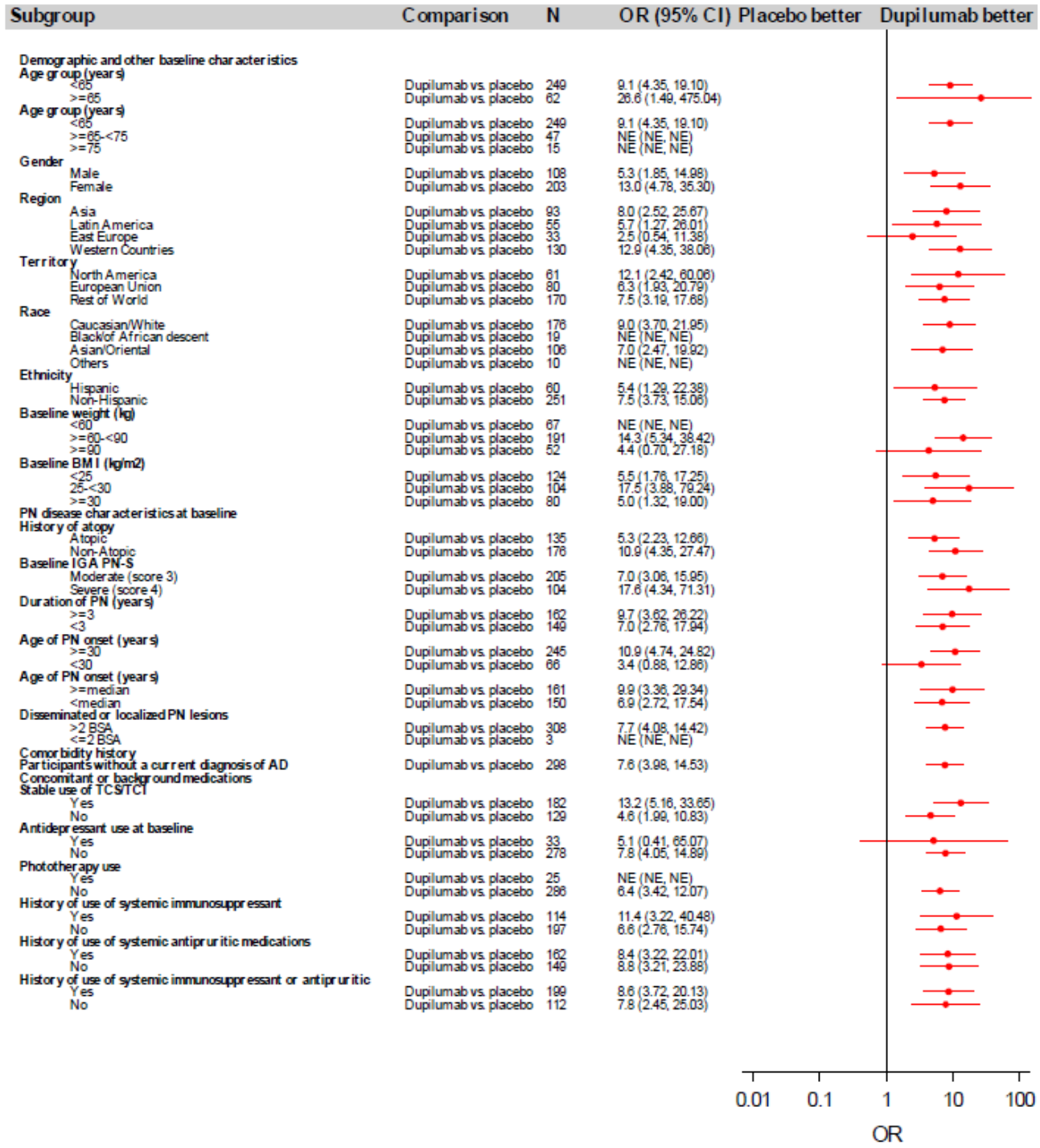
Race: A higher responder rate was observed in the dupilumab group as compared to the placebo group in the subgroup category of participants of Black/African Descent (5/11 [45.5%] versus 1/8 [12.5%]) and in the subgroup category "Others" (2/5 [40.0%] versus 1/5 [20.0%]), with a similar trend to that observed in Asian (32/54 [59.3%] versus 8/52 [15.4%]) and Caucasian (51/83 [61.4%] versus 20/93 [21.5%]) participants.

Body weight: A higher responder rate was observed in the dupilumab group as compared to the placebo group in the subgroup of participants with baseline body weight <60 kg (15/33 [45.5%] versus 7/34 [20.6%]), which was similar to the responder rates observed in the higher body weight groups ≥60 to <90 kg (63/93 [67.7%] versus 18/98 [18.4%]), and ≥90 kg (12/27 [44.4%] versus 5/25 [20%]).

Disseminated or localized PN lesions: No meaningful conclusions could be drawn in the subgroup of participants with disseminated or localized PN lesions ≤2 BSA due to the small number of participants in this category (3 participants).

Phototherapy use: In those participants who had a prior history of phototherapy use, 75% (9/12) in the dupilumab group were responders compared to 7.7% (1/13) in the placebo group. In those participants who did not have a prior history of phototherapy use, 57.4% (81/141) in the dupilumab group were responders compared to 20.0% (29/145) in the placebo group. The responder rates suggest that there was a similar trend of dupilumab benefit.

Figure 25. Proportion of participants with an improvement (reduction) in WI-NRS by ≥4 points from baseline to Week 24 by subgroups - Pooled ITT population

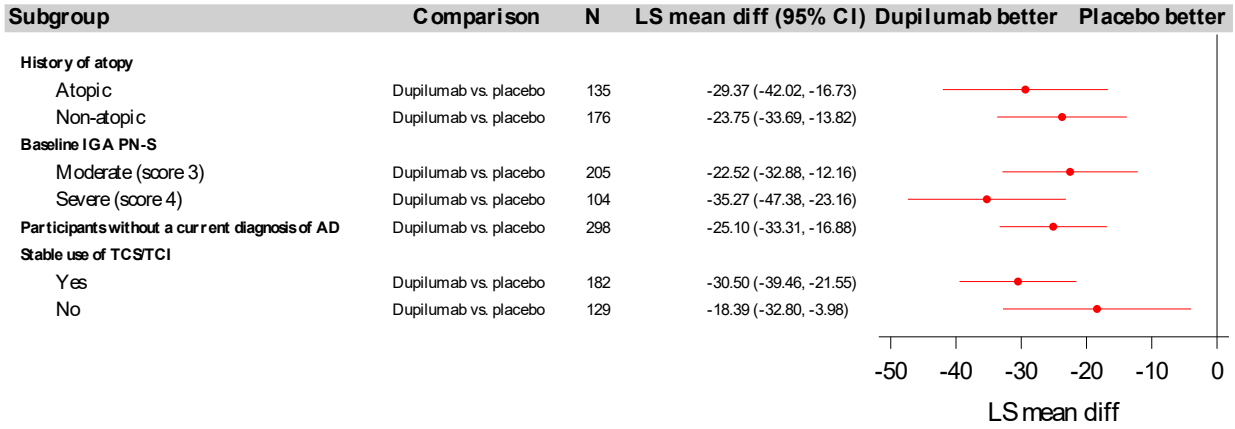


Note: <=2 BSA would indicate a participant with only 2 symmetric body areas affected, such as both arms or both legs.

Subgroup analyses - Percent change from baseline to Week 24 in WI-NRS

Results from subgroup analyses for the treatment effect of dupilumab on the LS mean percent change in WI-NRS from baseline to Week 24 are shown below.

Figure 26. LS mean percent change from baseline to Week 24 in WI-NRS by subgroups - Pooled ITT population



Subgroup analyses - Proportion of participants with IGA PN S 0 or 1 score at Week 24

Subgroup analyses for the treatment effect of dupilumab on the proportion of participants with an IGA PN S 0 ("clear") or 1 ("almost clear") score at Week 24 are shown in the figure below.

A significant quantitative treatment-by-subgroup interaction was detected with regard to stable use of TCS/TCI (nominal p=0.0287). While the magnitude of the treatment effect was greater in the subgroup of participants with stable use of TCS/TCI at baseline (dupilumab: 48.4%; placebo: 11.0%) as compared to the subgroup of participants with no use of TCS/TCI (dupilumab: 43.5%; placebo: 25.4%), the treatment difference was driven by a lower placebo response, while the dupilumab responder rate was similar. Given a similar trend of dupilumab benefit that was statistically significant between both subgroup categories, this interaction is unlikely to be clinically meaningful.

A trend toward a lower magnitude of dupilumab treatment effect was observed in the subgroup of participants who were taking stable doses of antidepressants at baseline based on an OR of 0.9. However, a numerically higher responder rate in the dupilumab group compared to the placebo group was observed in participants who were taking stable doses of antidepressants (6/16 [37.5%] versus 4/17 [23.5%]), which was a similar trend to that shown in the dupilumab responder rate in those participants who were not taking antidepressants (65/137 [47.4%] versus 23/141 [16.3%]).

While a trend toward a higher magnitude of dupilumab treatment effect was observed in male participants as compared to female participants, both subgroups showed a higher responder rate in the dupilumab group as compared to the placebo group (26/49 [53.1%] versus 8/59 [13.6%] in males, and 45/104 [43.3%] versus 19/99 [19.2%] in females) that was statistically significant and clinically meaningful in both genders.

The odds ratio or 95% CI could not be calculated (ie, NE) in some specific subgroup categories:

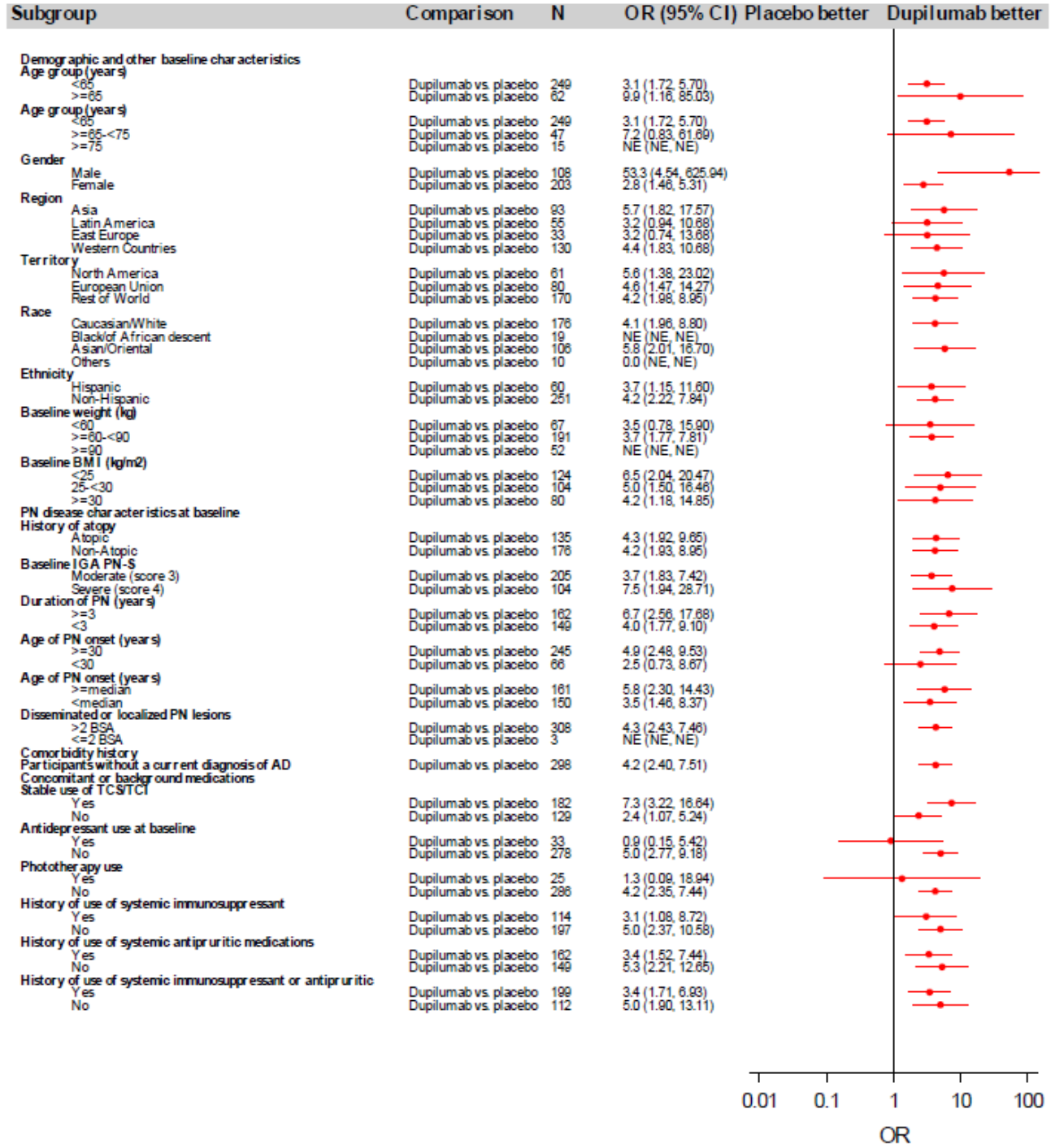
Age: A higher responder rate was observed in the dupilumab group as compared to the placebo group in the subgroup of participants aged ≥75 years (4/8 [50.0%] versus 0/7 [0%]) which is a similar trend of dupilumab treatment effect to that observed in other age subcategories.

Race: A higher responder rate was observed in the dupilumab group as compared to the placebo group in the subgroup category of participants of Black/African descent (4/11 [36.4%] versus 1/8 [12.5%]) and in the subgroup category "Others" (2/5 [40.0%] versus 1/5 [20.0%]), which was a similar trend of dupilumab treatment benefit to that observed in Asian (25/54 [46.3%] versus 7/52 [13.5%]) and Caucasian participants (40/83 [48.2%] versus 18/93 [19.4%]). No meaningful conclusions could be drawn for the race category "Others" due to the small number of participants.

Body weight: A higher responder rate was observed in the dupilumab group as compared to the placebo group in the subgroup of participants with baseline body weight ≥90 kg (13/27 [48.1%] versus 5/25 [20.0%]), which was similar to the responder rates in the lower body weight groups.

Disseminated or localized PN lesions: No meaningful conclusions could be drawn in the subgroup of participants with disseminated or localized PN lesions ≤2 BSA due to the small number of participants in this category (3 participants).

Figure 27. Proportion of participants with IGA PN-S 0 or 1 score at Week 24 by subgroups - Pooled ITT population



Note: <=2 BSA would indicate a participant with only 2 symmetric body areas affected, such as both arms or both legs.

Efficacy in participants with and without comorbid atopic history

In participants with or without comorbid atopic history, the dupilumab treatment effect in improving pruritus was consistent with that observed in the overall PN population as measured by the proportion of participants with improvement (reduction) in WI-NRS by ≥4 points from baseline to Week 12 and Week 24 and the percent change from baseline to Week 24 in WI-NRS.

The treatment effect in improving PN skin lesions was consistent to that observed in the overall PN population as measured by the proportion of participants with IGA PN-S 0 ("clear") or 1 ("almost clear") score at Week 12 and Week 24.

The dupilumab treatment effect in improving skin pain, sleep, HRQoL, and mental health was consistent with that in the overall PN population as measured by Skin Pain-NRS, Sleep-NRS, DLQI, and HADS, respectively.

Table 29. Summary of the primary and key secondary efficacy endpoints by history of atopy - Pooled ITT population

Parameter	Atopic				Non-atopic				Overall			
	Placebo[a] (N=68)	Dupilumab 300 mg Q2W[a] (N=67)	Difference (95% CI)[b] for Dupilumab vs. Placebo	P-value[c]	Placebo[a] (N=90)	Dupilumab 300 mg Q2W[a] (N=86)	Difference (95% CI)[b] for Dupilumab vs. Placebo	P-value[c]	Placebo[a] (N=158)	Dupilumab 300 mg Q2W[a] (N=153)	Difference (95% CI)[b] for Dupilumab vs. Placebo	P-value[c]
Proportion of participants with WI-NRS improvement (reduction) by ≥4 points from baseline to Week 24	14 (20.6%)	39 (58.2%)	38.4% (22.34%, 54.42%)	<.0001	16 (17.8%)	51 (59.3%)	45.9% (33.16%, 58.72%)	<.0001	30 (19.0%)	90 (58.8%)	42.7% (32.60%, 52.71%)	<.0001
Odds ratio			5.3 (2.23, 12.66)				10.9 (4.35, 27.47)				7.6 (4.03, 14.24)	
Proportion of participants with WI-NRS improvement (reduction) by ≥4 points from baseline to Week 12	12 (17.6%)	29 (43.3%)	27.1% (11.87%, 42.36%)	0.0011	18 (20.0%)	33 (38.4%)	19.4% (5.40%, 33.37%)	0.0066	30 (19.0%)	62 (40.5%)	22.7% (12.40%, 33.08%)	<.0001
Odds ratio			4.1 (1.66, 10.08)				2.6 (1.25, 5.26)				3.1 (1.77, 5.43)	
Proportion of participants with IGA PN-S 0 or 1 score at Week 24	11 (16.2%)	35 (52.2%)	32.1% (15.99%, 48.21%)	0.0003	16 (17.8%)	36 (41.9%)	27.7% (14.16%, 41.14%)	0.0001	27 (17.1%)	71 (46.4%)	29.6% (19.22%, 39.94%)	<.0001
Odds ratio			4.3 (1.92, 9.65)				4.2 (1.93, 8.95)				4.2 (2.42, 7.37)	
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	5 (7.4%)	25 (37.3%)	28.2% (14.53%, 41.93%)	0.0003	9 (10.0%)	29 (33.7%)	26.9% (14.86%, 38.92%)	<.0001	14 (8.9%)	54 (35.3%)	27.5% (18.43%, 36.51%)	<.0001
Odds ratio			6.5 (2.09, 20.45)				6.4 (2.37, 17.29)				6.5 (3.05, 13.67)	

WI-NRS: worst-itch numeric rating scale; IGA PN-S: Investigator's global assessment for prurigo nodularis - stage; CMH: Cochran-Mantel Haenszel; CI: confidence interval.

a Values presented are number and percent of responders.

b CMH response rate difference and odds ratio.

c Nominal p-values. No hierarchical testing procedure for pooled data.

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

Atopic comorbidity history in this study was pre-defined in the eCRF and was defined as a history of atopic dermatitis, allergic rhinitis, allergic rhinoconjunctivitis, asthma, food allergy, or eosinophilic esophagitis

PGM=PRODOPS/SAR231893/OVERALL/ISE_PN_2021/REPORT/PGM/eff_sum_endpo_stra_i_t.sas OUT=REPORT/OUTPUT/eff_sum_endpo_stra_key_i_t_i.rtf (01MAR2022 2:32)

Efficacy in participants with or without use of stable doses of TCS/TCI

182 (58.5%) participants had stable concomitant use of low-to-medium potency TCS/TCI during the treatment intervention period.

The proportion of participants with improvement in WI-NRS by ≥4 points from baseline to Week 24 was observed in participants with or without stable use of TCS/TCI, with a numerically greater treatment effect in those participants who used TCS/TCI. At Week 12, the proportion of participants with improvement in WI NRS by ≥4 points did not meet nominal statistical significance in those participants who did not use stable TCS/TCI (p=0.0869) but did reach nominal significance in those participants who used stable doses of TCS/TCI (p<0.0001).

The proportion of participants with IGA PN S 0 ("clear") or 1 ("almost clear") score at Week 24 was observed in participants with or without stable use of TCS/TCI, with a numerically greater treatment effect in those participants who used TCS/TCI.

The proportion of participants with both an improvement (reduction) in weekly average WI-NRS by ≥4 points from baseline to Week 24 and an IGA PN S 0 or 1 score at Week 24 was also observed in participants with or without stable use of TCS/TCI, with a numerically greater treatment effect in the participants with a stable use of TCS/TCI.

There was a trend of dupilumab treatment benefit in improving HRQoL, skin pain, and mental health in those participants with or without stable use of TCS/TCI, with a numerically greater treatment

difference in those participants who had stable use of TCS/TCI, as measured by DLQI, Skin Pain NRS, and HADS, respectively.

Table 30. Summary of the primary and key secondary efficacy endpoints by stable use of TCS/TCI - Pooled ITT population

Parameter	Stable use of TCS/TCI(Yes)				Stable use of TCS/TCI(No)				Overall			
	Placebo[a] (N=91)	Dupilumab 300 mg Q2W[a] (N=91)	Difference (95% CI)[b] for Dupilumab vs. Placebo	P-value[c]	Placebo[a] (N=67)	Dupilumab 300 mg Q2W[a] (N=62)	Difference (95% CI)[b] for Dupilumab vs. Placebo	P-value[c]	Placebo[a] (N=158)	Dupilumab 300 mg Q2W[a] (N=153)	Difference (95% CI)[b] for Dupilumab vs. Placebo	P-value[c]
Proportion of participants with WI-NRS improvement (reduction) by ≥4 points from baseline to Week 24	12 (13.2%)	54 (59.3%)	45.7% (33.46%, 57.95%)	<.0001	18 (26.9%)	36 (58.1%)	38.2% (21.13%, 55.26%)	<.0001	30 (19.0%)	90 (58.8%)	42.7% (32.60%, 52.71%)	<.0001
Odds ratio			13.2 (5.16, 33.65)				4.6 (1.99, 10.83)				7.6 (4.03, 14.24)	
Proportion of participants with WI-NRS improvement (reduction) by ≥4 points from baseline to Week 12	12 (13.2%)	38 (41.8%)	27.9% (15.29%, 40.59%)	<.0001	18 (26.9%)	24 (38.7%)	15.1% (-2.18%, 32.48%)	0.0869	30 (19.0%)	62 (40.5%)	22.7% (12.40%, 33.08%)	<.0001
Odds ratio			4.9 (2.15, 10.93)				1.9 (0.88, 4.28)				3.1 (1.77, 5.43)	
Proportion of participants with IGA PN-S 0 or 1 score at Week 24	10 (11.0%)	44 (48.4%)	36.5% (23.90%, 49.19%)	<.0001	17 (25.4%)	27 (43.5%)	19.4% (2.19%, 36.63%)	0.0319	27 (17.1%)	71 (46.4%)	29.6% (19.22%, 39.94%)	<.0001
Odds ratio			7.3 (3.22, 16.64)				2.4 (1.07, 5.24)				4.2 (2.42, 7.37)	
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	5 (5.5%)	35 (38.5%)	31.6% (20.48%, 42.79%)	<.0001	9 (13.4%)	19 (30.6%)	21.4% (6.36%, 36.42%)	0.0070	14 (8.9%)	54 (35.3%)	27.5% (18.43%, 36.51%)	<.0001
Odds ratio			13.0 (3.90, 43.33)				3.5 (1.31, 9.37)				6.5 (3.05, 13.67)	

WI-NRS: worst-itch numeric rating scale; IGA PN-S: Investigator's global assessment for prurigo nodularis - stage; CMH: Cochran-Mantel Haenszel; CI: confidence interval.

a Values presented are number and percent of responders.

b CMH response rate difference and odds ratio.

c Nominal p-values. No hierarchical testing procedure for pooled data.

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

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Treatment effect after study intervention discontinuation

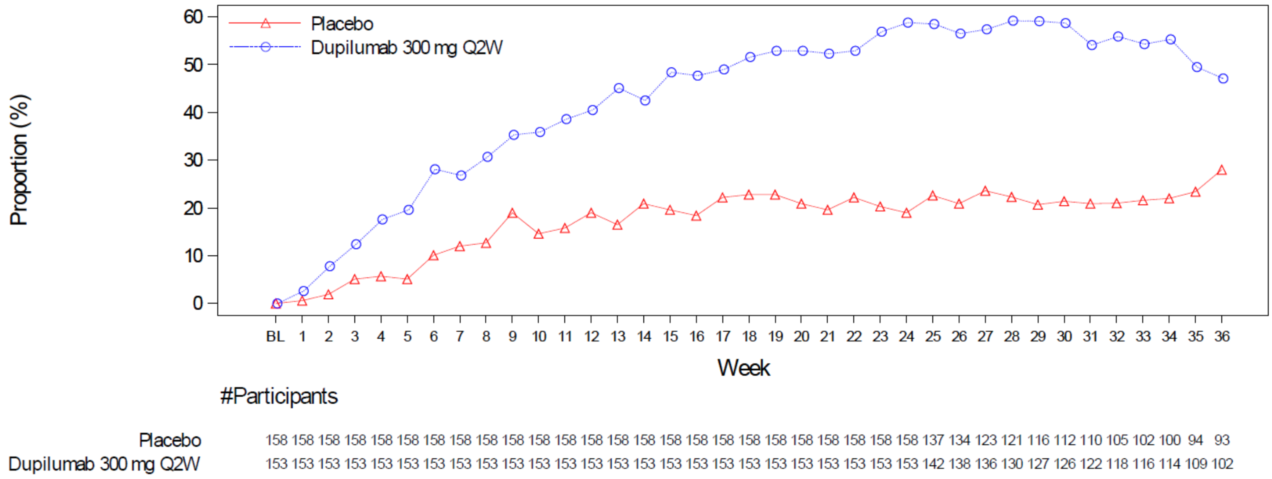
Data presented were derived after the primary data base lock if not indicated otherwise.

Proportion of participants with an improvement (reduction) in WI-NRS by ≥4 points from baseline up to Week 36

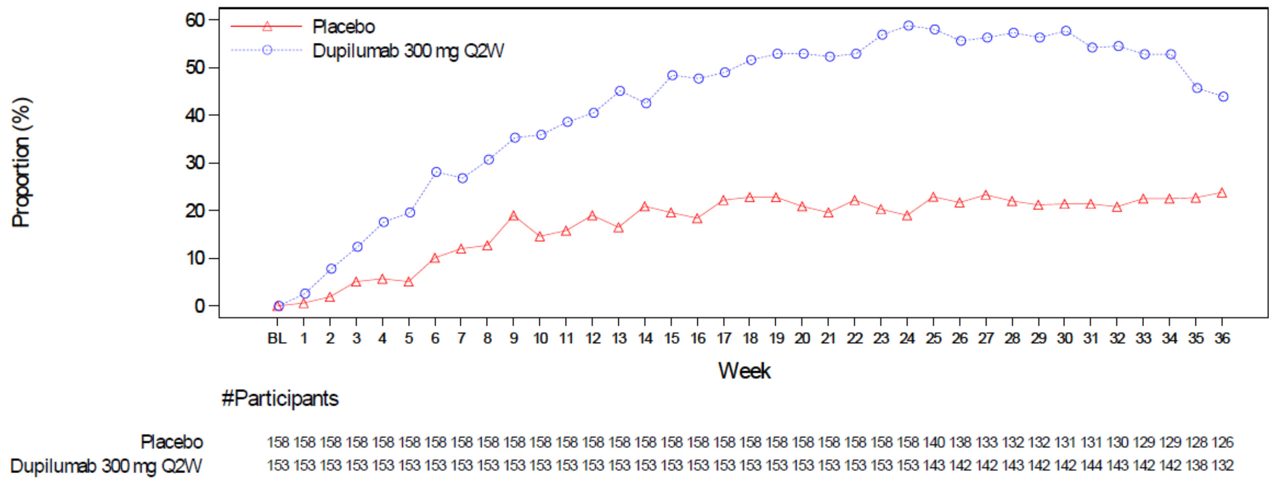
The proportion of participants with an improvement (reduction) in WI-NRS by ≥4 points from baseline observed at Week 24 in the dupilumab group decreased from 58.8% (90/153) to 47.1% (48/102) at the end of the 12-week post-intervention follow-up period. In contrast, within the placebo group the number of responders at Week 24 increased from 19.0% (30/158) to 28.0% (26/93).

Figure 28. Proportion of participants with an improvement (reduction) in WI-NRS by ≥4 points from baseline up to Week 36 – Pooled ITT population

a) Data based on primary data base lock



b) Data based on final data base lock

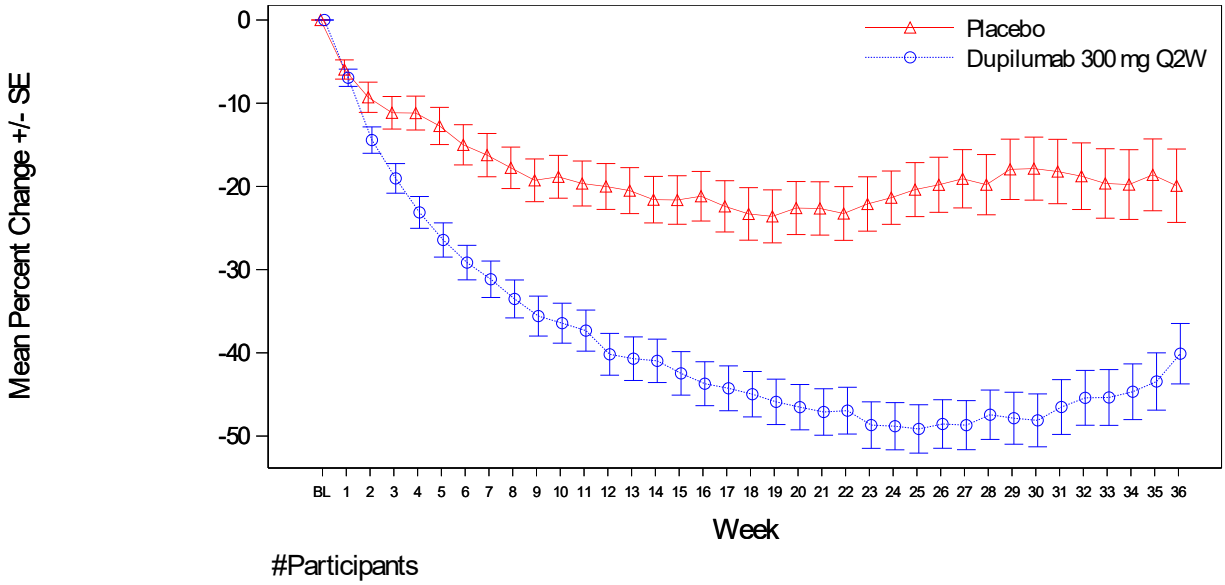


Note: Data collected after study intervention discontinuation were included. Data post the select prohibited medications/procedures and/or rescue medications that impacted efficacy were set to missing and imputed by WOCF. Missing data after study intervention discontinuation for lack of efficacy were imputed by WOCF.
Note: the analysis was based on final lock data.
PGM=PRODOPS/SAR231893/OVERALL/ISE_PN_2021/EXPLO/PGM/e_eff_resp_bywk_i_g.sas OUT=EXPLO/OUTPUT/e_eff_resp_winrs_bywk36_i_g_x.rtf (03AUG2022 3:10)

Change from baseline in WI-NRS over time up to Week 36

Off treatment, participants showed a gradual loss of response through Week 36 (-40.10%; n=102), compared with that observed at Week 24. There was no rebound (worsening of disease above baseline) observed in the dupilumab treatment group for any of the endpoints evaluated during the follow-up period.

Figure 29. Mean percent change from baseline in WI-NRS over time up to Week 36 - Pooled ITT population



#Participants

Placebo	158 158 156 156 156 155 154 151 152 151 150 152 151 152 152 151 148 148 148 146 143 142 142 141 140 137 134 123 121 116 112 110 105 102 100 94 93
Dupilumab 300 mg Q2W	153 153 152 152 152 151 152 151 152 152 151 152 152 152 152 152 152 152 152 151 152 151 151 150 151 142 138 136 130 127 126 122 118 116 114 109 102

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.
Ongoing participants who have missing data at a timepoint after Week 24 due to the data cut at the primary database lock or discontinued study participants who could not reach this timepoint from randomization date are excluded from this timepoint.

Among the participants who were responders at Week 24, the rate of loss of response was approximately 38.7% and 31.4 % by Week 36 within the dupilumab and placebo group, respectively. A significant proportion of participants in both treatment groups are still ongoing in the follow up period and censored for KM estimates.

Table 31. Time to first loss of response from Week 24 for participants with WI-NRS improvement (reduction) from baseline ≥4 points at Week 24 - Pooled ITT population

a) Data based on primary data base lock

	Placebo (N=30)	Dupilumab 300 mg Q2W (N=90)
Number of participants with loss of response of WI-NRS improvement (reduction) from baseline ≥ 4 points after Week 24	8 (26.7)	31 (34.4)
Kaplan-Meier estimate for probability of a participant with event (95% CI) up to		
Week 25	0.071 (0.013 to 0.204)	0.056 (0.021 to 0.117)
Week 26	0.179 (0.065 to 0.337)	0.102 (0.050 to 0.175)
Week 27	0.179 (0.065 to 0.337)	0.136 (0.075 to 0.216)
Week 28	0.179 (0.065 to 0.337)	0.148 (0.084 to 0.231)
Week 29	0.261 (0.115 to 0.434)	0.161 (0.093 to 0.245)
Week 30	0.261 (0.115 to 0.434)	0.173 (0.102 to 0.259)
Week 31	0.261 (0.115 to 0.434)	0.224 (0.142 to 0.318)
Week 32	0.261 (0.115 to 0.434)	0.251 (0.163 to 0.348)
Week 33	0.261 (0.115 to 0.434)	0.290 (0.196 to 0.391)
Week 34	0.261 (0.115 to 0.434)	0.317 (0.219 to 0.419)
Week 35	0.314 (0.146 to 0.497)	0.387 (0.279 to 0.493)
Week 36	0.314 (0.146 to 0.497)	0.387 (0.279 to 0.493)
HR, 95% CI vs. placebo[a]		1.120 (0.498, 2.518)
P-value vs. placebo[a]		0.7836

b) Data based on final data base lock

	Placebo (N=30)	Dupilumab 300 mg Q2W (N=90)
Number of participants with loss of response of WI-NRS improvement (reduction) from baseline ≥ 4 points after Week 24	10 (33.3)	37 (41.1)
Kaplan-Meier estimate for probability of a participant with event (95% CI) up to		
Week 25	0.069 (0.012 to 0.198)	0.056 (0.021 to 0.117)
Week 26	0.172 (0.063 to 0.327)	0.101 (0.050 to 0.174)
Week 27	0.172 (0.063 to 0.327)	0.135 (0.074 to 0.214)
Week 28	0.207 (0.084 to 0.367)	0.157 (0.091 to 0.240)
Week 29	0.276 (0.131 to 0.443)	0.169 (0.100 to 0.253)
Week 30	0.276 (0.131 to 0.443)	0.180 (0.108 to 0.266)
Week 31	0.276 (0.131 to 0.443)	0.225 (0.145 to 0.316)
Week 32	0.276 (0.131 to 0.443)	0.247 (0.163 to 0.340)
Week 33	0.276 (0.131 to 0.443)	0.281 (0.192 to 0.376)
Week 34	0.276 (0.131 to 0.443)	0.327 (0.232 to 0.424)
Week 35	0.314 (0.157 to 0.484)	0.419 (0.316 to 0.520)
Week 36	0.352 (0.185 to 0.524)	0.419 (0.316 to 0.520)
HR, 95% CI vs. placebo[a]		1.137 (0.552, 2.344)
P-value vs. placebo[a]		0.7270

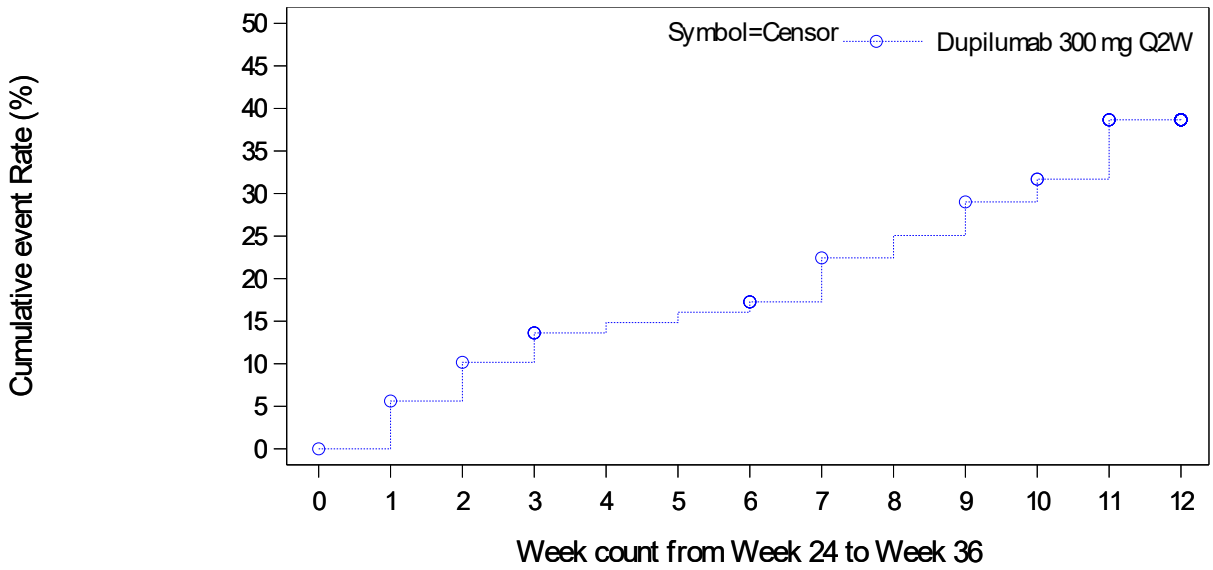
Note: the analysis was based on final lock data.

a HR: hazard ratio; derived from Cox proportional hazards model, including intervention, 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 (EFC16459 or EFC16460) as covariates.

PGM=PRODOPS/SAR231893/OVERALL/ISE_PN_2021/EXPLO/PGM/e_eff_km_loss_i_t.sas OUT=EXPLO/OUTPUT/e_eff_km_loss_winrs_i_t_x.rtf (03AUG2022 3:11)

Figure 30. Kaplan-Meier curve of time to first loss of response for participants with WI-NRS improvement (reduction) from baseline ≥4 points at Week 24 from Week 24 to Week 36

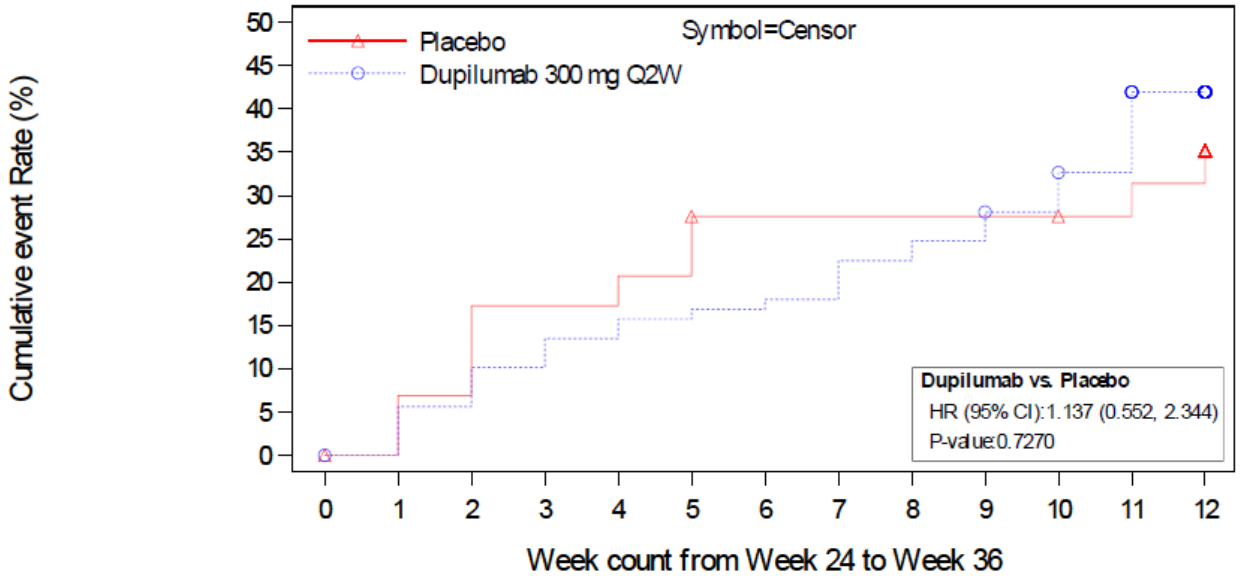
a) Data based on primary data base lock



Number at Risk

Dupilumab 300 mg Q2W	90	89	83	78	71	70	69	64	59	57	53	49	38

b) Data based on final data base lock



Number at Risk

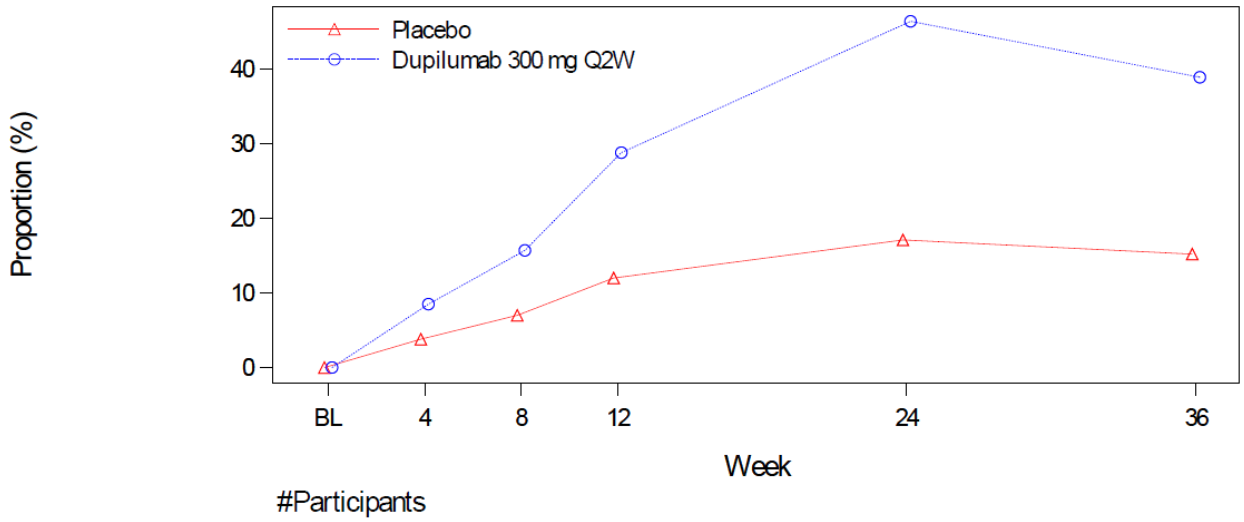
Placebo	30	29	27	24	24	23	20	20	20	20	20	19	18
Dupilumab 300 mg Q2W	90	89	84	80	77	75	74	73	69	67	63	58	45

Note: the analysis was based on final lock data.
PGM=PRODOPS/SAR231893/OVERALL/ISE_PN_2021/EXPLO/PGM/e_eff_km_loss_i_g.sas
OUT=EXPLO/OUTPUT/e_eff_km_loss_winrs_i_g_x.rtf (03AUG2022 3:11)

Proportion of participants with an IGA PN-S 0 or 1 score over time up to Week 36

The proportion of participants with an IGA PN-S 0 ("clear") or 1 ("almost clear") score observed at Week 24 decreased at Week 36 from 46.4% (71/153) to 38.9% (42/108) in the dupilumab group and from 17.1% (27/158) to 15.2 % (15/99) in the placebo group. Of the 51 participants treated with dupulimab, that have currently completed the 12-week follow-up, 15 (29.4%) had a return of at least mild disease (IGA PN-S score ≥2) at Week 36 while this was observed in 8/18 (44.4 %) participants that received placebo and with a completed follow-up.

Figure 31. Proportion of participants with an IGA PN-S 0 or 1 score over time up to Week 36 - Pooled ITT population



#Participants

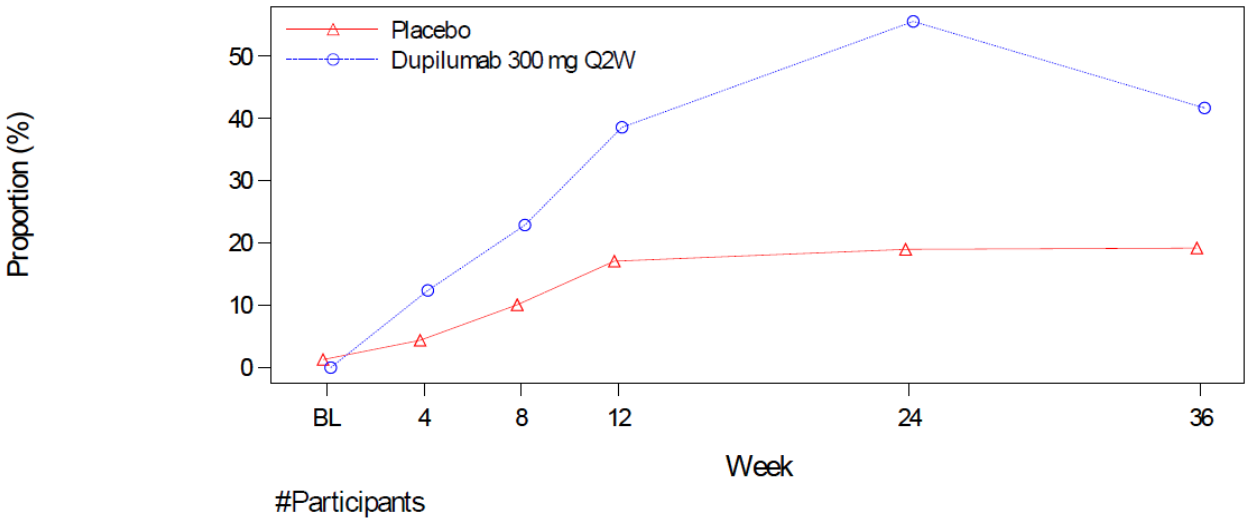
Placebo	158	158	158	158	158	99
Dupilumab 300 mg Q2W	153	153	153	153	153	108

Proportion of participants with an IGA PN-A 0 or 1 score over time up to Week 36

The proportion of participants with an IGA PN-A 0 ("clear") or 1 ("almost clear") score observed at Week 24 decreased at Week 36 from 55.6% (85/153) to 41.7% (45/108) in the dupilumab group and remained rather unchanged (19.0% (30/158) to 19.2.% 19/99) in the placebo group.

Of the 85 participants who were exposed to dupilumab and were responders at Week 24, 65 had completed the post-intervention follow-up period as of the data cut-off date. 24 (36.9%) had a return of at least mild disease activity (IGA PN-A ≥2) at Week 36 while this was observed in 9/21 (42.9%) participants in the placebo group that have completed the follow-up.

Figure 32. Proportion of participants with an IGA PN-A 0 or 1 score over time up to Week 36 - Pooled ITT population



#Participants

Placebo	158	158	158	158	158	99
Dupilumab 300 mg Q2W	153	153	153	153	153	108

2.5.3. Discussion on clinical efficacy

Design and conduct of clinical studies

Efficacy data for the new indication PN is derived from the 2 pivotal, phase 3, replicate studies EFC16460 (PRIME 2) and EFC16459 (PRIME). Both studies were designed as multinational, multicenter, randomized, double-blind, placebo-controlled, parallel-group studies, to assess the efficacy and safety of dupilumab in adult participants with PN whose disease was inadequately controlled on topical prescription therapies or when those therapies were not advisable. The studies included 24-week treatment and a 12 week follow-up period. Dupilumab was administered subcutaneously 300 mg, Q2W (after an initial loading dose of 600mg) which is the approved dosing regimen for adult patients with AD and for patients ≥12 years with asthma. Efficacy data were provided based on the primary data base lock for both studies.

Studies EFC16460 and EFC16459 included participants with diagnosis of PN with an age range of 18-80 years. Participants with an average score of ≥7 (range 0-10) in the worst-itch numeric scale (WI-NRS) within 7 days prior to the start of treatment (indicating severe pruritus) and with a minimum of 20 PN lesions (grade 3: moderate or grade 4 on the IGA-PN score) were eligible. Only participants with a history of failing to treatment with medium-to-superpotent TCS or when TCS were medically not advisable were included. Participants who were on a stable regimen of low to medium potency TCS or TCI at the screening visit were allowed to continue their topical TCS or TCI application once daily, without tapering, from screening to Week 24. Secondary PN due to other skin morbidities, medications and other medical conditions were excluded. Recruitment of participants with a history of atopy (medical history of AD, allergic rhinitis/rhinoconjunctivitis, asthma, or food allergy) were capped at 60% and up to 10% of the enrolled atopic participants were allowed to have active mild AD; moderate-to-severe AD was excluded.

The goal of this design was to mirror the overall PN patient population consistent with real-world estimates of overall prevalence while trying to minimize potential confounders on the efficacy evaluations.

Overall, the protocol-defined patient population of studies EFC16460 and EFC16459 is considered to be appropriate to evaluate the effects of dupilumab in PN. As there are no authorised systemic treatments for PN, a placebo control design can be accepted.

The primary objective of both studies was to evaluate the effect of dupilumab on the itch response in PN using the proportion of participants with improvement (reduction) in WI-NRS by ≥4 from baseline to week 12 (EFC16460) or week 24 (EFC16459) as *primary endpoint*. This reflects an improvement in the WI-NRS score from severe pruritus (>7) to moderate pruritus (>3). The 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") that has been recently validated for PN. The choice of the primary endpoint is reasonable given that severe itch is the cardinal symptom of PN that drives the itch-scratch cycle leading to the PN lesions and that also have a dominant effect on the participant's quality of life.

Initially, the timing for the primary endpoint in studies EFC16460 and EFC16459 was identical. However, after the primary analysis of study EFC16460 (data cut-off: 27-Sept-2021) the ongoing study EFC16459 was amended on 21-Oct-2021 to move the timing of the primary endpoint from week 12 to week 24 based on the efficacy data observed within study EFC16460. The rather late change of primary endpoint adds uncertainty. However, the consistency of results from both studies provide reassurance and sufficient clarification was provided by the MAH in response to the Request for Supplementary Information with regard to the timing of patient flow for both studies. One month after

the first pre-planned database lock for Study ECF16460, and following an analysis of the data relating to the P.E.P. at Week 12, a protocol amendment was implemented for Study ECF16459 to delay measurement of the P.E.P. until Week 24. This was based on preliminary efficacy findings supporting this change. This change of primary endpoint was sufficiently substantiated and did not raise further concerns.

Both studies planned to randomise n=150 patients (n=75 per group), in order to have 90% power to detect the difference of 28% between dupilumab and placebo at the 2-sided significance level of 0.05.

The primary analysis was planned to be conducted by means of a Cochrane-Mantel-Haenszel test stratified by history of atopy (atopic or non-atopic), stable use of TCS/TCI (yes or no), and region (countries combined) and covariate of baseline anti-depressant use (yes or no). The analysis was planned to be conducted in the ITT set, comprising all randomized subjects regardless if treatment kit is used or not.

The primary estimand is a composite estimand, participants taking selected prohibited medications and/or rescue medications prior to week 12 (week 24 in study EFC16459) were planned to be considered non-responders. In light of different patterns for the intercurrent event of taking selected prohibited medications and/or rescue medications this strategy was not fully supported by the CHMP as it may favour the dupilumab arm. At the CHMP's request, the MAH provided sensitivity analysis addressing a treatment policy estimand, using all observed data irrespective of the intercurrent event. This as-observed analyses are considered more robust and relevant and are preferred as basis for the regulatory decision.

Similarly, participants with missing values were also considered non-responders and in light of higher discontinuation rates in the control groups, there was uncertainty whether the dupilumab group might have been favoured by this approach. Additional analyses provided by the MAH suggested that results are robust. Given that numerical results differ only very little between the analyses targeting the different estimands, the CHMP agreed to include the results of the prespecified analysis in section 5.1 of the SmPC.

The proportion of participants with IGA PN-S score of 0 or 1 at week 24 (representing 0-5 nodules) was used as *key secondary endpoint* to further evaluate the effect of dupilumab on the number of PN skin lesions. Other objectives were to demonstrate improvement of HRQoL, skin pain, sleep quality, and mental health.

Efficacy data and additional analyses

In study EFC16460, 160 participants (dupilumab: 82; placebo: 78) were randomized and 151 participants (dupilumab: 75; placebo: 76) were randomized in study EFC16459 leading to a total of 311 participants in the pooled ITT population. Participants had active disease at baseline with a mean WI-NRS score of 8.5, with 66.3% and 33.7% of participants having an IGA PN-S score of 3 (moderate) or 4 (severe), respectively, and 55.0% and 40.5% of participants having an IGA PN-A score of 3 (moderate) or 4 (severe), respectively. 43.4% of the participants had a history or current diagnosis of atopy, 9.6% had active mild AD. 58.5% participants received background medication with TCS or TCI and were required to be on stable dosing regimen (maintaining the same medicine (low to medium potency TCS) and the same frequency used from 2 weeks prior to screening). In the randomized and exposed population, 265 (85.2%) participants completed the 24 week study intervention period. The percentage of participants permanently discontinuing study intervention was lower in the dupilumab group (3 [2.0%]) compared to the placebo group (41 [25.9%]). This was mainly driven by a higher proportion of participants in the placebo group that discontinued treatment due to lack of efficacy either as reasons for discontinuation by the Investigator or as the reason for withdrawal by the subject

indicating a treatment effect of dupilumab. At the time of the primary data cut-off, 195 (62.7%) participants had completed the study period (i.e., entire study intervention and post-intervention follow-up periods). Of note, 73 participants (55 [34.4%] in EFC16460 and 18 [11.9%] in EFC16459) were still ongoing in the follow-up period (38 in the dupilumab group and 35 in the placebo group) which accounts for 23.5% of exposed participants. At the CHMP request, complete efficacy data for the ITT population were provided based on the final database lock of both PN studies. Updated efficacy data are overall consistent with the conclusion for the efficacy data bases on the primary data base lock that are further described below.

Both studies, EFC16460 and EFC16459, reached the primary endpoint as well as key secondary endpoints.

In study EFC16460, at Week 12 the proportion of participants with a reduction in the WI-NRS by ≥4 from baseline (*primary endpoint*) was significantly higher in the dupilumab group as compared to the placebo group (37.2% versus 22.0%; p=0.0216). Similar differences were observed in study EFC16459 (44.0% versus 15.8%, p=0.0003) where however the timing of the primary endpoint was moved from Week 12 to Week 24. In study EFC16459, at Week 24 a higher proportion of participants with reduction in WI-NRS by ≥4 points (primary endpoint) can be observed (60.0% versus 18.4%; p<0.0001) that were also consistent with the effect observed at Week 24 in EFC16460 (57.7% versus 19.5%).

Subsequently, in the pooled ITT population a significant difference is observed at Week 12 in the dupilumab group (40.5% versus 19.0%; p<0.0001) that was further increased at Week 24 (58.8% versus 19.0%; p<0.0001). The treatment effect of dupilumab started to appear within the first weeks and further increased over time.

Mean change and mean percent changes of WI-NRS over time up to Week 24 were both similar and overall consistent with the observed reduction in itch severity (WI-NRS reduction of ≥4) points showing show a mean reduction of -4.77 and -2.65 and a mean percent change of -53.44 and -27.97 at Week 24 for dupilumab and placebo respectively. A continuous reduction in WI-NRS is observed to a lesser extent in the placebo group. The overall reduction in WI-NRS at Week 24 by 2.2 points in the dupilumab group as compared to placebo is supportive for the beneficial treatment effect of dupilumab seen for the primary endpoint.

Regarding the *key secondary* endpoint a significantly difference in the proportion of participants with an IGA PN-S score of 0 or 1 (indicating no or only a low number of PN lesions) was observed at Week 24 (dupilumab: 71 (46.4%); placebo: 27 (17.1%); p<0.0001) in the pooled ITT population. This treatment effect of dupilumab on PN lesions was consistent between both pivotal studies and do overall indicate a profound reduction of PN lesions after dupilumab treatment. Still, the number of responders for the secondary endpoint (IGA PN-S score 0 or 1) is lower as compared to the number of responders for the primary endpoint (improvement by ≥4 points in the WI-NRS score) indicating a limited correlation between reduction in the severity of pruritus and reduction of PN lesions.

The quality of PN lesions was further assessed using the IGA PN-Score that evaluates the percent of nodules that show excoriations and/or crusts showing a nominally significant at Week 12 and Week 24, with the greatest treatment difference observed at Week 24 (56.2% versus 18.4%, nominal p<0.0001). These data indicate that similar to the observed overall improvement in PN lesions, as seen by reduction in PN-S score, an improved healing of remaining PN lesions can be observed after dupilumab treatment.

Consistent with the observed reduction of itch severity and PN lesions a significant improvement in DLQI and Skin Pain-NRS was observed at Week 24. A similar trend towards improved quality of life at Week 24 is also noted in Sleep-NRS and HADS while nominal p-values are reported as these were not

part of the hierarchical testing procedure or the procedure broke before the analysis. Overall, the improvement in the above mentioned scores supports the beneficial effect of dupilumab on patients' quality of life.

Subgroup analyses showed an overall lowered efficacy for the primary and key secondary outcomes in participants with high BMI or high body weight. Body weight has been previously identified as the primary factor responsible for dupilumab PK variability in the other approved indications. No dose adjustment is recommended with respect to body weight or BMI in the PN population by the MAH as it does not significantly impair the efficacy. This is considered acceptable by the CHMP.

Only 6.1% of subjects enrolled in the pivotal studies were Black or African American despite the fact that PN is more common in this patient population. A total of 19 Black or African American subjects were enrolled across the two studies, and 11 of these were randomised to receive dupilumab. Thus, uncertainty regarding the dupilumab treatment effect remains which is, however, sufficiently reflected in the current wording of the SmPC.

In the ITT population, 58.5% of participants used stable TCS/TCI during the studies with stable regimen defined as the administration of the same medication (low to medium potency TCS) at the same frequency (once or twice daily) used continuously starting from 2 weeks prior to screening. These participants were required to continue their topical application once daily without tapering from Screening to Week 24.

With regard to the primary and key secondary outcomes of studies EFC16460 and EFC16459, a treatment response with dupilumab was seen in participants with and without use of TCS/TCI at Week 24 whereas at Week 12 a significance was only reached in participants with use of TCS/TCI. Of note, there appears to be no additive treatment effect of dupilumab as treatment responses in the dupilumab group were similar between both, WI-NRS and PN-S responses. There is however, an apparent imbalance in the placebo group in the number of responders in participants without use of TCS/TCI as compared to participants that received TCS/TCI. Overall, these data indicate a treatment effect of dupilumab irrespective of whether TCS/TCI were used. Additional figures showing the WI-NRS response over time in subgroups of participants with and without stable use of TCS/TCI were provided in response to the Request for Supplementary Information and did not give rise for further concerns on this efficacy aspect.

Further analyses for loss of response in WI-NRS or PN-S responders were provided by the MAH suggesting a loss of treatment effect within the 12-week follow-up period effect after administration of dupilumab was discontinued. Overall, efficacy data from the 12-week follow-up period suggest a loss of response after discontinuation of dupilumab treatment that is irrespective to changes in the TCS/TCI background therapy during the follow-up period. This information has been included in section 5.1 of the SmPC: "*Once treatment was discontinued after 24 weeks, there was an indication towards recurrence of signs and symptoms within the 12-week follow-up period.*"

The loss of response after 12 weeks is only suggested with the present data and a longer follow-up period would have been more appropriate to evaluate the maintenance of efficacy of dupilumab in PN as also suggested by the prior Scientific Advice procedure. Therefore, no information is available for healthcare professionals (HCPs) and patients regarding long-term use, nor withdrawal and retreatment. Information on missing efficacy data beyond week 24 were added in section 4.2 of the SmPC *"PN clinical trial data are available for patients treated up to 24 weeks."*

The MAH claimed that "Dupilumab is intended for long-term treatment". This was not supported by the CHMP as clinical data for dupilumab treatment in PN are only available for a treatment period of 24 weeks and no further clinical data are planned to be generated in PN by the MAH. The MAH's justification for this initial claim is based on the immunological similarities between AD and PN with

regard to type-2 inflammation and pruritus development. It is argued that the similar clinical responses seen in AD can enable transfer of data and conclusions on treatment efficacy and long-term treatment maintenance from the more extensive AD development program (including 52-week treatment as well as OLE data) to the PN population. While it may be assumed that data on long-term treatment with dupilumab in PN can be similar to the other indications for which dupilumab is already approved (AD in particular), this would have to be demonstrated by further clinical data to exclude disease-specific differences in the treatment response and upon treatment discontinuation on a long-term base. Since the MAH didn't plan to generate further clinical data in the long-term use, they have submitted a revised wording to remove the use in long term treatment.

2.5.4. Conclusions on the clinical efficacy

The efficacy results from the two pivotal phase 3 studies (EFC16460 and EFC16459) demonstrated that the 300mg Q2W dose regimen provided statistically significant reductions in the severity of pruritus and the number of PN lesions (as measured by WI-NRS and PN-S scores) at Week 24 compared to placebo, in adult patients with PN whose disease was inadequately controlled on topical prescription therapies or when those therapies were not advisable.

The treatment effect was observed in participants with moderate and severe disease, atopic and non-atopic participants and was irrespective of whether stable concomitant topical therapy was applied or not. Uncertainties regarding the demonstration of efficacy in the patient population of Black and African American remain as the number of included participants was limited, however, this is sufficiently reflected in the current wording of the SmPC.

A major limitation is missing long-term efficacy data since both studies only included a 24-week treatment period. At Week 12, the treatment effect was significant for the primary and secondary endpoints in both studies. However, the effect was overall low in studies EFC16460 and continued to increase beyond Week 24. Accordingly, the timing for the primary endpoint was changed in study EFC16459 from Week 12 to Week 24 prior to the database lock. Overall, the greatest treatment effect for dupilumab was observed at Week 24. Further data on the maintenance of long-term efficacy beyond Week 24 are missing and the MAH currently does not plan to conduct any further studies in PN. Therefore, the initial claim for long-term use was not acceptable to the CHMP. The MAH submitted a revised indication claim in which the long-term treatment has been removed.

Updated complete efficacy data for the ITT population were provided within the MAHs response to the Request for Supplementary Information. First indications for a loss-of-response in the dupilumab group were noted after treatment discontinuation in the 12-week follow-up period that corresponds to the time to complete clearance of dupilumab. This is adequately reflected in Section 5.1.

Overall, the improvements seen at Week 12 and Week 24 in the primary and secondary endpoints of the pivotal studies are considered clinically meaningful and support the approval of dupilumab in adult patients with PN from an efficacy point-of-view. From an efficacy point of view, the new indication: "Dupixent is indicated for the treatment of adults with moderate-to-severe prurigo nodularis (PN) who are candidates for systemic therapy" is approvable.

2.6. Clinical safety

Introduction

Dupilumab was first approved in the European Union (EU) in September 2017. As of the time of the data cut-off for this dossier, dupilumab is approved in the EU for multiple atopic diseases, including the treatment of moderate-to-severe atopic dermatitis (AD; adults and adolescents), severe atopic dermatitis (children 6 to 11 years), severe asthma with type 2 inflammation (adults and adolescents), and for the treatment of chronic rhinosinusitis with nasal polyposis (CRSwNP) in adults. An application for the new indication eosinophilic esophagitis (EoE; adolescents 12 years and older) has been submitted in parallel to this PN application.

The primary safety pool in the AD submission consisted of dupilumab 300 mg Q2W and QW dose groups from three placebo-controlled studies of 16 week treatment duration.

The primary safety pool in the asthma submission consisted of dupilumab 300 mg Q2W and 200 mg Q2W dose groups from 2 placebo-controlled studies of 24-week and 52-week treatment duration, respectively. The safety profile observed in the AD primary safety pool was similar to that observed in the asthma safety pool with few differences.

In the AD studies (primary safety pool), a greater proportion of patients in dupilumab groups reported TEAEs related to **conjunctivitis** than placebo. These imbalances were not observed in the asthma studies. In the CRSwNP studies, incidences for conjunctivitis (broad and narrow) in dupilumab-treated patients were lower than the percentages for AD and similar to those of asthma, although higher compared to placebo group. In the CRSwNP studies, conjunctivitis was typically mild/moderate in intensity (none severe/serious or requiring treatment discontinuation) and required primarily topical treatment with full recovery. **Herpes infections** (excluding eczema herpeticum) also occurred in AD studies at a higher incidence in dupilumab-treated patients compared to placebo, and were balanced in CRSwNP and asthma studies.

In one asthma study (EFC13579), a numerical imbalance for SAEs under (MedDRA SOC) **cardiac disorders** (placebo: 0/634 [0.0%]; dupilumab (200mg Q2W): 4/631 [0.6%]; dupilumab 300mg Q2W: 10/632 [1.6%]. However, a broad database search for CV events followed by a blinded adjudication analysis by 3 independent cardiologists did not support a notable difference in the safety profile between dupilumab and placebo for MACE, MACE plus hospitalization for unstable angina events, as well as for CV deaths. A similar imbalance has not been observed in any other placebo controlled study in asthma, AD, or CRSwNP.

Across all studies for asthma, AD and CRSwNP, dupilumab-treated subjects have shown a greater mean, initial and transient, **increase from baseline in blood eosinophil levels** compared to placebo, which was predominantly a laboratory finding without any associated AEs. However, in Phase 3 asthma studies (EFC13579, EFC13691, and LTS12551) and Phase 3 CRSwNP studies (EFC14146 and EFC14280) investigators were instructed to report elevations of eosinophil counts >3.0 Giga/L as a TEAE, whether or not the increased eosinophil count was associated with symptoms. This is reflected in higher incidence of PTs under (HLT) Eosinophilic disorders and (PT) Eosinophil count increased, in asthma and to a lesser extent in CRSwNP, as compared to AD where reporting asymptomatic eosinophilia was not required.

In asthma Study EFC13579, a numerically greater proportion of patients reported TEAEs under (MedDRA SOC) **hepatobiliary disorders** in the dupilumab group than placebo. A similar imbalance has not been observed in any other placebo controlled study, either in asthma, AD and CRSwNP. In addition, PTs of which had higher relative risk in dupilumab-treated patients in the CRSwNP studies, were compared to the AD and asthma indications. The rates for the PTs **hypertension and arthralgia**, were similar to those observed in patients with AD, asthma or CRSwNP treated with dupilumab 300 mg q2w.

Table 32. Treatment-emergent adverse events comparison in the atopic dermatitis, asthma, CRSwNP, and PN studies - Safety pools

	Atopic Dermatitis Studies[a]			Asthma Studies[b]			CRSwNP Studies[c]		PN Studies[d]	
		Dupilumab			Dupilumab			Dupilumab		Dupilumab
No. of patients with at least 1 TEAE	Placebo (N=517) n (%)	300 mg q2w (N=529) n (%)	300 mg qw (N=518) n (%)	Placebo (N=792) n (%)	200 mg q2w (N=779) n (%)	300 mg q2w (N=788) n (%)	Placebo (N=282) n (%)	300 mg q2w (N=440) n (%)	Placebo (N=157) n (%)	300 mg q2w (N=152) n (%)
CMQ: Conjunctivitis – narrow	11 (2.1%)	49 (9.3%)	41 (7.9%)	17 (2.1%)	10 (1.3%)	14 (1.8%)	1 (0.4%)	7 (1.6%)	2 (1.3%)	6 (3.9%)
CMQ: Conjunctivitis - broad	14 (2.7%)	60 (11.3%)	57 (11.0%)	24 (3.0%)	12 (1.5%)	21 (2.7%)	1 (0.4%)	12 (2.7%)	3 (1.9%)	8 (5.3%)
HLT: Herpes viral infections	18 (3.5%)	34 (6.4%)	25 (4.8)	16 (2.0%)	9 (1.2%)	10 (1.3%)	2 (0.7%)	7 (1.6%)	0	5 (3.3%)
HLT: Eosinophilic disorders	2 (0.4%)	9 (1.7%)	1 (0.2%)	2 (0.3%)	21 (2.7%)	18 (2.3%)	1 (0.4%)	5 (1.1%)	0	0
PT: Eosinophil count increased	0	2 (0.4%)	3 (0.6%)	2 (0.3%)	8 (1.0%)	7 (0.9%)	0	1 (0.2%)	0	1 (0.7%)
SOC: Hepatobiliary disorders	2 (0.4%)	2 (0.4%)	1 (0.2%)	4 (0.5%)	12 (1.5%)	18 (2.3%)	0	0	2 (1.3%)	0
SOC: Hepatobiliary disorders (serious adverse events)	0	0	0	1 (0.1%)	2 (0.3%)	5 (0.6%)	0	0	1 (0.6%)	0
SOC: Cardiac disorders	4 (0.8%)	3 (0.6%)	5 (1.0%)	11 (1.4%)	11 (1.4%)	19 (2.4%)	6 (2.1%)	2 (0.5%)	3 (1.9%)	1 (0.7%)
SOC: Cardiac disorders (serious adverse events)	1 (0.2%)	1 (0.2%)	2 (0.4%)	0	4 (0.5%)	10 (1.3%)	1 (0.4%)	1 (0.2%)	2 (1.3%)	0
PT Hypertension	8 (1.5%)	9 (1.7%)	6 (1.2%)	12 (1.5%)	18 (2.3%)	10 (1.3%)	3 (1.1%)	12 (2.7%)	3 (1.9%)	2 (1.3%)
PT Arthralgia	10 (1.9%)	16 (3.0%)	5 (1.0%)	30 (3.8%)	18 (2.3%)	22 (2.8%)	5 (1.8%)	14 (3.2%)	0	2 (1.3%)

a Pooled data: Studies R668-AD-1021 (select doses), R668-AD-1334, and R668-AD-1416 (16 weeks monotherapy) (Primary Safety Pool [pool 2]
b Pooled data: Studies DRI12544 and EFC13579 (pooled safety population 24 weeks for DRI12544 and 52 weeks for EFC13579)
c Pooled data: Studies EFC14146 and EFC14280 (24-week intervention period for both studies)
d Pooled data: Studies EFC16460 and EFC16459 at the cut-off dates of 31 August 2021 and 23 November 2021, respectively.
Note: For the atopic dermatitis studies, the treatment period is defined as period starting from the first dose date to the date of the Week 16 visit (study day 113 relative to the first dose date if the week 16 visit is unavailable) or date of early termination visit, whichever comes first.
At each level of patient summarization, a patient is counted once if the patient reported one or more events.

Safety Data for PN

Main safety data

The main safety population is derived from pooled safety from the 2 pivotal phase 3 studies, EFC16460 and EFC16459 that included a 24-week treatment period and a 12-week follow up. Participants in the dupilumab group were treated 300mg Q2W after an initial loading dose of 600mg (see Section 2.5.2 for further description). The off-treatment follow-up period of the 2 studies currently remains ongoing for 23.6 % participants (55 in EFC16460 and 18 in EFC16459) at the time of the data cut-off (EFC16460: 30 August 2021; EFC16459: 12 November 2021).

Table 33. Data pool for integrated summary of safety

Treatment	EFC16460 (LIBERTY-PN PRIME2)	EFC16459 (LIBERTY-PN PRIME)	Safety Pool Data	Primary Objective
Placebo	82	75	157	Pooled safety assessment of the dupilumab 300 mg Q2W dose regimen versus placebo in the intended indication
Dupilumab 300 mg Q2W, after an initial loading dose of 600 mg (2 injections of 300 mg)	77	75	152	

Analyses were performed on the safety population, defined as all participants randomly assigned to study intervention and who took at least 1 dose of study intervention. Participants were analysed according to the intervention they actually received.

The observation period for the main safety population consisted of:

- Pre-treatment period: period up to first IMP administration.
- Treatment-emergent period: period from the first IMP administration to the last IMP administration + 98 days and including the on-treatment period
- Post-treatment period: period starting after the end of the treatment emergent period

Supportive safety data

SUSARs and deaths reported from ongoing Phase 1/2/3 and Phase 4 interventional studies with dupilumab in other indications are further provided as supportive safety data.

Patient exposure

Main safety population (Study EFC16460 & EFC16459)

Disposition

The main safety population comprised 309 participants (152 in the dupilumab group and 157 in the placebo group) from Studies EFC16460 and EFC16459. Among the 309 participants treated, 265 (85.8%) completed the 24 week study intervention period and 44 (14.2%) prematurely discontinued the intervention. At the time of the data cut-off, 23.6% of the participants have currently not completed the treatment follow-up period. A lower percentage of participants discontinued the study intervention in the dupilumab group as compared to the placebo group (2.0% and 26.1%, respectively); the main reasons for permanent study intervention discontinuation prior to Week 24 were withdrawal by participant (0.7% and 11.5%, respectively) and lack of efficacy (0.7% and 10.2%, respectively). None of the premature intervention discontinuation in the dupilumab group was due to an AE.

Table 34. Participant disposition - Pooled safety population

n (%)	Placebo (N=157)	Dupilumab 300 mg Q2W (N=152)	All (N=309)
Randomized and exposed	157 (100)	152 (100)	309 (100)
Completed the 24-week study intervention period	116 (73.9)	149 (98.0)	265 (85.8)
Did not complete the 24-week study intervention period	41 (26.1)	3 (2.0)	44 (14.2)
Reason for permanent study intervention withdrawal prior to Week 24			
Adverse event	5 (3.2)	0	5 (1.6)
Related to COVID-19	0	0	0
Not related to COVID-19	5 (3.2)	0	5 (1.6)
Lack of efficacy	16 (10.2)	1 (0.7)	17 (5.5)
Poor compliance to protocol	2 (1.3)	1 (0.7)	3 (1.0)
Withdrawal by participant	18 (11.5)	1 (0.7)	19 (6.1)
Other	0	0	0
Related to COVID-19	0	0	0
Not related to COVID-19	0	0	0
Reason for permanent study intervention withdrawal prior to Week 12			

n (%)	Placebo (N=157)	Dupilumab 300 mg Q2W (N=152)	All (N=309)
Adverse event	4 (2.5)	0	4 (1.3)
Related to COVID-19	0	0	0
Not related to COVID-19	4 (2.5)	0	4 (1.3)
Lack of efficacy	9 (5.7)	1 (0.7)	10 (3.2)
Poor compliance to protocol	1 (0.6)	1 (0.7)	2 (0.6)
Withdrawal by participant	10 (6.4)	1 (0.7)	11 (3.6)
Other	0	0	0
Related to COVID-19	0	0	0
Not related to COVID-19	0	0	0
Reason for permanent study intervention withdrawal from Weeks 12 through Week 24			
Adverse event	1 (0.6)	0	1 (0.3)
Related to COVID-19	0	0	0
Not related to COVID-19	1 (0.6)	0	1 (0.3)
Lack of efficacy	7 (4.5)	0	7 (2.3)
Poor compliance to protocol	1 (0.6)	0	1 (0.3)
Withdrawal by participant	8 (5.1)	0	8 (2.6)
Other	0	0	0
Related to COVID-19	0	0	0
Not related to COVID-19	0	0	0
Participant's reason when withdrawal by participant prior to Week 24			
Adverse event	2 (1.3)	0	2 (0.6)
Related to COVID-19	0	0	0
Not related to COVID-19	2 (1.3)	0	2 (0.6)
Study procedure	1 (0.6)	0	1 (0.3)
Lack of efficacy	6 (3.8)	1 (0.7)	7 (2.3)
Other	9 (5.7)	0	9 (2.9)
Related to COVID-19	0	0	0
Not related to COVID-19	9 (5.7)	0	9 (2.9)
Completed the study period	88 (56.1)	107 (70.4)	195 (63.1)
Did not complete the study period	34 (21.7)	7 (4.6)	41 (13.3)
Ongoing in study follow-up period	35 (22.3)	38 (25.0)	73 (23.6)
Reason for study discontinuation			
Adverse event	3 (1.9)	0	3 (1.0)
Poor compliance to protocol	1 (0.6)	0	1 (0.3)
Withdrawal by participant	30 (19.1)	7 (4.6)	37 (12.0)
Site terminated by sponsor	0	0	0
Study terminated by sponsor	0	0	0
Other	0	0	0
Related to COVID-19	0	0	0
Not related to COVID-19	0	0	0
Status at last contact			
Alive	121 (77.1)	113 (74.3)	234 (75.7)
Dead	0	0	0

This is a further breakdown of the reasons for withdrawal by participant reported above, as collected in the standard CRF form.
Participants are grouped according to the study intervention actually exposed to.
Percentages are calculated using the number of participants exposed as denominator.

n (%)	Placebo (N=157)	Dupilumab 300 mg Q2W (N=152)	All (N=309)

Note: one participant (ID: 016460-826-0001-30003) in dupilumab group was alive at the status of last contact on 10SEP2021, but was not counted in this table due to data cutoff by 30AUG2021; one participant (ID: 016459-032-0003-10001) in placebo group was alive at the status of last contact on 24NOV2021, but was not counted in this table due to data cutoff by 12NOV2021.

For the status of last contact, ongoing participants were excluded as the corresponding CRF page was not collected.

Study period = study intervention period + post-intervention follow-up period.

Exposure

The duration of IMP exposure was higher in the dupilumab group compared to the placebo group, with a mean (SD) exposure of 166.8 (17.6) days in the dupilumab group and 145.9 (44.3) days in the placebo group. Cumulative exposure to dupilumab was 69.42 participant-years.

Table 35. Extent of exposure to investigational medicinal product - Pooled safety population

	Placebo (N=157)	Dupilumab 300 mg Q2W (N=152)
Cumulative duration to treatment exposure (participant years)	62.72	69.42
Duration of IMP exposure (days)		
Number	157	152
Mean (SD)	145.9 (44.3)	166.8 (17.6)
Median	169.0	169.0
Min ; Max	15 ; 183	29 ; 183
Duration of IMP exposure by category [n (%)]		
Missing duration	0	0
>0 and ≤2 weeks	0	0
>2 and ≤4 weeks	4 (2.5)	0
>4 and ≤8 weeks	8 (5.1)	2 (1.3)
>8 and ≤12 weeks	6 (3.8)	1 (0.7)
>12 and ≤16 weeks	13 (8.3)	0
>16 and ≤20 weeks	7 (4.5)	0
>20 and ≤24 weeks	21 (13.4)	27 (17.8)
>24 weeks and ≤24 weeks + 3 days	87 (55.4)	110 (72.4)
>24 weeks + 3 days	11 (7.0)	12 (7.9)
Cumulative duration of treatment exposure by category [n (%)]		
>0 week	157 (100)	152 (100)
>2 weeks	157 (100)	152 (100)
>4 weeks	153 (97.5)	152 (100)
>8 weeks	145 (92.4)	150 (98.7)
>12 weeks	139 (88.5)	149 (98.0)
>16 weeks	126 (80.3)	149 (98.0)
>20 weeks	119 (75.8)	149 (98.0)
>24 weeks	98 (62.4)	122 (80.3)
Number of participants with study treatment by number of injections [n (%)]		
1 injection	0	0
2 injections	3 (1.9)	0
3 injections	6 (3.8)	1 (0.7)
4 injections	2 (1.3)	1 (0.7)
5 injections	3 (1.9)	0
6 injections	2 (1.3)	1 (0.7)
7 injections	9 (5.7)	0

	Placebo (N=157)	Dupilumab 300 mg Q2W (N=152)
8 injections	6 (3.8)	0
9 injections	3 (1.9)	0
10 injections	5 (3.2)	0
11 injections	4 (2.5)	1 (0.7)
12 injections	15 (9.6)	13 (8.6)
13 injections	99 (63.1)	135 (88.8)

IMP: Investigational medicinal product

Percentages are calculated using the number of participants in the Safety population with a non-missing duration of exposure as denominator

Note: Two injections for loading dose on Day 1.

Compliance to study and background intervention

Participants in both dupilumab and placebo groups had a high (≥98.7%) mean injection compliance rate, with no difference observed between intervention groups. Accidental IMP overdose was reported for 9 (5.9%) participants in the dupilumab group and 7 (4.5%) participants in the placebo group. None of these participants experienced any symptoms.

Mean compliance to background intervention was generally high throughout the studies and similar between intervention groups (91.32% and 88.81% from baseline to Week 12 in the dupilumab and placebo participants, respectively, and 89.80% and 86.30% from baseline to Week 24, respectively).

Medical history

Atopic history

134 (43.4%) participants (66 [43.4%] in the dupilumab group and 68 [43.3%] in the placebo group) had a history of atopic comorbidity at baseline including any of the following diseases: atopic dermatitis, allergic rhinitis, allergic rhinoconjunctivitis, asthma, food allergy, and eosinophilic esophagitis. Of these, 51 (16.5%) participants had ≥2 atopic comorbidities. The most frequently reported ongoing atopic condition was allergic rhinitis (25.0% participants in the dupilumab group and 19.7% participants in the placebo group).

Comorbidities and medical or surgical history

The most frequently reported non-atopic, non medical/surgical histories in the safety pool were comorbid conditions associated with PN (57.9% participants in the dupilumab group and 55.4% participants in the placebo group). By PT, the 3 most commonly reported conditions were hypertension (22.7%), type 2 diabetes mellitus (9.4%), and hypothyroidism (8.4%). Events under the SOC Psychiatric disorders were reported in 14.9% participants overall, with depression and anxiety being the most common PTs (5.8% and 4.9%, respectively). Overall, the most frequently reported non-atopic and non-comorbid conditions in the pooled safety population included gastroesophageal reflux disease (23 [7.4%] participants), appendicectomy (20 [6.5%] participants), caesarean section, and menopause (both 18 [5.8%] participants).

Prior medications

The most commonly used prior medications by standardized medication name were emollients and protectives (39.2%), clobetasol propionate (29.8%), mometasone furoate (23.0%), clobetasol (15.5%), betamethasone dipropionate and all other non-therapeutic products (13.9% each), hydroxyzine hydrochloride and methylprednisolone aceponate (11.3% each), and betamethasone valerate (11.0%) These prior medications were primarily used for the treatment of PN.

Almost all participants in the safety pool (308/309, 99.7%) had received topical medications and 66.7% had used systemic medications for PN before first IMP injection. The most frequently used medications within these 2 classes were TCS (98.4%) and antihistamines (53.4%), respectively, with similar proportions of participants in the dupilumab and placebo treatment groups. Systemic non-steroidal immunosuppressants were used by 20.7% of participants (dupilumab: 23.7%; placebo: 17.8%), antidepressants by 8.4% of participants (7.2% and 9.6%), gabapentinoids by 2.6% (3.3% and 1.9%), and opioid receptor antagonists by 2.3% of participants (2.6% and 1.9%). Phototherapy (8.1% of participants) was the most frequently reported prior procedure (7.9% and 8.3%).

Concomitant medication

All participants received at least 1 concomitant medication during the study. The concomitant medications taken by the highest number of participants in either dupilumab or placebo groups by standardized medication name were emollients and protectives (39.5% and 36.9%), mometasone furoate (13.8% and 18.5%), tozinameran (12.5% and 6.4%), acetylsalicylic acid (9.9% and 3.8%), and paracetamol (9.9% and 12.7%). Concomitant prohibited medications were used by 7 (4.6%) and 22 (14.0%) participants in the dupilumab and placebo groups, respectively, with systemic immunosuppressive/ immunomodulating drugs used by 1.3% in the dupilumab group and 11.5% in the placebo group. High potency or superpotent TCS were also initiated as rescue medications by a lower percentage of participants in the dupilumab group compared to the placebo group (7.2% and 21.7%, respectively). As of the cut-off date for these studies, 25.0% in dupilumab group and 21.7% in placebo group received at least one dose of a COVID-19 vaccine.

Adverse events

Overall summary of treatment emergent adverse events

The percentage of participants who reported at least 1 TEAE was 63.8% in the dupilumab group and 56.7% in the placebo group. Treatment-emergent SAEs occurred in 4.6% versus 7.6% participants in the dupilumab and placebo groups, respectively. TEAEs leading to permanent intervention discontinuation were reported in 0% of dupilumab-treated participants versus 2.5% in the placebo group. No deaths were reported in either intervention group during the intervention period.

Table 36. Overview of adverse event profile: Treatment-emergent adverse events - Pooled safety population

n (%)	Placebo (N=157)	Dupilumab 300 mg Q2W (N=152)
Participants with any TEAE	89 (56.7)	97 (63.8)
Participants with any severe TEAE	9 (5.7)	5 (3.3)
Participants with any treatment emergent SAE	12 (7.6)	7 (4.6)
Participants with any TEAE leading to death	0	0
Participants with any TEAE leading to permanent study intervention discontinuation	4 (2.5)	0
Participants with any treatment emergent AESI	2 (1.3)	1 (0.7)
Participants with any treatment emergent other selected AE	18 (11.5)	16 (10.5)
Participants with any TEAE related to IMP	21 (13.4)	26 (17.1)

TEAE: Treatment emergent adverse event, SAE: Serious adverse event, AESI: Adverse event of special interest

n (%) = number and percentage of participants with at least one TEAE.

Note: one participant (ID: 016460-380-0001-30003) in placebo group had pre-treatment AE leading to permanent study intervention discontinuation, and this participant was not counted in this table.

When adjusted by exposure, the incidence rate of participants with any TEAEs was 183.9 participants

per 100 PY in the dupilumab group and 172.9 participants per 100 PY in the placebo group. The incidence of SAEs was notably lower in the dupilumab group compared to the placebo group (7.2 versus 13.8 participants per 100 PY in the 2 groups, respectively); a similar trend was observed for other TEAE categories except for TEAE related to IMP (30.1 versus 26.1 participants per 100 PY in the dupilumab group and in the placebo group, respectively).

Table 37. Overview of exposure adjusted adverse event profile: Treatment-emergent adverse events - Pooled safety population

nP/PY (nP/100 PY)	Placebo (N=157)	Dupilumab 300 mg Q2W (N=152)
Participants with any TEAE	89/51.5 (172.9)	97/52.7 (183.9)
Participants with any severe TEAE	9/87.6 (10.3)	5/96.9 (5.2)
Participants with any treatment emergent SAE	12/87.1 (13.8)	7/96.6 (7.2)
Participants with any TEAE leading to death	0/90.0	0/99.0
Participants with any TEAE leading to permanent study intervention discontinuation	4/88.9 (4.5)	0/99.0
Participants with any treatment emergent AESI	2/89.1 (2.2)	1/98.7 (1.0)
Participants with any treatment emergent other selected AE	18/81.9 (22.0)	16/92.0 (17.4)
Participants with any TEAE related to IMP	21/80.4 (26.1)	26/86.4 (30.1)

TEAE: Treatment emergent adverse event, SAE: Serious adverse event, AESI: Adverse event of special interest

nP = number of participants with at least one event, PY= total patient-years in the corresponding observational period, nP/100 PY= number of participants with at least one event per 100 patient-year

Note: for participants with event, patient-years are calculated up to the date of the first incidence; for participants without event, patient-years correspond to the length of exposure to the treatment emergent period.

Note: one participant (ID: 016460-380-0001-30003) in placebo group had pre-treatment AE leading to permanent study intervention discontinuation, and this participant was not counted in this table.

The most frequent TEAEs by SOC (≥10% in either intervention group) were Infections and infestations (dupilumab: 24.3%; placebo: 23.6%), Skin and subcutaneous tissue disorders (dupilumab: 16.4%; placebo: 14.6%), and Nervous system disorders (dupilumab 12.5%; placebo: 10.2%).

The incidence of TEAEs at the SOC level was generally similar in the dupilumab and the placebo groups, with the exception of Musculoskeletal and connective tissue disorders and Gastrointestinal disorders, where TEAEs were reported with a higher incidence in the dupilumab group, mainly driven by the HLGT of joint disorders and the PT of diarrhoea for the 2 respective SOCs.

At the PT level, TEAEs reported more frequently (≥1% higher) in the dupilumab group compared to placebo were:

- Nasopharyngitis (3.9% vs. 1.9%)
- Dizziness (2.6% vs. 0%)
- Diarrhoea (2.6% vs. 0.6%)
- Eczema (2.0% vs. 0%)
- Blood creatine phosphokinase increased (3.3% vs. 0.6%)
- Conjunctivitis and conjunctivitis allergic (both 2.0% vs. 0.6%)
- Myalgia (2.0% vs. 0.6%)
- Accidental overdose (5.9% vs. 4.5%).

TEAEs that were reported less frequently (≥1% lower) by PT in the dupilumab group compared to placebo were:

- COVID-19 (0.7% vs. 3.2%)
- Neurodermatitis (2.6% vs. 7.0%)

- Injection site pain (0.7% vs. 3.2%)
- Folliculitis (0.7% vs. 2.5%).

Table 38. Number (%) of participants with TEAE(s) that occurred with a frequency ≥2% in any intervention group by primary SOC and PT - Pooled safety population

Primary System Organ Class Preferred Term n (%)	Placebo (N=157)	Dupilumab 300 mg Q2W (N=152)	Dupilumab 300 Q2W vs placebo Relative risk ratio (95% CI)
Any event	89 (56.7)	97 (63.8)	1.12 (0.94 to 1.34)
Infections and infestations	37 (23.6)	37 (24.3)	1.03 (0.69 to 1.53)
Nasopharyngitis	3 (1.9)	6 (3.9)	2.02 (0.52 to 7.83)
Conjunctivitis	1 (0.6)	3 (2.0)	3.03 (0.32 to 28.36)
COVID-19	5 (3.2)	1 (0.7)	0.21 (0.03 to 1.72)
Folliculitis	4 (2.5)	1 (0.7)	0.25 (0.03 to 2.28)
Nervous system disorders	16 (10.2)	19 (12.5)	1.23 (0.65 to 2.30)
Headache	9 (5.7)	8 (5.3)	0.92 (0.36 to 2.32)
Dizziness	0	4 (2.6)	NC (NC to NC)
Eye disorders	5 (3.2)	8 (5.3)	1.66 (0.56 to 4.94)
Conjunctivitis allergic	1 (0.6)	3 (2.0)	3.06 (0.33 to 28.54)
Gastrointestinal disorders	8 (5.1)	14 (9.2)	1.80 (0.78 to 4.17)
Diarrhoea	1 (0.6)	4 (2.6)	4.09 (0.47 to 35.48)
Skin and subcutaneous tissue disorders	23 (14.6)	25 (16.4)	1.12 (0.66 to 1.88)
Neurodermatitis	11 (7.0)	4 (2.6)	0.37 (0.12 to 1.14)
Eczema	0	3 (2.0)	NC (NC to NC)
Musculoskeletal and connective tissue disorders	7 (4.5)	15 (9.9)	2.20 (0.93 to 5.25)
Myalgia	1 (0.6)	3 (2.0)	3.16 (0.33 to 30.33)
General disorders and administration site conditions	13 (8.3)	10 (6.6)	0.79 (0.36 to 1.75)
Injection site reaction	2 (1.3)	3 (2.0)	1.52 (0.25 to 9.12)
Injection site pain	5 (3.2)	1 (0.7)	0.21 (0.03 to 1.74)
Investigations	9 (5.7)	11 (7.2)	1.26 (0.54 to 2.95)
Blood creatine phosphokinase increased	1 (0.6)	5 (3.3)	5.23 (0.60 to 45.25)
Injury, poisoning and procedural complications	14 (8.9)	14 (9.2)	1.03 (0.51 to 2.10)
Accidental overdose	7 (4.5)	9 (5.9)	1.33 (0.51 to 3.51)

TEAE: Treatment emergent adverse event, SOC: System organ class, PT: Preferred term
Confidence intervals are Cochran-Mantel-Haenszel stratified by study
MedDRA 24.1
n (%) = number and percentage of participants with at least one TEAE during the entire treatment-emergent period
Table sorted by SOC internationally agreed order and decreasing percentage of PT in dupilumab 300mg Q2W group
Only PT with at least one 2% in at least one group are presented.

Treatment-emergent adverse events by Investigator causality assessment

The percentage of participants with TEAEs assessed by the Investigator as related to IMP was 17.1% in the dupilumab group and 13.4% in the placebo group.

The SOC General disorders and administration site conditions had the highest proportion of participants with IMP-related TEAEs (7 [4.6%] and 11 [7.0%] participants in the dupilumab and placebo group, respectively), followed by Infections and infestations (9 [5.9%] versus 2 [1.3%]). At the PT level, the most frequently reported events were in the placebo group: injection site pain (0.7% versus 3.2%) and neurodermatitis (1.3% versus 2.5%). TEAEs of conjunctivitis allergic were considered related to the IMP in 2.0% of dupilumab participants versus 0% in the placebo group, and TEAEs of injection site reactions in 2.0% and 1.3% in the 2 respective groups.

Table 39. Number (%) of participants with TEAE(s) related to IMP as per Investigator's judgment by Primary SOC and PT - Pooled safety population

Primary System Organ Class Preferred Term n (%)	Placebo (N=157)	Dupilumab 300 mg Q2W (N=152)
Any event	21 (13.4)	26 (17.1)
Infections and infestations	2 (1.3)	9 (5.9)
Oral herpes	0	2 (1.3)
Conjunctivitis	0	1 (0.7)
Cystitis	0	1 (0.7)
Nasopharyngitis	0	1 (0.7)
Paronychia	0	1 (0.7)
Pharyngitis	0	1 (0.7)
Rhinitis	0	1 (0.7)
Tinea versicolour	0	1 (0.7)
Dermatitis infected	1 (0.6)	0
Sepsis	1 (0.6)	0
Immune system disorders	0	1 (0.7)
Seasonal allergy	0	1 (0.7)
Metabolism and nutrition disorders	0	1 (0.7)
Hyperhomocysteinaemia	0	1 (0.7)
Psychiatric disorders	1 (0.6)	0
Adjustment disorder with anxiety	1 (0.6)	0
Nervous system disorders	4 (2.5)	3 (2.0)
Dizziness	0	1 (0.7)
Headache	3 (1.9)	1 (0.7)
Presyncope	0	1 (0.7)
Hypoaesthesia	1 (0.6)	0
Eye disorders	3 (1.9)	4 (2.6)
Conjunctivitis allergic	0	3 (2.0)
Chalazion	0	1 (0.7)
Eczema eyelids	1 (0.6)	0
Eye pruritus	1 (0.6)	0
Eyelid oedema	1 (0.6)	0
Respiratory, thoracic and mediastinal disorders	1 (0.6)	0

Primary System Organ Class Preferred Term n (%)	Placebo (N=157)	Dupilumab 300 mg Q2W (N=152)
Oropharyngeal discomfort	1 (0.6)	0
Gastrointestinal disorders	2 (1.3)	2 (1.3)
Nausea	0	1 (0.7)
Odynophagia	0	1 (0.7)
Constipation	1 (0.6)	0
Mesenteritis	1 (0.6)	0
Skin and subcutaneous tissue disorders	7 (4.5)	3 (2.0)
Neurodermatitis	4 (2.5)	2 (1.3)
Urticaria	2 (1.3)	1 (0.7)
Rash erythematous	1 (0.6)	0
Musculoskeletal and connective tissue disorders	2 (1.3)	2 (1.3)
Arthralgia	0	1 (0.7)
Joint stiffness	0	1 (0.7)
Myalgia	1 (0.6)	1 (0.7)
Back pain	1 (0.6)	0
Reproductive system and breast disorders	1 (0.6)	0
Heavy menstrual bleeding	1 (0.6)	0
Intermenstrual bleeding	1 (0.6)	0
General disorders and administration site conditions	11 (7.0)	7 (4.6)
Injection site reaction	2 (1.3)	3 (2.0)
Asthenia	0	1 (0.7)
Injection site erythema	0	1 (0.7)
Injection site oedema	0	1 (0.7)
Injection site pain	5 (3.2)	1 (0.7)
Chest discomfort	1 (0.6)	0
Fatigue	1 (0.6)	0
Injection site pruritus	1 (0.6)	0
Injection site swelling	2 (1.3)	0
Pyrexia	1 (0.6)	0
Investigations	1 (0.6)	3 (2.0)
Blood creatine phosphokinase increased	0	2 (1.3)
Eosinophil count increased	0	1 (0.7)
Fibrin D dimer increased	1 (0.6)	0

TEAE: Treatment emergent adverse event, SOC: System organ class, PT: Preferred term
MedDRA 24.1
n (%) = number and percentage of participants with at least one TEAE related to IMP during the entire treatment-emergent period
Table sorted by SOC internationally agreed order and decreasing percentage of PT in dupilumab 300mg Q2W group

Serious adverse event/deaths/other significant events

Adverse events by severity

For 88/152 (57.8%) participants in the dupilumab group who experienced any TEAE, the intensity of the reported events was mild or moderate. A lower proportion of participants in the dupilumab group compared to the placebo group experienced a severe TEAE (3.3% versus 5.7%).

Table 40. Number (%) of participants with treatment emergent AE(s) by Primary SOC and PT by severity- Pooled safety population

Primary System Organ Class Preferred Term Intensity n (%)	Placebo (N=157)	Dupilumab 300 mg Q2W (N=152)
Any AE		
Missing	2 (1.3)	4 (2.6)
Mild	49 (31.2)	63 (41.4)
Moderate	29 (18.5)	25 (16.4)
Severe	9 (5.7)	5 (3.3)

Within the dupilumab group, 2 of the 5 participants with severe events experienced an SAE (see following section):

- **papillary thyroid cancer** (1 participant)
- **uterine leiomyoma**, **pyelonephritis acute**, and **pelvic inflammatory disease** (1 participant)

The remaining 3 events within the dupilumab group were non-serious, none required permanent IMP discontinuation.

- episodes of severe headache that recovered without corrective treatment (2 participants)
- severe neurodermatitis that resolved upon corrective treatment and was assessed by the Investigator as not related to the IMP (1 participant)

Serious adverse events

Treatment-emergent SAEs were reported by 7 (4.6%) participants in the dupilumab group and 12 (7.6%) participants in the placebo group. All treatment-emergent SAEs were reported by single participants only, with the exception of acute myocardial infarction, which was reported by 2 (1.3%) participants in the placebo group (0 participants in the dupilumab group).

Table 41. Number (%) of participants with treatment emergent SAE(s) by Primary SOC and PT - Pooled safety population

Primary System Organ Class Preferred Term n (%)	Placebo (N=157)	Dupilumab 300 mg Q2W (N=152)
Any event	12 (7.6)	7 (4.6)
Infections and infestations	2 (1.3)	2 (1.3)
COVID-19 pneumonia	0	1 (0.7)
Pelvic inflammatory disease	0	1 (0.7)
Pyelonephritis acute	0	1 (0.7)
COVID-19	1 (0.6)	0
Sepsis	1 (0.6)	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	2 (1.3)	3 (2.0)
Lipoma	0	1 (0.7)
Papillary thyroid cancer	0	1 (0.7)
Uterine leiomyoma	0	1 (0.7)
Cutaneous T-cell lymphoma	1 (0.6)	0
Hodgkin's disease	1 (0.6)	0
Large granular lymphocytosis	1 (0.6)	0
Nervous system disorders	1 (0.6)	0
Cauda equina syndrome	1 (0.6)	0

Primary System Organ Class Preferred Term n (%)	Placebo (N=157)	Dupilumab 300 mg Q2W (N=152)
Cardiac disorders	2 (1.3)	0
Acute myocardial infarction	2 (1.3)	0
Respiratory, thoracic and mediastinal disorders	0	2 (1.3)
Asthma	0	1 (0.7)
Interstitial lung disease	0	1 (0.7)
Gastrointestinal disorders	2 (1.3)	0
Duodenal ulcer perforation	1 (0.6)	0
Inflammatory bowel disease	1 (0.6)	0
Mesenteritis	1 (0.6)	0
Hepatobiliary disorders	1 (0.6)	0
Cholecystitis acute	1 (0.6)	0
Skin and subcutaneous tissue disorders	1 (0.6)	0
Neurodermatitis	1 (0.6)	0
Musculoskeletal and connective tissue disorders	1 (0.6)	1 (0.7)
Musculoskeletal chest pain	0	1 (0.7)
Rotator cuff syndrome	1 (0.6)	0
Injury, poisoning and procedural complications	1 (0.6)	0
Alcohol poisoning	1 (0.6)	0

SAE: Serious adverse event, SOC: System organ class, PT: Preferred term

MedDRA 24.1

n (%) = number and percentage of participants with at least one treatment emergent SAE during the entire treatment-emergent period

Table sorted by SOC internationally agreed order and decreasing percentage of PT in dupilumab 300mg Q2W group

In the dupilumab group, 7 participants experienced a SAEs. None of the treatment-emergent SAEs were considered related to the IMP by the Investigator or led to permanent IMP discontinuation:

1. One participant reported 3 SAEs (**uterine leiomyoma** [between Day 37 and Day 67 ie, 8 to 38 days after the 4th IMP dose], **pyelonephritis acute** [6 days after the 5th IMP dose], and **pelvic inflammatory disease** [7 days after the 8th IMP dose]; all of severe intensity). The participant developed pyelonephritis acute that resolved upon corrective treatment with levofloxacin. No action was taken with the IMP. During workup of the acute pyelonephritis, a CT scan was performed which showed a pelvic mass and abdominal ultrasound showed bilateral hydronephrosis. This pelvic mass was removed by total hysterectomy and pathology confirmed uterine leiomyoma. Post-surgery, the patient developed an infection and pelvic inflammatory disease which resolved after corrective treatment with antibiotics. None of the 3 SAEs were considered related to IMP by the Investigator or led to permanent IMP discontinuation.
2. One participant with a prior history of allergy reported an SAE of **asthma** 1 day after the 5th IMP injection. The event was likely triggered by first intake of celecoxib (COX-2 selective non-steroidal anti-inflammatory drug), prescribed for osteoporosis. Causality was assessed by the Investigator as not related to the IMP.
3. One participant experienced an SAE of **interstitial lung disease** which occurred on Day 4, 3 days after the 2nd IMP dose. Corrective treatment and mechanical ventilation as described in the

participant narrative were started and the participant was recovering at the time of the study data cut-off.

4. One participant developed **papillary thyroid cancer**. This participant had a medical history of benign thyroid nodule before study entry. During the study, at Day 64, a head and neck ultrasound had shown nodules and at Day 151 (10 days after the 12th IMP dose), a biopsy confirmed the diagnosis of papillary thyroid cancer. The event did not lead to permanent study intervention discontinuation and was considered not related to the IMP by the Investigator. No corrective treatment was administered, and the event had not resolved as of the time of the study data cut-off.
5. One Participant experienced an SAE of moderate **musculoskeletal chest pain** on Day 120, 7 days after the 10th IMP dose. Workup for a myocardial infarction was negative. The event was considered not related to IMP by the Investigator and did not lead to permanent study intervention discontinuation. The event had resolved with anti-inflammatory corrective treatment as of the time of the study data cut-off.
6. One participant reported an SAE of moderate **COVID-19 pneumonia** on Day 48 (5 days after the 5th ,IMP dose) which required corrective treatment as described in the participant narrative and resolved within 6 days.
7. One Participant experienced an SAE of moderate **lipoma** on Day 162 (7 days after the 13th IMP dose). This event qualified as an SAE due to the participant being hospitalized for the surgery. The event did not lead to permanent study intervention discontinuation and was considered not related to the IMP by the Investigator. The participant recovered upon administration of corrective treatment.

In the placebo group, 12 participants experienced a total of 15 treatment-emergent SAEs. Three participants reported more than 1 treatment-emergent SAE: 1) **Sepsis** and **mesenteritis** (not resolved) 2) **Duodenal ulcer perforation** and **inflammatory bowel disease** 3) **Cutaneous T-cell lymphoma** (not resolved) and **large granular lymphocytosis** (not resolved). Except the events of sepsis and mesenteritis, all other treatment-emergent SAEs in the placebo group were considered by the Investigator as not related to IMP. Administration of IMP was permanently discontinued in 2 participants: 1) **duodenal ulcer perforation** and 2) **Hodgkin's disease** (not resolved). Six treatment-emergent SAEs were not resolved as indicated above. For the SAE of and inflammatory bowel disease corrective treatment was started.

Deaths

Main safety population (Study EFC16460 & EFC16459)
No deaths were reported.

Supportive safety population
17 new deaths were reported in ongoing studies in other dupilumab indications. All fatal events were assessed as non-related to the IMP by the Investigator. The majority of the events leading to death (13/17) were reported in participants with moderate to severe COPD enrolled in EFC15804 and EFC15805 studies.

Adverse events of special interest and other selected adverse event groupings

Adverse events of special interest and other selected AE groupings were searched in the database using predefined search criteria as listed below. In addition a medical review was conducted for specific AESIs.

Table 42. Selections for AESIs and other AEs of interest

AE Grouping	Criteria
AESI	
Anaphylactic reaction	Anaphylactic reaction algorithmic approach (Introductory Guide for Standardised MedDRA Queries (SMQs) Version 18.1): includes anaphylactic reaction narrow SMQ (20000021) terms and programmatic identification of cases based on occurrence of at least two preferred terms meeting the algorithm criteria occurring within 24 hours of each other. The latter cases identified using the algorithm underwent blinded medical review taking into account the timing of events relative to each other and to IMP administration for final determination of whether it was an anaphylactic reaction.
Systemic hypersensitivity reactions	SMQ [20000214] hypersensitivity narrow search and [AE corrective treatment/therapy = "Y" or Action taken with IMP = "Drug withdrawn" or Action taken with IMP = "Drug interrupted"] followed by blinded medical review (documented process) for selection of relevant systemic hypersensitivity events.
Helminthic infections	CMQ10544 based on all PTs of the HLGT "Helminthic disorder"
Any severe type of conjunctivitis	CMQ10498 based on PTs[a] and "Severe" ticked in Adverse Events eCRF page
Any severe type of blepharitis	CMQ10497 based on HLT "Lid, lash and lacrimal infections, irritations and inflammations" and "Severe" ticked in Adverse Events eCRF page
Keratitis	CMQ10642 based on the following PTs [keratitis, allergic keratitis, ulcerative keratitis, atopic keratoconjunctivitis, herpes ophthalmic, ophthalmic herpes simplex, corneal infection]
Clinically symptomatic eosinophilia (or eosinophilia associated with clinical symptoms)[b]	CMQ10641 based on HLT "Eosinophilic disorders" or PT "Eosinophil count increased"
Pregnancy of a female participants entered in a study as well as pregnancy occurring in a female partner of a male participant entered in a study with IMP/NIMP	"Pregnancy" or "Partner Pregnancy" checked on the Pregnancy eCRF page as reported by the investigator
Significant ALT elevation	"ALT Increase" and AESI answer "Yes" checked on AE eCRF as reported by the investigator (ALT >5 x ULN in participants with baseline ALT ≤2 x ULN; OR ALT >8 x ULN if baseline ALT >2 x ULN)
Symptomatic overdose with IMP	Symptomatic Overdose is answered Yes, with Overdose of IMP answered Yes on AE eCRF.
Symptomatic overdose with NIMP	Symptomatic Overdose is answered Yes, with Overdose of NIMP answered Yes on AE eCRF.
Other selected AE Grouping	
Serious injection site reactions or severe injection site reactions that last longer than 24 hours	HLT "Injection site reactions" and either with serious status, or with severe status and (AE end date/time - AE start date/time) ≥24 hours or ongoing
Severe or serious infection	Primary SOC "Infections and infestations" and with severe or serious status
Drug-related hepatic disorder	SMQ [20000006] Drug-related hepatic disorders - narrow
Injection site reaction	HLT "Injection site reactions"
Malignancy	SMQ [20000091] - Malignant or unspecified tumors narrow
Suicidal behavior	CMQ10639 based on the following PTs [Completed suicide, Suicidal ideation, Depression suicidal, Suicidal behavior, Suicide attempt]
Conjunctivitis (narrow)	CMQ10644 based on the following PTs [Conjunctivitis, Conjunctivitis allergic, Conjunctivitis bacterial, Conjunctivitis viral, Atopic keratoconjunctivitis]

AE Grouping	Criteria
Conjunctivitis (broad)	CMQ10645 based on the following PTs [Conjunctivitis, Conjunctivitis allergic, Conjunctivitis bacterial, Conjunctivitis viral, Atopic keratoconjunctivitis, Blepharitis, Dry eye, Eye irritation, Eye pruritus, Lacrimation increased, Eye discharge, Foreign body sensation in eyes, Photophobia, Xerophthalmia, Ocular hyperaemia, Conjunctival hyperaemia]
Conjunctivitis (FDA)[c]	CMQ10643 based on the following PTs [Conjunctivitis, Conjunctivitis allergic, Conjunctivitis bacterial, Conjunctivitis viral, Eye irritation, Eye inflammation, Giant papillary conjunctivitis]
Keratitis (FDA)[c]	CMQ30102 based on the following PTs [keratitis, ulcerative keratitis, allergic keratitis, atopic keratoconjunctivitis, ophthalmic herpes simplex]

MedDRA Version 24.1 coding dictionary applied.

a CMQ10498 based on the following PTs: Adenoviral conjunctivitis, Conjunctival irritation, Conjunctival oedema, Conjunctival ulcer, Conjunctivitis, Conjunctivitis allergic, Conjunctivitis chlamydial, Conjunctivitis gonococcal neonatal, Conjunctivitis tuberculous, Conjunctivitis viral, Giant papillary conjunctivitis, Inclusion conjunctivitis, Ophthalmia neonatorum, Seasonal allergy, Herpes simplex virus conjunctivitis neonatal, Conjunctival hyperaemia, Inclusion conjunctivitis neonatal, Conjunctivitis bacterial, Pingueculitis, Photoelectric conjunctivitis, Oculorespiratory syndrome, Acute haemorrhagic conjunctivitis, Blebitis, Ligneous conjunctivitis, Noninfective conjunctivitis, Oculoglandular syndrome, Conjunctivitis fungal, Conjunctival suffusion.

b All cases of eosinophilia reported as TEAEs are included in the analysis. Cases associated with clinical symptoms are further described in the study CSR.

c Labeling subgroup of preferred terms included in the USPI for Dupixent.

Treatment-emergent AESIs

Systemic hypersensitivity reaction is the only category for which TEAEs were reported (dupilumab: 1; placebo: 2).

Other selected AE groupings

The overall incidence of events in other selected AE groupings was similar between dupilumab and placebo (10.5% and 11.5%). Conjunctivitis (either by broad, narrow, or conjunctivitis FDA cluster was mor frequently observed in dupilumab-treated participants as compared to placebo. Less participants in the dupilumab group compared to the placebo group experienced TEAEs of potential drug related hepatic disorders and injection site reactions.

Table 43. Number (%) of participants with treatment emergent AESIs and other selected AE grouping events by category and PT - Pooled safety population

Category Preferred Term n (%)	Placebo (N=157)	Dupilumab 300 mg Q2W (N=152)
Any treatment emergent AESI	2 (1.3)	1 (0.7)
Anaphylactic reactions (medically reviewed)	0	0
Systemic hypersensitivity reactions (medically reviewed)	2 (1.3)	1 (0.7)
Dermatitis allergic	0	1 (0.7)
Urticaria	2 (1.3)	0
Helminthic infections	0	0
Any severe type of conjunctivitis	0	0
Any severe type of blepharitis	0	0
Keratitis	0	0
Clinically symptomatic eosinophilia (or eosinophilia associated with clinical symptoms)	0	0
Pregnancy of a female participant entered in a study as well as pregnancy occurring in a female partner of a male participant entered in a study with IMP/NIMP	0	0

Category Preferred Term n (%)	Placebo (N=157)	Dupilumab 300 mg Q2W (N=152)
Significant ALT elevation	0	0
Symptomatic overdose with IMP	0	0
Symptomatic overdose with NIMP	0	0
Other selected AEs	18 (11.5)	16 (10.5)
Serious injection site reactions or severe injection site reactions that last longer than 24 hours	0	0
Severe or serious infection	3 (1.9)	2 (1.3)
COVID-19 pneumonia	0	1 (0.7)
Pelvic inflammatory disease	0	1 (0.7)
Pyelonephritis acute	0	1 (0.7)
COVID-19	1 (0.6)	0
Cellulitis	1 (0.6)	0
Sepsis	1 (0.6)	0
Drug-related hepatic disorder	3 (1.9)	0
Alanine aminotransferase increased	2 (1.3)	0
Gamma-glutamyltransferase increased	1 (0.6)	0
Injection site reaction	9 (5.7)	6 (3.9)
Injection site reaction	2 (1.3)	3 (2.0)
Injection site erythema	0	1 (0.7)
Injection site oedema	0	1 (0.7)
Injection site pain	5 (3.2)	1 (0.7)
Injection site pruritus	1 (0.6)	0
Injection site swelling	2 (1.3)	0
Malignancy	2 (1.3)	1 (0.7)
Papillary thyroid cancer	0	1 (0.7)
Cutaneous T-cell lymphoma	1 (0.6)	0
Hodgkin's disease	1 (0.6)	0
Large granular lymphocytosis	1 (0.6)	0
Suicidal behavior	0	0
Conjunctivitis (narrow)	2 (1.3)	6 (3.9)
Conjunctivitis	1 (0.6)	3 (2.0)
Conjunctivitis allergic	1 (0.6)	3 (2.0)
Conjunctivitis viral	1 (0.6)	0
Conjunctivitis (broad)	3 (1.9)	8 (5.3)
Conjunctivitis	1 (0.6)	3 (2.0)
Conjunctivitis allergic	1 (0.6)	3 (2.0)
Conjunctival hyperaemia	0	1 (0.7)
Foreign body sensation in eyes	0	1 (0.7)
Conjunctivitis viral	1 (0.6)	0
Eye pruritus	1 (0.6)	0
Conjunctivitis (FDA)[a]	2 (1.3)	6 (3.9)
Conjunctivitis	1 (0.6)	3 (2.0)
Conjunctivitis allergic	1 (0.6)	3 (2.0)
Conjunctivitis viral	1 (0.6)	0
Keratitis (FDA)[a]	0	0

AESI: Adverse event of special interest, PT: Preferred term, IMP: Investigational medicinal product, NIMP: Noninvestigational medicinal product

MedDRA 24.1

Category Preferred Term n (%)	Placebo (N=157)	Dupilumab 300 mg Q2W (N=152)

a Labeling subgroup of preferred terms included in the USPI for Dupixent.

n (%) = number and percentage of participants with at least one AESI/other AE grouping event during the entire treatment-emergent period.

Note: Table sorted by AESI/other AE grouping category and decreasing percentage of PT in dupilumab 300mg Q2W group within each category.

Anaphylactic reactions / systemic hypersensitivity (AESI)

No anaphylactic reactions were reported in the pooled safety population (Table 19 alt). Systemic hypersensitivity reactions (medically reviewed) were reported in 1 (0.7%) participant in the dupilumab group and 2 (1.3%) participants in the placebo group. None of the events were severe or serious nor did any event have multi-organ involvement. All events affected only the skin. All 3 participants were ADA-negative.

The dupilumab-treated participant who experienced an event of mild dermatitis allergic 12 days after the 12th IMP dose had a medical history of active mild AD. The symptoms were localized to facial and hand areas with no systemic symptoms reported. The IMP was continued unchanged and the participant recovered after receiving corrective treatment. The event was assessed by the Investigator as not related.

Hypersensitivity reactions reported in placebo participants were two events of urticaria. The first event was of mild intensity and reported as generalized urticaria. The event occurred 4 days after the 6th IMP dose, and involved the lower legs, arms and abdomen. No abnormal laboratory results or systemic symptoms were reported at the time of the event. The event was assessed as related to the IMP by the Investigator and led to permanent study intervention discontinuation. No corrective treatment was administered and the participant recovered. The second urticaria event was of moderate severity and reported on trunk and arms 11 days after the 3rd IMP dose. No permanent study intervention discontinuation was required and the event resolved after corrective treatment.

Injection site reactions (other selected AE groupings)

In the safety pool, events identified by high level term injection site reactions were reported in 6 (3.9%) participants in the dupilumab group and 9 (5.7%) participants in the placebo group. Of these, 10 participants (3 in the dupilumab group and 7 in the placebo group) only had 1 TEAE of injection site reaction during the study (of which 3 participants at Day 1). In both intervention groups, the incidence of events decreased over time.

No injection site reactions meeting the criteria of serious, or severe that lasted longer than 24 hours were reported in the pooled safety population.

Infections

Severe or serious infection (other selected AE groupings)

The incidence of severe or serious infections was low in both intervention groups (dupilumab: 2 [1.3%]; placebo: 3 [1.9%]). Most events (5/6) were unrelated, with one related event in the placebo group; none of the events led to permanent intervention discontinuation.

In the 2 dupilumab-treated participants, reported infections were all SAEs (see previous section above):

- severe **pyelonephritis acute** and **severe pelvic inflammatory**.
- moderate **COVID-19** pneumonia lasting 6 days.

For both participants, events were assessed as unrelated to IMP and resolved upon administration of corrective medications.

In placebo-treated participants, 2 serious and 1 nonserious events were reported, all of severe intensity.

- SAE of **COVID-19** (assessed as unrelated to the IMP; resolved with sequelae).
- SAE of **sepsis** (assessed as related to the IMP; the participant had not recovered from the event as of the study cut-off date).
- Non-serious event of severe **cellulitis** (assessed as unrelated to the IMP; resolved without sequelae after corrective treatment with oral antibiotics).

Severe conjunctivitis (AESI) and conjunctivitis events (other selected AE groupings)
No cases of severe conjunctivitis were reported for the pooled safety population.

The proportion of participants who experienced TEAEs of non-severe conjunctivitis based on the broad/narrow CMQs and conjunctivitis FDA cluster criteria was higher in the dupilumab group compared with the placebo group: 8 (5.3%) versus 3 (1.9%) participants using the broad CMQ, and 6 (3.9%) versus 2 (1.3%) participants using either the narrow CMQ or the conjunctivitis FDA cluster. The events captured only in the broad CMQ were foreign body sensation in eyes, conjunctival hyperaemia, and eye pruritus.

None of the events (broad CMQ) were serious or led to permanent study intervention discontinuation. Except 1 event of conjunctivitis allergic in a dupilumab-treated participant that was reported as resolving with corrective medication after 5 months from event onset all other events were resolved as of the cut-off date of the studies. Three events of conjunctivitis allergic and 1 event of conjunctivitis reported in the dupilumab group and 1 event (eye pruritus) in the placebo group were assessed as related to the IMP.

Table 44. Summary of participants with conjunctivitis (broad) - Pooled safety population

Conjunctivitis (broad)	Placebo (N=157)	Dupilumab 300 mg Q2W (N=152)
Participants with any specific TEAE	3 (1.9)	8 (5.3)
Participants with any severe TEAE	0	0
Participants with any SAE (regardless of treatment emergent status)	0	0
Participants with any treatment-emergent SAE	0	0
Participants with any AE leading to death	0	0
Participants with any TEAE leading to permanent study intervention discontinuation	0	0
Participants with any TEAE related to IMP reported by investigator	1 (0.6)	4 (2.6)
Exposure adjusted TEAE summary		
Total time at risk[a] (in 100 PY)	0.88	0.96
Number of Participants with any TEAE per 100 PY[b]	3.41	8.34
Number of TEAEs	4	9
Number of TEAE per 100 PY[c]	4.45	9.09
Maximal intensity		
Moderate	0	2 (1.3)
Severe	0	0
Corrective treatment		
Yes	1 (0.6)	8 (5.3)
Outcome		
Fatal	0	0
Not recovered/Not resolved	0	0
Recovered	3 (1.9)	7 (4.6)
Recovered with sequelae	0	0
Recovering	0	1 (0.7)
Unknown	0	0
Time to onset of first TEAE (days)		
Number	3	8
Mean (SD)	16.7 (26.3)	76.0 (75.6)
Median	2.0	52.5
Q1 ; Q3	1.0 ; 47.0	22.5 ; 114.5
Min ; Max	1 ; 47	8 ; 221
Kaplan-Meier estimates for probability of a Participant with ≥1 TEAE (95% CI) up to		
12 weeks	0.019 (0.005 to 0.051)	0.040 (0.016 to 0.080)
24 weeks	0.019 (0.005 to 0.051)	0.046 (0.020 to 0.088)
Hazard ratio vs. Placebo (95% CI)[d]		2.62 (0.69 to 9.89)
Average duration of TEAEs (days)[e]		
Number	3	7
Mean (SD)	4.3 (3.2)	17.1 (10.9)
Median	3.0	14.0
Q1 ; Q3	2.0 ; 8.0	11.0 ; 29.0
Min ; Max	2 ; 8	3 ; 35
Average duration of TEAEs [n(%)]		
>0 to ≤2 days	1 (0.6)	0

Conjunctivitis (broad)	Placebo (N=157)	Dupilumab 300 mg Q2W (N=152)
>2 to ≤7 days	1 (0.6)	1 (0.7)
>7 days to ≤1 month	1 (0.6)	5 (3.3)
>1 to ≤3 months	0	1 (0.7)
>3 to ≤6 months	0	0
>6 months	0	0
Cumulative duration of TEAEs (days)[f]		
Number	3	7
Mean (SD)	7.0 (7.8)	22.0 (22.1)
Median	3.0	14.0
Q1 ; Q3	2.0 ; 16.0	11.0 ; 29.0
Min ; Max	2 ; 16	3 ; 69
Cumulative duration of TEAEs [n(%)]		
>0 to ≤2 days	1 (0.6)	0
>2 to ≤7 days	1 (0.6)	1 (0.7)
>7 days to ≤1 month	1 (0.6)	5 (3.3)
>1 to ≤3 months	0	1 (0.7)
>3 to ≤6 months	0	0
>6 months	0	0
Primary System Organ Class Preferred Term n (%)		
Infections and infestations		
Conjunctivitis	1 (0.6)	3 (2.0)
Conjunctivitis viral	1 (0.6)	0
Eye disorders		
Conjunctivitis allergic	1 (0.6)	3 (2.0)
Conjunctival hyperaemia	0	1 (0.7)
Foreign body sensation in eyes	0	1 (0.7)
Eye pruritus	1 (0.6)	0

TEAE: Treatment emergent adverse event; SAE serious adverse event

MedDRA 24.1

a Sum of total time-to-first TEAE and total-to-censoring.

b Number of participants with any TEAE divided by total time at risk in 100 PY

c Number of TEAEs divided by total patient-years of the corresponding observational period in 100 PY

d Estimated based on PH cox regression model with actual study intervention group and study as covariates.

e Average duration is the average over all occurrences that resolved.

f Cumulative duration is the total duration of the event over time.

Severe blepharitis (AESI)

No events of severe blepharitis were reported in the safety pooled population.

Keratitis (AESI and other selected AE groupings)

No events of severe keratitis were identified in the safety pooled population, based on CMQ search AESI or keratitis FDA cluster criteria (other selected AE groupings).

Skin infections (excluding herpetic infections)

The incidence of skin infections (excluding herpetic infections) identified in the safety pool based on defined criteria was lower in the dupilumab group (7 [4.6%] participants) compared to the placebo

group (14 [8.9%] participants). Two participants in the dupilumab group and 1 participant in the placebo group had past or current history of AD. None of the reported events were serious or led to permanent intervention discontinuation. The only severe infection was cellulitis, a nonserious event reported in a placebo-treated participant that was considered as unrelated to the IMP and resolved without sequelae upon corrective therapy.

The most frequently reported PT pertaining to skin infections was folliculitis (1 [0.7%] versus 4 [2.5%] in the dupilumab and placebo groups, respectively), followed by cellulitis (1 [0.7%] versus 2 [1.3%]), and dermatitis infected and postoperative wound infection (both reported in 0 participants in the dupilumab group versus 2 [1.3%] participants in the placebo group). Two participants in the dupilumab group and 5 participants in the placebo group had multiple skin infections. Of the total number of participants reporting skin infections, 12 were treated with systemic antibiotics (4 in the dupilumab group and 8 in the placebo group) and 1 placebo participant was treated with systemic antifungals for a fungal skin infection.

Herpes infections

In the safety pool, 5 (3.3%) participants in the dupilumab group and 0 participants in the placebo group experienced events within the herpes viral infections HLT. The 5 cases in the dupilumab group include PTs of genital herpes simplex, herpes zoster, ophthalmic herpes zoster (reported by 1 participant each), and oral herpes (reported by 2 participants).

None of the events were serious and all were of moderate intensity, except for the event of herpes zoster which was of mild intensity. Both events of oral herpes were considered related to IMP by the Investigator and occurred in participants with a medical history of herpes infections. None of the events required permanent IMP discontinuation.

All participants had recovered with corrective treatment after a duration of 6 to 11 days, except for the participant with the event of ophthalmic herpes zoster (which occurred approximately 3 months after the 13th IMP dose) who had recovered after a duration of 36 days. The participant who experienced the event of genital herpes simplex (11 days after the 9th IMP dose) had a medical history of genital herpes and AD. None of the other participants with TEAEs of herpes infection had a past or current medical history of AD. The participant who experienced an event of herpes zoster (on the day of the 9th IMP dose) had no medical history of herpes infections. Among PN participants there were no reported cases of eczema herpeticum.

Helminthic infection (AESI)

No treatment-emergent helminthic infections were reported in the pooled safety population.

Malignancy

Malignancy (other selected AE groupings)

In the safety pool, a total of 3 malignancies were reported; 1 (0.7%) and 2 (1.3%) participants in the dupilumab and placebo groups, respectively. All events were reported as SAE and are also described in the respective paragraphs above. None of the events were assessed by the Investigator as related to the IMP.

1. In the dupilumab group, an SAE of **papillary thyroid cancer** was reported in a participant with a history of thyroid nodule. The event did not lead to permanent intervention discontinuation and had not resolved as of the time of the study data cut-off.

2. In the placebo group, a participant developed an SAE of **Hodgkin's disease**, which required IMP discontinuation and administration of corrective treatment. As of the cut-off date of the study the participant had not recovered.
3. The second placebo-treated participant developed malignancies reported **cutaneous T-cell lymphoma** and **large granular lymphocytosis**.

Other events

Significant ALT elevation (AESI) and potential drug-related hepatic disorder (other selected AE groupings)

No cases of significant ALT elevation (ALT >5 x ULN in participants with baseline ALT ≤2 x ULN or ALT >8 x ULN if baseline ALT >2 x ULN) (AESI) were reported in the safety pooled population. There were no cases meeting Hy's law criteria (ALT >3 × ULN and total bilirubin >2 × ULN).

Three (1.9%) participants in the placebo group reported potential drug related hepatic disorder while non was observed in the dupilumab group. All 3 placebo-treated participants reported an increase in hepatic enzymes (i.e. alanine aminotransferase increased and gamma-glutamyltransferase). All three events were nonserious and of mild or moderate intensity, none led to permanent intervention discontinuation or were assessed as related to the IMP by the Investigator. ALT levels returned back to normal for both participants. As of the cut-off dates of the studies the reported outcomes for the 2 events of ALT increase were 'resolving' and 'resolved', respectively; for the GGT increase the reported outcome was 'not resolved', noting that the participant refused to have laboratory tests rechecked. No trigger factors were reported for these events in any of the participants.

Musculoskeletal and connective tissue disorders (SOC)

TEAEs in the SOC Musculoskeletal and connective tissue disorders were more frequently reported in the dupilumab group as compared to the placebo group (15 [9.9%] versus 7 [4.5%] participants). Of note, a higher number of participants (5 [3.3%]) experienced TEAEs within the Joint disorders HLGT in the dupilumab group as compared to placebo (1 [0.6%]) participants. PTs under the Joint disorders HLGT were of a single occurrence except for arthralgia, which was reported in 2 (1.3%) participants in the dupilumab group versus 0 participants in the placebo group.

For 18 out of the 22 participants, events of Musculoskeletal and connective tissue disorders were considered not related to IMP by the Investigator. Of the 4 related events, 2 were reported in dupilumab-treated participants (arthralgia and joint stiffness) and 2 in placebo (back pain and myalgia). Both events of arthralgia were nonserious and mild, and none led to permanent study intervention discontinuation. The event considered related to IMP by the Investigator occurred in a participant with history of type 2 diabetes mellitus, and no history of joint pain or atopic disease. No corrective treatment was started and the event had not recovered as of the time of the study data cut-off. This participant also reported TEAEs of myalgia and sciatica, both not resolved by the study data cut-off. The Investigator assessed myalgia and arthralgia as related, and sciatica as not related.

Table 45. Number (%) of participants with TEAEs by primary SOC Musculoskeletal and connective tissue disorders

Primary System Organ Class Preferred Term n (%)	Placebo (N=157)	Dupilumab 300 mg Q2W (N=152)
Musculoskeletal and connective tissue disorders	7 (4.5)	15 (9.9)
Myalgia	1 (0.6)	3 (2.0)
Arthralgia	0	2 (1.3)
Back pain	1 (0.6)	2 (1.3)
Bone pain	0	1 (0.7)
Joint stiffness	0	1 (0.7)
Musculoskeletal chest pain	0	1 (0.7)
Musculoskeletal pain	1 (0.6)	1 (0.7)
Neck pain	0	1 (0.7)
Oligoarthritis	0	1 (0.7)
Osteoporosis	0	1 (0.7)
Spinal osteoarthritis	0	1 (0.7)
Spinal retrolisthesis	0	1 (0.7)
Synovial cyst	0	1 (0.7)
Tenosynovitis	1 (0.6)	1 (0.7)
Inguinal mass	1 (0.6)	0
Muscle contracture	1 (0.6)	0
Rotator cuff syndrome	1 (0.6)	0

Cardiovascular events

Serious TEAEs in the Cardiac disorders SOC, Nervous system disorders SOC, and Vascular disorders SOC, or with a PT of pulmonary embolism, and any event with an outcome of death, regardless of cause or timing, were reviewed. Cardiovascular thromboembolic events (cardiovascular deaths, non-fatal myocardial infarctions, and non-fatal strokes) were reported in 0 participants in the dupilumab group and 2 (1.3%) participants in the placebo group (SAEs of acute myocardial infarction for both cases).

Clinically symptomatic eosinophilia (AESI)

No clinically symptomatic eosinophilia events were reported in the safety pooled population.

Pregnancy and partner pregnancy (AESI)

No pregnancies or partner pregnancies were reported in the safety pool.

Suicidal behavior (other selected AE groupings)

No events of suicidal behavior were reported in the safety pool.

Adverse drug reactions

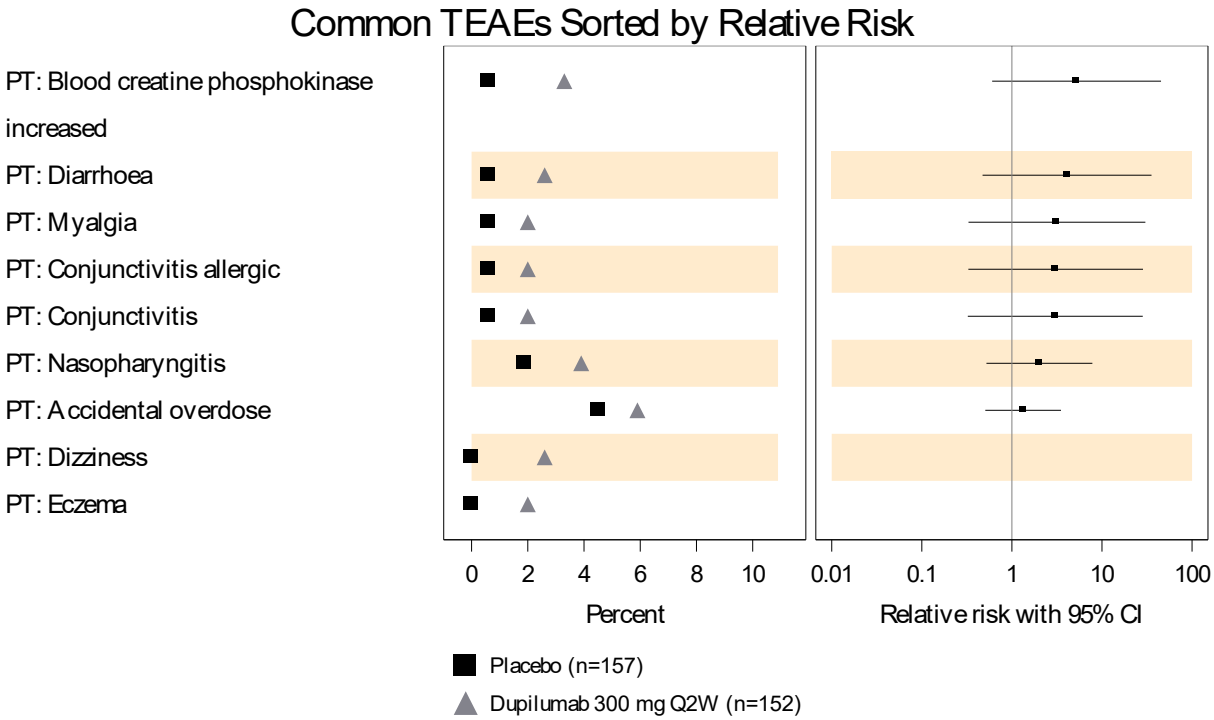
The primary assessment for ADRs was conducted on the pooled safety population, comprised of all participants in the 2 pivotal studies EFC16460 and EFC16459 who received at least one dose of study intervention (N=309). The analysis was based on individual PTs.
The qualification of a TEAE PT as an ADR is based on the following quantitative and qualitative criteria:

Quantitative Criteria: The PTs with incidence ≥2% in the dupilumab group, a difference of ≥1% versus the placebo group, and with the lower bound of the 95% CI of relative risk >1 compared to placebo.

Qualitative Criteria: Medical judgement was applied to confirm the PTs which met quantitative criteria as ADRs. The seriousness, severity, outcome of the TEAE and impact on IMP administered were also considered.

Selected AEs/AE grouping which have been previously established as ADRs for other approved indications (AD and/or asthma and/or CRSwNP) were assessed for a numerical imbalance between groups. None of the PTs met the quantitative ADR criteria (≥2% incidence with ≥1% difference and lower bound of the 95% CI of relative risk >1).

Figure 33. Forest plot of relative risk ratio (95% CI) of TEAEs with PT ≥2% in dupilumab 300mg Q2W group and difference ≥1% versus placebo group - Pooled safety population



Confidence intervals are Cochran-Mantel-Haenszel stratified by study

Amongst ADRs observed in dupilumab-treated participants in the AD and/or asthma and/or CRSwNP programs, PTs of conjunctivitis and conjunctivitis allergic evaluated from the perspective of the FDA conjunctivitis cluster and the narrow CMQ were considered as ADRs for PN based on an imbalance between dupilumab and placebo in the PN safety pool, and in the absence of an alternative etiology. All other AEs/AE groupings identified as ADRs for previous indications were not observed in the PN safety pool or were reported with a higher incidence in the placebo group, or were observed in a low number of dupilumab-treated participants in PN studies and therefore not considered to be ADRs for the PN program.

In summary, ADRs identified for the PN indication are PTs of conjunctivitis and conjunctivitis allergic.

Laboratory findings

Hematology

Red blood cells, platelets and coagulation

No relevant changes from baseline mean values were observed over time for the hematology parameters hemoglobin, hematocrit, RBCs, platelets in the dupilumab and placebo groups.

The overall number of participants with potentially clinically significant abnormalites for RBC, platelets or coagulation during the TEAE period (regardless of baseline values) was low and similar across intervention groups, except for PCSA of increased hematocrit (≥0.55 v/v [male]; ≥0.5 v/v [female]) which was less frequently reported in the dupilumab group compared to the placebo group (6.6% versus 15.0%, respectively).

No participants had PCSAs related to RBC, platelets or coagulation that were considered SAEs or were TEAEs that led to permanent intervention discontinuation.

White blood cells

No relevant mean changes from baseline were observed over time for white blood cell parameters (WBC count, neutrophils, lymphocytes, monocytes, basophils and eosinophils).

The overall number of participants with PCSAs for WBC parameters (regardless of baseline values) during the TEAE period was generally balanced across intervention groups, with the exception of increased basophils >0.1 x 10^9/L, reported with a higher incidence in the dupilumab group as compared to the placebo group (10.6% versus 5.9% participants). The highest on-treatment mean increase in basophils from baseline was 0.015 x 10^9/L in the dupilumab group. The most frequently reported PCSA in either intervention group was for increased monocytes >0.7 x 109/L (21.9% in the dupilumab group and 24.2% in the placebo group.

No participants had PCSAs related to changes in WBC parameters that were serious TEAEs or were TEAEs that led to permanent intervention discontinuation. One participant in the placebo group reported an SAE of large granular lymphocytosis; this participant had a reported PCSA for low WBCs during the study intervention period.

Table 46. White blood cells-Number of participants with abnormality (PCSA) during the treatment-emergent period - Pooled safety population

Laboratory parameter PCSA criteria n/N1 (%)	Placebo (N=157)	Dupilumab 300 mg Q2W (N=152)
Leukocyte Count (WBC)		
< 3 * 10^9/L (Non-Black); < 2 * 10^9/L (Black)	5/153 (3.3)	2/152 (1.3)
≥ 16 * 10^9/L	1/153 (0.7)	0/152
Neutrophils		
< 1.5 * 10^9/L (Non-Black); < 1 * 10^9/L (Black)	6/153 (3.9)	9/151 (6.0)
Lymphocytes		
> 4 * 10^9/L	0/153	0/151
Monocytes		
> 0.7 * 10^9/L	37/153 (24.2)	33/151 (21.9)
Basophils		
> 0.1 * 10^9/L	9/153 (5.9)	16/151 (10.6)
Eosinophils		
> 0.5 * 10^9/L or > ULN (if ULN ≥ 0.5 * 10^9/L)	16/153 (10.5)	17/151 (11.3)

TE: Treatment emergent, PCSA: Potentially clinically significant abnormality

The number (n) represents the subset of the total number of participants who met the criterion in question at least once during the TE period.

The denominator (/N1) for each parameter within a intervention group is the number of participants for the intervention group who had that parameter assessed during the TE period

For PCSA including condition based only on change from baseline, the denominator is restricted to participants having a baseline and at least one post-baseline value during the TE period

Special Assessment of blood eosinophils

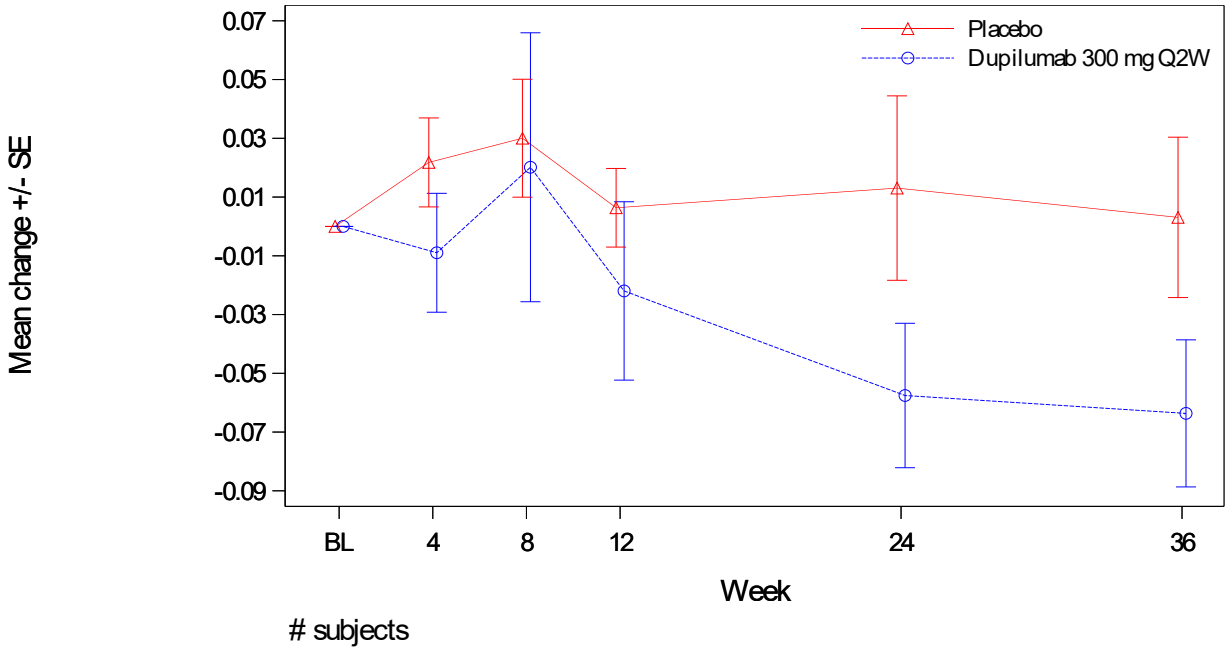
In the safety pooled population, mean (SD) blood eosinophil counts at baseline were 0.318 (0.340) x 10^9/L and 0.259 (0.202) x 10^9/L in the dupilumab and the placebo groups, respectively. No significant changes in the mean blood eosinophil values were observed in either groups over the intervention period. A minimal transient increase from baseline in blood eosinophils was observed at Week 8 in both the dupilumab and placebo groups (mean change from baseline + 0.02 x 10^9/L and + 0.03 x 10^9/L,

respectively). A slight decrease in mean and median eosinophil count from baseline to Week 24 was observed in the dupilumab group (-0.058 x 10^9/L and -0.040 x 10^9/L, respectively).

A lower incidence was observed in the dupilumab group (5.7%) compared to the placebo group (9.4%) for increased eosinophils >0.5 x 10^9/L or >ULN (if ULN ≥0.5 x 10^9/L) in participants with normal/missing values. Similar percentages were reported for the total number of participants of the overall safety pool population, regardless of baseline values.

Post-baseline blood eosinophil count ≥5 x 10^9/L was reported in 1 (0.7%) participant in the dupilumab group versus none in the placebo group. No events of clinically symptomatic eosinophilia were reported. The 1 participant in the dupilumab group with eosinophil count ≥5 x 10^9/L was observed with a post-baseline peak blood eosinophil count of 6.01 x 10^9/L on Day 62 (Week 8); this event was not reported as a TEAE. The value returned to normal at the next unscheduled visit on Day 70 (0.12 x 10^9/L), was still slightly elevated at EOT visit (1.06 x 10^9/L) and was within normal levels at end of study visit. This participant did not have history of atopic conditions and had normal eosinophil counts at screening. This participant also reported TEAEs of pharyngitis and headache (3 episodes, 2 of which occurred around the time of eosinophil elevation); these events were not considered related.

Figure 34. Eosinophils (10^9/L): Mean change (+/- SE) from baseline - Pooled safety population



Only on-treatment values are included, except for the Week 36 visit

Clinical Chemistry

Metabolic parameters

No relevant mean changes from baseline were observed over time for metabolic parameters (cholesterol, total protein, and creatine phosphokinase) in the dupilumab and placebo groups in the safety pool.

The proportion of participants with PCSAs for metabolic parameters (regardless of baseline values) during the TEAE period was similar between the 2 intervention groups, with the exception of increased glucose ≥200 mg/dL (unfasted) or ≥126 mg/dL (fasted), reported with a higher incidence in the dupilumab group as compared to the placebo group (4.6% versus 1.9% participants). All of these participants except 1 in the placebo group were diabetic or had diabetes during the study.

The most frequently reported PCSA was for decreased glucose ≤70 mg/dL and LLN, which had a similar incidence between intervention groups (7.9% in the dupilumab group and 7.1% in the placebo group).

No participants had PCSAs related to changes in metabolic parameters that were serious TEAEs or were TEAEs that led to permanent intervention discontinuation in the safety pool.

An imbalance at PT level was observed for participants with TEAEs of blood creatine phosphokinase increased (dupilumab: 3.3%; placebo: 0.6%). The incidence of participants with PCSAs were similar between intervention groups both for increased CPK >3 ULN (3.3% and 4.5% in dupilumab and placebo participants, respectively) and increased CPK >10 ULN (0.7% versus 1.3%). None of the events reported in the dupilumab group were severe, serious, or led to permanent IMP discontinuation. For 1 participant in the dupilumab group an increase of >10 x ULN in CPK levels was seen at Week 24 (EOT visit). This increase was not reported as an adverse event and CPK values returned to normal within one week.

Electrolytes

No relevant mean changes from baseline in electrolytes (sodium, potassium, chloride or bicarbonate) were observed in the dupilumab and placebo groups in the safety pool.

The number of participants with PCSAs was overall low and balanced across intervention groups for all electrolyte parameters (regardless of baseline values) during the TEAE period. The most frequently reported PCSA was decreased sodium, reported with a lower percentage in the dupilumab group compared to the placebo group (0% and 1.9%, respectively).

No participants had PCSAs related to changes in electrolytes that were serious TEAEs or were TEAEs that led to permanent intervention discontinuation in either group of the safety pool.

Renal function

No relevant mean changes from baseline were observed for renal function parameters (creatinine, creatinine clearance, uric acid, and blood urea nitrogen) across dupilumab and placebo groups in the safety pool.

The proportion of participants with PCSAs for renal function parameters (regardless of baseline values) was generally comparable between intervention groups during the TEAE period except for PCSAs for creatinine clearance ≥30 - <60 mL/min (moderate decrease in GFR), which were reported with a higher incidence in the dupilumab group as compared to the placebo group (22.2% versus 8.3%, respectively) among the participants with baseline creatinine clearance ≥60 - <90 mL/min (mild decrease in GFR).

In addition, 1 participant in the placebo group with a PCSA for decreased creatinine clearance <15 mL/min (end stage renal disease) on Day 57 (9 mL/min) reported a nonserious TEAE of mild blood creatinine increase on the same day. The event did not lead to treatment intervention discontinuation and was considered not related to the IMP by the Investigator. The event resolved on Day 63 without corrective treatment, with creatinine clearance of 221 mL/min and all the other renal function parameters demonstrating normal values.

No participants had PCSAs for abnormalities in renal function parameters that were considered serious TEAEs or were TEAEs that led to permanent intervention discontinuation.

The most frequently reported PCSA in both intervention groups was increased uric acid >6.86 mg/dL, with a similar incidence in the dupilumab and placebo groups (25.7% and 27.3%, respectively).

Liver function
No relevant mean changes from baseline were observed for liver function parameters (ALT, AST, ALP, total bilirubin, and albumin) in the dupilumab and placebo intervention groups during the intervention period in the safety pool, except for LDH.

A decrease from baseline in mean LDH was observed in the dupilumab group over time up to Week 12 (mean [SD] change from baseline: -0.094 [0.134] x ULN), and was sustained up to Week 24 (mean [SD] change from baseline: -0.089 [0.137] x ULN). Mean (SD) change from baseline to last on-treatment assessment was -0.087 [0.134] x ULN. Mean LDH values remained relatively unchanged in the placebo group throughout the study.

The number of participants with PCSAs for liver function parameters was low and similar between intervention groups regardless of their baseline PCSA status. No participants experienced a PCSA that met the Hy's law criteria (ALT >3 x ULN and total bilirubin >2 x ULN).

No participants had PCSAs for abnormalities in liver function parameters that were considered serious TEAEs or were TEAEs that led to permanent intervention discontinuation.

No participants reported PCSAs that met AESI criteria for significant ALT elevation; 3 participants, all in the placebo group, reported PCSAs that met other selected AE groupings criteria for drug-related potential hepatic disorders.

Urinalysis
The percentage of participants with positive results for urine protein in the dipstick urinalysis was generally similar between intervention groups during the 24-week intervention period, except at Week 8 (7.7% participants in the dupilumab group versus 12.9% participants in the placebo group).

Vital signs

Blood pressure and orthostatic changes
No relevant mean changes from baseline were observed over time for vital sign parameters (SBP, DBP, HR, respiratory rate, body temperature and weight) across intervention groups in the safety pool.

The proportion of participants with PCSAs for SBP or HR was generally low and balanced between the intervention groups. For diastolic blood pressure (≥110 mmHg and increase from baseline ≥10 mmHg) and weight (≥5% decrease from baseline) the incidence of PCSAs was higher in the dupilumab group compared with the placebo group (2.6% versus 0.7%, and 10.1% versus 7.9% for the 2 parameters, respectively). Among these 5 participants with PCSAs in DBP, 2 in the dupilumab group had history of hypertension. No headache or dizziness were reported for any of these patients around the day when the vital sign measurement was taken.

No participants had TEAEs of abnormalities in vital signs that were considered serious or that led to permanent intervention discontinuation.

Electrocardiogramm
In studies EFC16460 and EFC16459 ECGs were performed locally and at screening (V1) and Week 24 (V6). These data were not pooled for safety analysis and were reported separately.

QTc Fridericia >480 msec was reported at Week 24 in 2/70 (2.9%) participants in the dupilumab group versus 0% in the placebo group in EFC16460, and in 1/73 (1.4%) and 2/67 (3.0%) participants in the dupilumab and placebo group, respectively, in EFC16459. In EFC16459, 1 placebo-treated participant

with an active medical condition of hypothyroidism was observed with increased QTcF >500 msec. The participant had baseline QTcF of 442 msec and the QTcF at EOT (14 days after the 13th IMP dose) was 528 msec, with an increase from baseline of 86 msec.

No participant in either study had TEAEs related to ECG abnormalities that were reported as SAEs or TEAEs leading to permanent study intervention discontinuation.

Immunogenicity

Incidence and characterization of anti-dupilumab antibodies
In the dupilumab group, 14 (9.8%) participants were ADA-positive while 5 (3.4%) ADA-positive participants were reported in the placebo group. Treatment-emergent ADA responses were observed in 11 (7.7%) participants in the dupilumab group and 3 (2.0%) in the placebo group. Of the total number of participants with treatment-emergent ADA responses, 2 (1.4%) in the dupilumab group versus none in the placebo group developed persistent responses. No participants had a treatment boosted ADA response. The majority of ADA-positive participants (8 [5.6%] participants in the dupilumab group and 3 [2.0%] in the placebo group) had low (<1000) ADA titer responses, with 3 (2.1%) dupilumab-treated participants versus none in the placebo group who exhibited moderate titer response (1000-10.000). There were no participants with high titer (>1000) responses. Positive NAb responses were observed in 4 (2.8%) participants in the dupilumab group and 2 (1.4%) participants in the placebo group. Among the NAb positive participants, 3 participants in the dupilumab group exhibited moderate titer ADA responses while the remaining participant had a low titer response.

Further details on ADA responses with regard to clinical pharmacodynamics and clinical efficacy can also be found in Section 2.4.2 and 2.5.2.

Association of anti-dupilumab antibodies to adverse events
In participants with treatment-emergent ADA, the proportion of those who had at least 1 TEAE was similar across intervention groups (63.6% in the dupilumab group and 66.7% in the placebo group). Among ADA-negative participants, a higher percentage of dupilumab-treated participants compared to placebo-participants reported TEAEs (64.4% versus 56.3). In treatment-emergent ADA positive participants, there was 1 SAE reported in a dupilumab participant (interstitial lung disease), occurring prior to testing positive for ADA) and no TEAEs leading to permanent intervention discontinuation. The SOCs with the most frequently reported events in the ADA-positive population were similar to those observed in the overall pooled safety population, except for Musculoskeletal and connective tissue disorders, which showed a numerical imbalance between groups in treatment emergent ADA participants (3 [27.3%] participants in the dupilumab group versus none in the placebo group).

In participants positive for NAb, 1 participant in each group experienced TEAEs: uterine leiomyoma and urticaria were reported in the same participant in the dupilumab group and headache was reported in 1 participant in the placebo group. The TEAE of urticaria was not associated with systemic symptoms and occurred after the first identified ADA positive response; the event was considered by the Investigator to be related to the IMP although there was a possible exposure to a food allergen as well.

Overall, the number of ADA-positive and Nab-positive participants is low. ADA formation did not appear to have any meaningful impact on the safety of dupilumab.

Safety in special populations

The incidence of TEAEs, SAEs, TEAEs leading to permanent intervention discontinuation, and AESIs/other selected AE groupings was analysed in subgroups based on the participant's demographics

and other baseline characteristics (age, gender, race, ethnicity, baseline weight, and baseline BMI) and the participant's PN disease characteristics.

Demographics and other baseline characteristics

Incidence of TEAEs were compared between dupilumab and placebo groups across all subgroups based on demographics and other baseline characteristics and were comparable with the overall safety population.

Table 47. Incidence of participants with a TEAE and relative risk ratio (95% CI) for dupilumab 300mg Q2W versus placebo within each level of demographic subgroup factors - Pooled safety population

Subgroup	Placebo (N=157)	Dupilumab 300 mg Q2W (N=152)	Relative risk ratio (95% CI)
Age (years)			
<65	73/133 (54.9)	72/115 (62.6)	1.13 (0.92 to 1.39)
≥65	16/24 (66.7)	25/37 (67.6)	1.02 (0.71 to 1.46)
Age (years)			
≥18-<65	73/133 (54.9)	72/115 (62.6)	1.13 (0.92 to 1.39)
≥65-<75	10/17 (58.8)	19/29 (65.5)	1.10 (0.67 to 1.79)
≥75	6/7 (85.7)	6/8 (75.0)	0.91 (0.56 to 1.47)
Gender			
Male	37/59 (62.7)	33/49 (67.3)	1.07 (0.81 to 1.42)
Female	52/98 (53.1)	64/103 (62.1)	1.16 (0.92 to 1.47)
Race			
Caucasian/White	52/92 (56.5)	47/82 (57.3)	1.02 (0.79 to 1.32)
Black/of African descent	5/8 (62.5)	11/11 (100)	1.38 (0.96 to 2.00)
Asian/Oriental	29/52 (55.8)	34/54 (63.0)	1.11 (0.81 to 1.52)
Others	3/5 (60.0)	5/5 (100)	1.67 (0.81 to 3.41)
Ethnicity			
Hispanic or Latino	17/31 (54.8)	16/28 (57.1)	1.04 (0.67 to 1.63)
Non-Hispanic or Latino	72/126 (57.1)	81/124 (65.3)	1.14 (0.93 to 1.39)
Baseline weight			
<60 kg	18/34 (52.9)	18/33 (54.5)	1.06 (0.69 to 1.64)
≥60- < 90 kg	55/98 (56.1)	59/92 (64.1)	1.13 (0.90 to 1.42)
≥90 kg	16/24 (66.7)	20/27 (74.1)	1.11 (0.76 to 1.62)
Baseline BMI			
<25 kg/m^2	41/70 (58.6)	28/53 (52.8)	0.92 (0.67 to 1.27)
≥25- < 30 kg/m^2	25/51 (49.0)	38/53 (71.7)	1.45 (1.05 to 1.99)
≥30 kg/m^2	21/33 (63.6)	31/46 (67.4)	1.05 (0.75 to 1.47)
Region[a]			
Asia	24/46 (52.2)	29/47 (61.7)	1.16 (0.82 to 1.65)
Latin America	17/29 (58.6)	16/25 (64.0)	1.08 (0.71 to 1.65)
East Europe	10/16 (62.5)	10/17 (58.8)	0.95 (0.55 to 1.64)
Western Countries	38/66 (57.6)	42/63 (66.7)	1.16 (0.89 to 1.52)
Territory[b]			

Subgroup	Placebo (N=157)	Dupilumab 300 mg Q2W (N=152)	Relative risk ratio (95% CI)
North America	19/32 (59.4)	22/28 (78.6)	1.30 (0.93 to 1.83)
European Union & United Kingdom	22/39 (56.4)	23/41 (56.1)	0.98 (0.67 to 1.44)
Rest of World	48/86 (55.8)	52/83 (62.7)	1.11 (0.87 to 1.42)

Confidence intervals are Cochran-Mantel-Haenszel stratified by study

BMI: Body Mass Index; TEAE: treatment emergent adverse event.

n (%) = number and percentage of participants with at least one TEAE out of the number of participants within the study intervention group and subgroup level

a Asia: Japan, China, South Korea, Taiwan; Eastern Europe: Russia, Hungary; Latin America: Argentina, Mexico, Chile; Western Countries: USA, Canada, France, Italy, Portugal, Spain, and UK.

b North America: USA, Canada; European Union and United Kingdom: France, Italy, Portugal, Spain, Hungary, and UK; Rest of World: Russia, Japan, China, Taiwan, South Korea, Argentina, Chile, and Mexico.

PN baseline characteristics

Incidence of TEAEs were compared between dupilumab and placebo groups across all subgroups based on baseline PN disease characteristics and were comparable with the overall safety population.

Table 48. Incidence of participants with a TEAE and relative risk ratio (95% CI) for dupilumab 300mg Q2W versus placebo within each level of disease characteristic subgroup factors - Pooled safety population

Subgroup	Placebo (N=157)	Dupilumab 300 mg Q2W (N=152)	Relative risk ratio (95% CI)
History of atopy			
atopic	36/68 (52.9)	44/66 (66.7)	1.22 (0.93 to 1.60)
non-atopic	53/89 (59.6)	53/86 (61.6)	1.04 (0.82 to 1.32)
Baseline IGA PN-S			
3	59/102 (57.8)	73/102 (71.6)	1.23 (1.01 to 1.51)
4	30/54 (55.6)	24/50 (48.0)	0.86 (0.59 to 1.26)
Duration of PN[a]			
<3 years	44/77 (57.1)	50/71 (70.4)	1.24 (0.97 to 1.58)
≥3 years	45/80 (56.3)	47/81 (58.0)	1.02 (0.78 to 1.33)
Age of PN onset:			
<30 years	19/34 (55.9)	19/32 (59.4)	1.03 (0.66 to 1.61)
≥30 years	70/123 (56.9)	78/120 (65.0)	1.15 (0.94 to 1.41)
Age of PN onset:			
<median	43/79 (54.4)	44/70 (62.9)	1.11 (0.85 to 1.46)
≥median	46/78 (59.0)	53/82 (64.6)	1.11 (0.87 to 1.42)
Disseminated or localized PN lesions			
>2 BSA	89/156 (57.1)	96/151 (63.6)	1.11 (0.93 to 1.33)
≤2 BSA	0/1	1/1 (100)	NC (NC to NC)
Current diagnosis of AD			
yes	4/7 (57.1)	5/6 (83.3)	2.13 (0.77 to 5.88)
no	85/150 (56.7)	92/146 (63.0)	1.11 (0.92 to 1.34)
Stable use of TCS/TCI[b]			

Subgroup	Placebo (N=157)	Dupilumab 300 mg Q2W (N=152)	Relative risk ratio (95% CI)
yes	53/90 (58.9)	59/91 (64.8)	1.09 (0.87 to 1.38)
no	36/67 (53.7)	38/61 (62.3)	1.16 (0.87 to 1.56)
Antidepressant use at baseline			
yes	8/17 (47.1)	9/16 (56.3)	1.18 (0.61 to 2.27)
no	81/140 (57.9)	88/136 (64.7)	1.12 (0.93 to 1.34)
Phototherapy use			
yes	7/13 (53.8)	8/12 (66.7)	1.20 (0.64 to 2.24)
no	82/144 (56.9)	89/140 (63.6)	1.11 (0.92 to 1.34)
History of use of systemic immunosuppressant			
yes	30/56 (53.6)	40/58 (69.0)	1.24 (0.93 to 1.65)
no	59/101 (58.4)	57/94 (60.6)	1.04 (0.83 to 1.31)
History of use of systemic antipruritic medications			
yes	44/78 (56.4)	56/84 (66.7)	1.16 (0.91 to 1.48)
no	45/79 (57.0)	41/68 (60.3)	1.08 (0.83 to 1.41)
History of use of systemic immunosuppressant or antipruritic			
yes	53/97 (54.6)	69/102 (67.6)	1.22 (0.98 to 1.53)
no	36/60 (60.0)	28/50 (56.0)	0.94 (0.68 to 1.29)

IGA PN-S: Investigator's global assessment for prurigo nodularis - stage; AD: Atopic dermatitis; TEAE: treatment emergent adverse event.

Confidence intervals are Cochran-Mantel-Haenszel stratified by study

n (%) = number and percentage of participants with at least one TEAE out of the number of participants within the study intervention group and subgroup level

a Derived as (Year of randomization - Year of first diagnosis of PN) + (month of randomization - month of first diagnosis of PN)/12.

b 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.

SAEs, TEAEs leading to permanent intervention discontinuation, and AESIs/other selected AE groupings

The incidence of SAEs was generally similar between dupilumab and placebo groups across all subgroups of participants based on demographics and baseline PN characteristics. A lower incidence of SAEs was observed in the dupilumab group as compared to the placebo group in the subgroup of atopic participants (1.2% versus 11.2%, risk ratio: 0.11 [95% CI: 0.01 to 0.81]). No increased incidence of SAEs was observed in the dupilumab group as compared to the placebo group in any subgroups by disease characteristics, including those for which a numerical difference in TEAE incidence was observed. In the dupilumab group, no meaningful differences were observed in SAE incidence between the subgroups of participants under stable regimen of TCS/TCI compared to participants that were not treated with TCS/TCI during the study (4.4% and 4.9%, respectively). The safety profile of these 2 subgroup categories were consistent with the overall safety pool. No TEAEs leading to permanent intervention discontinuation were reported in the dupilumab group. The limited number of participants who experienced AESIs/other selected AE groupings across subgroups did not allow meaningful interpretation of results.

Discontinuation due to adverse events

Adverse events leading to permanent intervention discontinuation

The incidence of TEAEs leading to permanent discontinuation from intervention was low overall, and all events occurred in placebo-treated participants (4 [2.5%] participants. All TEAEs were of a single occurrence and included 2 nonserious events of **neurodermatitis** and **urticaria** (assessed as related to the IMP) and 2 serious events of **Hodgkin's disease** and **duodenal ulcer perforation.** Three of the 4 events resolved; the SAE of Hodgkin's disease had not resolved at the time of the study data cut-off and the participant was receiving corrective treatment.

Table 49. Number (%) of participants with TEAE(s) leading to permanent study intervention discontinuation by primary SOC and PT - Pooled safety population

Primary System Organ Class Preferred Term n (%)	Placebo (N=157)	Dupilumab 300 mg Q2W (N=152)
Any event	4 (2.5)	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1 (0.6)	0
Hodgkin's disease	1 (0.6)	0
Gastrointestinal disorders	1 (0.6)	0
Duodenal ulcer perforation	1 (0.6)	0
Skin and subcutaneous tissue disorders	2 (1.3)	0
Neurodermatitis	1 (0.6)	0
Urticaria	1 (0.6)	0

TEAE: Treatment emergent adverse event, SOC: System organ class, PT: Preferred term

MedDRA 24.1

n (%) = number and percentage of participants with at least one TEAE leading to permanent intervention discontinuation

Table sorted by SOC internationally agreed order and by decreasing percentage of PT in dupilumab 300 mg Q2W group.

Post marketing experience

No post-marketing data is available for the PN indication.

2.6.1. Discussion on clinical safety

Dupilumab is currently approved for treatment of atopic dermatitis, asthma and chronic rhinosinusitis with nasal polyposis.

The main safety data for this application are derived from pooled data of participants with PN aged 18 years and older exposed to dupilumab 300mg Q2W (initial loading dose of 600mg) in the two pivotal placebo-controlled phase 3 studies EFC16460 and EFC16459 conducted during the PN development program. These studies included a 24-week treatment period and a 12-week follow up. No long-term safety data were generated within the PN development program. Cut-off dates for the integrated safety analysis are 30 August 2021 (EFC16460) and 12 November 2021 (EFC16459).

Based on the initial safety data submitted for this application the follow-up period remained ongoing for 23.6% of the participants (55 in EFC16460 and 18 in EFC16459). Clinical study report addenda were provided for both studies including the prior missing safety data from 73 participants that were ongoing in the 12-week follow-up period based on a database lock date of 03-Mar-2022 and 20-Dec-2021, respectively.

SUSAR and fatal events from other ongoing Phase 1/2/3 studies and Phase 4 interventional studies in other indications reported until 20 December 2021 were provided as supportive safety data.

A total of 309 participants were exposed (152 dupilumab; 157 placebo) within studies EFC16460 and EFC16459. Mean exposure for dupilumab and placebo are 166.8 (69.42 py) and 145.9 (62.72 py) days, respectively. Almost all patients within the dupilumab group (98.0%) completed the 24-week treatment period while 26.1% discontinued study intervention in the placebo group, mostly due to lack of efficacy (either by investigator's decision or as reason for withdrawal) as a consequence of the observed treatment effect within the dupilumab group.

A slightly higher incidence of TAES occurred in the dupilumab group as compared to placebo (63.8% vs. 56.7%). The most frequent TEAEs by SOC were *infections and infestations* (dupilumab: 24.3%; placebo: 23.6%) and *skin and subcutaneous tissue disorders* (dupilumab: 16.4%; placebo: 14.6%). Apparent imbalances between TEAS by SOCs are observed for the SOCs *musculoskeletal and connective tissue disorders* (dupilumab: 15 [9.9%]; placebo: 7 [4.5%]) and *gastrointestinal disorders* (dupilumab: 14 [9.2%]; placebo: 8 [5.1%]) and for *blood creatine phosphokinase increased* (dupilumab: 5 [3.3%]; placebo: 1 [0.6]).

Frequent (≥1%) TEAEs in the dupilumab group were *nasopharyngitis*, *dizziness*, *diarrhoea*, *eczema*, *blood creatine phosphokinase increased*, *conjunctivitis* and *conjunctivitis allergic*, *myalgia*, and *accidental overdose*. In contrast, *COVID-19*, *neurodermatitis*, *injection site pain* and *folliculitis* appeared less frequent (≤1%) as compared to placebo.

Treatment-emergent SAEs were reported by 7 (4.6%) participants in the dupilumab group and 12 (7.6%) participants in the placebo group. All SAEs in the dupilumab group were assessed as not related to dupilumab which is considered acceptable.

No deaths were reported within studies EFC16460 and EFC16459 as of the cut-off date. 17 deaths are reported in participants with other indications that were all assessed as non-related to the IMP. Overall, no indications for new safety signal emerge from the reported SUSARs or fatal events.

Adverse events of special interest and other selected AEs of interest including anaphylactic reactions, hypersensitivity and different infections (e.g. *conjunctivitis, blepharitis, keratitis, herpes*) were further evaluated. Number of treatment emergent adverse events of special interest were generally low and included only a total of 3 events of systemic hypersensitivity reactions (dupilumab: 1; placebo: 2). No anaphylactic events were reported. The overall incidence of other selected AEs of interest was similar

between the groups (dupilumab: 16 [10.5%], placebo: 18 [11.5%]). The occurrence of *conjunctivitis* (either defined by narrow, broad or FDA criteria) were increased in the dupilumab group (broad: 8 vs. 3; narrow: 6 vs. 2; FDA: 6 vs. 2). None of the events were serious or led to study discontinuation and two moderate cases are reported in the dupilumab group. All cases resolved except for one participant as of the cut-off dates of the safety analysis, the event was reported as resolved 6 months after event onset. No events of severe *blepharitis* or *keratitis* were reported.

In the absence of an alternative aetiology, the PTs of conjunctivitis and conjunctivitis allergic are considered by the MAH as ADRs for the indication of PN and section 4.8 of the SmPC has been updated which is acceptable.

Injection site reactions were reported in 6 (3.9%) and 9 (5.7%) participants in the dupilumab and placebo group, respectively. All ISR were of short duration and all recovered without corrective treatment and without sequelae.

The number of severe or serious infections was low (dupilumab: 2; placebo: 3). None of the events led to permanent study intervention discontinuation. Section 4.8 of the SmPC has been updated with this information for the PN indication. Nine (9) events of COVID-19 were reported with a higher incidence in the placebo group (dupilumab: 2; placebo: 7). Out of the 9 events, one event was severe and two events were serious. None of the events were assessed as related to the IMP or led to permanent study intervention discontinuation.

A higher number of herpes infection were observed in dupilumab-treated (5 vs. 0). All events were of moderate or of mild intensity. Two events of oral herpes were assessed as related to dupilumab. All participants recovered after treatment within 6-36 days. Contrary to the higher incidence of herpes infections in the dupilumab group other skin infections were increased in patients treated with placebo (14 [8.9%]) as compared to dupilumab (7 [4.6%]) with folliculitis and cellulitis being the most frequent.

The effect of treatment on blood eosinophils was overall small. A minimal increase was observed within the first 8 weeks for the dupilumab and the placebo group while eosinophil counts were slightly decreased in the dupilumab group at week 24 and week 36 as compared to baseline while no relevant change was observed within the placebo group. Increased eosinophils were observed in 17 (11.3%) and 16 (10.5%) of participants in the dupilumab and placebo group. No event of clinically symptomatic eosinophilia was reported.

There is an imbalance of TEAEs within the SOC musculoskeletal and connective tissue disorders (dupilumab: 15 [9.9%]; placebo: 7 [4.5%]) while no clear increase for one specific PT can be observed. Events of myalgia, arthralgia and back pain are reported >1 whereas all other PTs were of single occurrence. There was one SAE (musculoskeletal chest pain), that was unrelated to the IMP.

TEAEs within the SOC gastrointestinal disorders where also reported more frequently as compared to placebo (dupilumab: 14 [9.2%]; placebo: 8 [5.1%]). This increase appears to be mainly driven by the PT of diarrhoea and no serious event occurred in the dupilumab group.

No cardiovascular thromboembolic events (cardiovascular deaths, non-fatal myocardial infarctions, and non-fatal strokes) were reported in the dupilumab group while 2 SAEs of acute myocardial infarction were observed in for placebo group. A total of 3 participants (dupilumab: 1; placebo 2) reported malignancies. All were assessed as non-related to the IMP which is endorsed.

Treatment-emergent ADAs were observed in 11 (7.7%) and 3 (2.0%) participants in the dupilumab and placebo group, respectively. The number of ADA-positive participants is comparable with the incidence of ADAs in the approved indications AD, asthma and CRSwNP. Most ADAs were low titer.

nAbs were observed in 4 participants in the dupilumab group. Overall, no apparent safety signal can be observed regarding ADA-formation in participants treated with PN.

Subgroup analysis did not give rise to an apparent increased risk for the incidence of TEAEs, SAEs, AESIs and other selected AE groupings related to participant's demographics or disease baseline characteristics.

The safety data from the age group ≥65 years and particularly ≥75 years (8 subjects exposed in the dupilumab group) was limited and long-term data in PN were lacking. Considering that patients with PN tend to be elderly, more data were requested to the MAH. In response, the MAH provided pooled data on dupilumab exposure and safety data from patients ≥65 years and ≥75 years from studies in the other indications AD, asthma, CRSwNP and EoE. As of 28 March 2022 (DLP of last DSUR), a total of 499 subjects over 65 years of age and 75 patients over 75 years of age have been exposed to dupilumab, across indications. No relevant changes in the incidence of TEAEs can be observed in this enlarged elderly safety population as compared to the total PN population. This is reflected in Section 5.2 of the SmPC.

As of the cut-off dates for the integrated safety analysis the follow-up period remained ongoing for 23.6% of the participants (55 in EFC16460 and 18 in EFC16459). Additional safety follow-up from participants that have completed the 12-week follow-up period after completion of the studies on 22 November 2021 (EFC16460) and 3 February 2022 (EFC16459) were provided by the MAH in response to Request for Supplementary Information. No new safety signals are apparent with this updated safety data.

Overall, based on the provided data, dupilumab appears to have an acceptable safety profile in PN that is similar to the other indications AD, asthma and CRSwNP for which dupilumab is already approved. No new relevant safety signals were apparent in the observed PN population, and all AEs are adequately reflected in the SmPC.

2.6.2. Conclusions on clinical safety

Overall, dupilumab treatment appears to be well tolerated with the proposed dose and method of administration (300 mg Q2W SC). The safety profile observed during the PN studies (EFC16460 and EFC16459) appears to be consistent with the important identified risks mentioned in the safety specification and the so far known safety profile of dupilumab established during the AD, asthma and CRSwNP development programs. No new key safety findings are to be reflected in the SmPC and RMP.

2.6.3. PSUR cycle

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

2.7. Risk management plan

The MAH submitted/was requested to submit an updated RMP version with this application.

The CHMP received the following PRAC Advice on the submitted Risk Management Plan:

The PRAC considered that the risk management plan version 8.1 is acceptable.

The CHMP endorsed this advice without changes.

Safety concerns

Important identified risks	Systemic hypersensitivity (including events associated with immunogenicity) Conjunctivitis and keratitis related events in AD patients
Important potential risk	None
Missing information	Use in pregnant and lactating women Long-term safety

AD: Atopic Dermatitis.

Pharmacovigilance plan

Study **Status**	**Summary of objectives**	**Safety concerns addressed**	**Milestones**	**Due dates**
Category 1				
Not applicable				
Category 2				
Not applicable				
Category 3				
Pregnancy registry (R668-AD-1639) Ongoing	To evaluate the effect of exposure to dupilumab on pregnancy and infant.	Use in pregnant and lactating women	Protocol submission	Submitted to PRAC in Jan-2018 (and amendment #1 in Sep-2018)
			Amended protocol (asthma cohorts) Final report	Submitted for information with EU-RMP v5.0 Jan-2027
Pregnancy Outcomes Database Study (R668-AD-1760) Ongoing	To measure the prevalence of adverse pregnancy and infant outcomes in a cohort of women with AD exposed to dupilumab during pregnancy compared to a disease-matched cohort exposed to systemic medication or phototherapy (but unexposed to	Use in pregnant and lactating women	Protocol submission (amendment 1)	Submitted for information with EU-RMP v5.0
			Final report	Apr-2027

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
	dupilumab) in AD patients and a disease-matched cohort who were not exposed to these treatments during pregnancy.			
A single-arm extension study of dupilumab in patients with AD who participated in previous dupilumab clinical trials; including a sub study consisting of standardized ophthalmology assessments (Phase IV) (R668-AD-1225) (LTS14041) Ongoing	To assess the long-term safety, efficacy, PK, and immunogenicity of REGN668 in adult patients with moderate-to-severe AD.	Long-term safety (Ophthalmology sub study: additional information on conjunctivitis and keratitis related events in AD patients)	Final report	Q3 2023
An open-label extension study to assess the long-term safety of dupilumab in patients ≥6 months to <18 years of age with AD (Phase III) (LTS1434) (R668-AD-1434) Ongoing	To assess the long-term safety of dupilumab in pediatric patients with AD.	Long-term safety of dupilumab in pediatric patients with AD	Final report	Q4 2024
An open-label study to evaluate the long-term safety and tolerability of dupilumab in pediatric patients with asthma who participated in a previous dupilumab asthma clinical study (Phase III) (LTS14424) Ongoing	To assess the long-term safety, tolerability and efficacy of dupilumab in pediatric patients with asthma	Long-term safety of dupilumab in pediatric patients with Asthma	Final report	Sep-2024
AD: Atopic Dermatitis; PK: Pharmacokinetic; PRAC: Pharmacovigilance Risk Assessment Committee; Q: Quarter; RMP: Risk Management Plan.				

Risk minimisation measures

Safety concern	Risk minimization measures	Pharmacovigilance activities

Safety concern	Risk minimization measures	Pharmacovigilance activities
Systemic hypersensitivity (including events associated with immunogenicity)	**Routine risk minimization measures:** SmPC sections 4.3, 4.4 and 4.8 PIL sections 2 and 4 Prescription only medicine **Additional risk minimization measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** Hypersensitivity questionnaire **Additional pharmacovigilance activities:** None
Conjunctivitis and keratitis related events in AD patients	**Routine risk minimization measures:** SmPC sections 4.4 and 4.8 PIL sections 2 and 4 Prescription only medicine **Additional risk minimization measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** Ophthalmology substudy in LTS14041 (R668-AD-1225)
Use in pregnant and lactating women	**Routine risk minimization measures:** SmPC sections 4.6 and 5.3 PIL section 2 Prescription only medicine A**dditional risk minimization measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** Pregnancy questionnaire **Additional pharmacovigilance activities:** • Pregnancy registry study (R668-AD-1639) • Pregnancy Outcomes Database Study (R668-AD-1760) in AD patients
Long-term safety	**Routine risk minimization measures:** Prescription only medicine **Additional risk minimization measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** Studies LTS14041 (R668-AD-1225), LTS1434 (R668-AD-1434), and LTS14424

AD: Atopic Dermatitis; EU: European Union; PIL: Patient Information Leaflet; PK: Pharmacokinetic; RMP: Risk Management Plan; SmPC: Summary of Product Characteristics.

2.8. Update of the Product information

As a consequence of this new indication, sections 4.1, 4.2, 4.4, 4.8, 5.1, 5.2 and 6.1 of the SmPC have been updated. The Package Leaflet has been updated accordingly. In addition the MAH took the opportunity to clarify in section 4.2 what needs to be done when a dose is missed for the different

treatment regimens.

Changes were also made to the PI to bring it in line with the current Excipients guideline, which were reviewed and accepted by the CHMP.

2.8.1. User consultation

A justification for not performing a full user consultation with target patient groups on the package leaflet has been submitted by the MAH and has been found acceptable for the following reasons:

The extension of indication is related to moderate to severe Prurigo nodularis in adult patients, who are candidates for systemic therapy. The changes only affected the sections 1, 2 and 3 of the package leaflet of Dupixent of the existing strengths/ presentations 300 mg solution for injection in pre-filled syringes and Dupixent 300 mg solution for injection in pre-filled pen. The instruction for use section was not amended. Therefore, neither a full user testing nor a bridging is required due to the fact that the changes are minor and the strength is similar to the previous authorised indication with AD.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

Prurigo nodularis (PN) is an inflammatory skin disease characterized by the presence of chronic pruritus for ≥6 weeks, a history and/or signs of repeated scratching, picking, or rubbing of the skin, and the presence of firm nodular lesions which are usually symmetrically distributed on areas of the trunk and extremities. Key histological features of PN include hyperkeratosis, irregular epidermal hyperplasia with hypergranulosis, dermal/lesional infiltrates of T-lymphocytes, mast cells, and eosinophils, and papillary dermal fibrosis.

Pruritus is the central manifestation in PN and the main driver of disease burden resulting in a significant quality of life impairment. In patients with PN, the itching is characteristically intense, causing people to scratch themselves and leading to the development of an itch-scratch cycle, which exacerbates the cellular damage in skin lesions, facilitates secondary infections and impairs quality of life. PN has a significant association with mental disorders such as anxiety and depression and is further associated with increased rates of obesity, mental health problems, endocrine, cardiovascular and renal disorders, HIV, and malignancy. PN patients have a higher all-cause mortality than patients without PN, likely due to the high comorbidity burden. Approximately 20% to 60% of patients have either past or current history of atopic dermatitis or other atopic disorders.

Limited data for the epidemiology of PN exist. A European study found an incidence rate of PN of 111 per 100 000 person-years. Prurigo nodularis is predominantly observed in older patients but also occasionally in younger patients with a median age of >50 years. Both genders are affected with a female predominance. Black patients are disproportionately affected with PN compared to Caucasian patients.

3.1.2. Available therapies and unmet medical need

There are no approved systemic therapies available for the treatment of PN and approved treatment options for PN are limited to a few specific TCS of which some are authorised nationally in the EU. Topical therapies, such as topical corticosteroids (TCS) and topical calcineurin inhibitors (TCI) are used as first-line therapy alone or in combination. Other topical therapies such as Vitamin D3 analogues, topical anesthetics, topical capsaicin are also used. Continuous use of emollients as supportive antipruritic care is recommended. Additional therapies used to treat PN include intralesional injections of corticosteroids, cryotherapy, and phototherapy. Due to the refractory nature of this disease to topical treatment, patients with PN often require off-label systemic treatment that include antihistamines, neuromodulatory agents (gabapentinoids, NKR 1 antagonists, antidepressants or μ-opioid receptor antagonists) and systemic immunosuppressants (oral corticosteroids, cyclosporine, and methotrexate).

Despite the use of systemic treatments in PN, none of these are currently approved. Overall, the currently available effective treatment options for PN are limited and do not always achieve satisfactory response in PN patients with severe disease. The therapy of PN remains challenging and of prolonged course. Based on the currently available therapies, there is an important unmet need for treatment options for patients with PN that are not adequately controlled with the current treatment options.

3.1.3. Main clinical studies

Efficacy and Safety Data are derived from 2 similarly designed pivotal phase 3 studies **EFC16460** (LIBERTY-PN PRIME2) and **EFC16459** (LIBERTY-PN PRIME). Both studies were designed as multinational, multicenter, randomized, double blind, placebo controlled, parallel-group studies, to assess the efficacy and safety of 24 week treatment with dupilumab 300 mg Q2W in adult participants with PN whose disease was inadequately controlled on topical prescription therapies or when those therapies were not advisable.

Initially, the timing for the primary endpoint in studies EFC16460 and EFC16459 was identical. However, after the primary analysis of study EFC16460 (data cut-off: 27-Sept-2021) the still ongoing study EFC16459 was amended on 21-Oct-2021 to move the timing of the primary endpoint from week 12 to week 24 based on the efficacy data observed within study EFC16460.

3.2. Favourable effects

In both pivotal studies (EFC16460 and EFC 16459) dupilumab 300mg Q2W demonstrated a statistically and clinically meaningful improvement in the severity of pruritus (reduction by ≥4 points in the WI-NRS) as compared to placebo at Week 12 (primary endpoint EFC16460) and Week 24 (primary endpoint EFC16459). In both pivotal studies, a statistical significant difference in the reduction of PN lesions (participants with IGA PN-S 0 or 1 score at Week 24; key secondary endpoint) was achieved.

At Week 12, the proportion of participants with a reduction in the WI-NRS by ≥4 from baseline in the dupilumab group as compared to placebo was 37.2% vs. 22.0% (p=0.0216) in study EFC16460 and 44.0% (dupilumab) versus 15.8% (placebo) (p=0.0003) in study EFC16459. At week 24, the treatment effect further increased in EFC16460 [57.7% versus 19.5%; p<0.0001; difference: 42.6% (95%CI, 29.06-56.08)] and to a similar extent in EFC16459 [60.0% versus 18.4%; p<0.0001; difference: 42.7% (95%CI, 27.76-57.72)].

Subsequently, in the pooled ITT population a significant difference is observed at Week 12 in the dupilumab group (40.5% versus 19.0%; p<0.0001) that was further increased at Week 24 (58.8% versus 19.0%; p<0.0001). The treatment effect of dupilumab started to appear within the first weeks and further increased over time.

Mean change and mean percent changes of WI-NRS over time up to Week 24 were both similar and overall consistent with the observed reduction in itch severity (WI-NRS reduction of ≥4) points showing show a mean reduction of -4.77 and -2.65 and a mean percent change of -53.44 and -27.97 at Week 24 for dupilumab and placebo respectively. A continuous reduction in WI-NRS is observed to a lesser extent in the placebo group. The overall reduction in WI-NRS at Week 24 by 2.2 points in the dupilumab group as compared to placebo is supportive for the beneficial treatment effect of dupilumab seen for the primary endpoint.

At Week 24, a slightly lower reduction of PN lesions (participants with IGA PN-S 0 or 1) was observed (EFC16460: 15.9% versus 44.9%; EFC16459: 18.4% versus 48.0%) as compared to reduction in pruritus severity. The first differences between dupilumab and placebo in WI-NRS and PN-S scores started to appear by 4 weeks after baseline.

Consistent with the observed reduction of itch severity and PN lesions a significant improvement in secondary endpoints to evaluate quality of life (e.g. DLQI) was observed at Week 24. Overall, the hierarchical testing consisting of 9 steps broke at step 8.

3.3. Uncertainties and limitations about favourable effects

The rather late change in the timing of the primary endpoint in study EFC16459 adds some uncertainty. However, it is acknowledged that it was motivated by external data: preliminary efficacy findings from study EFC16460, and the overall consistency of the efficacy results between both studies provides reassurance regarding the validity of the efficacy data. Adequate clarifications regarding the precise timing of the change in the primary endpoint in Study EFC16459 were provided by the MAH. Therefore, the CHMP didn't raise specific concerns with regards to this change.

Participants taking selected prohibited medications and/or rescue medications prior to week 12 (week 24 in study EFC16459) were considered as non-responders. A treatment policy estimand would have been preferred. Sensitivity analysis addressing a treatment policy estimand, using all observed data irrespective of the intercurrent event were provided by the MAH.

Similarly, participants with missing values were also considered non-responders and in light of higher discontinuation rates in the control groups, there was uncertainty whether the dupilumab group might have been favoured by this approach. Additional analyses provided by the MAH suggested that results are robust.

Only 6.1% of subjects enrolled in the pivotal studies were Black or African American. Interpretation of results observed for this subpopulation is difficult as only a total of 19 patients were enrolled with 11 patients being treated with dupilumab. The treatment responses seem to principally follow the responses observed for the White and Asian participants as well as the overall study population. This uncertainty has been adequately reflected in the SmPC.

Long-term efficacy data are missing as treatment period of studies EFC16459 and EFC16460 was 24 Weeks. No long-term extension studies were conducted for the new indication of PN and are currently not planned by the MAH. Since the MAH didn't plan to generate further clinical data in the long-term use, they have submitted a revised wording to remove the use in long term treatment and added the information that no clinical trial data are available for patients treated up to 24 weeks in the SmPC.

3.4. Unfavourable effects

The safety data are derived from pooled data of participants with PN aged 18 years and older exposed to dupilumab 300mg Q2W (initial loading dose of 600mg) in the two pivotal placebo-controlled phase 3 studies EFC16460 and EFC16459 conducted during the PN development program.

A slightly higher incidence of TAES occurred in the dupilumab group as compared to placebo (63.8% vs. 56.7%). The SOCs with the highest proportion of participants with TEAEs in the dupilumab group compared to the placebo group were: infections and infestations (24.3% vs. 23.6%), skin and subcutaneous tissue disorders (16.4% vs. 14.6%), nervous system disorders (12.5% vs. 10.2%), musculoskeletal and connective tissue disorders (9.9% vs. 4.5%), gastrointestinal disorders (9.2% vs. 5.1%).

The most frequently reported TEAEs by PT, in the dupilumab group compared to the placebo group, by at least 1% were: nasopharyngitis (3.9% vs. 1.9%), dizziness (2.6% vs. 0%), diarrhoea (2.6% vs. 0.6%), eczema (2.0% vs. 0%), blood creatine phosphokinase increased (3.3% vs. 0.6%), conjunctivitis and conjunctivitis allergic (both 2.0% vs. 0.6%), myalgia (2.0% versus 0.6%), accidental overdose (5.9% vs. 4.5%)

Treatment-emergent SAEs were reported by 7 (4.6%) participants in the dupilumab group and 12 (7.6%) participants in the placebo group. All SAEs in the dupilumab group were assessed as not related to dupilumab which is considered acceptable. No deaths were reported within studies EFC16460 and EFC16459 as of the cut-off date.

Adverse events of special interest and other selected AEs groupings were further evaluated. The occurrence of conjunctivitis (using the broad CMQ cluster) was increased in the dupilumab group (5.3% vs. 1.9%). A higher number of herpes infection were observed in dupilumab-treated (3.3% vs. 0.0%). All events were of moderate or of mild intensity. Two events of oral herpes were assessed as related to dupilumab. All participants recovered after treatment within 6-36 days. Injection site reactions were reported in 3.9% vs 5.7% participants in the dupilumab and placebo group, respectively. All ISR were of short duration and all recovered without corrective treatment and without sequelae. The number of severe or serious infections was low (1.3% vs. 1.9%). None of the events led to permanent study intervention discontinuation.

Subgroup analysis did not give rise to an apparent increased risk for the incidence of TEAEs, SAEs, AESIs and other selected AE groupings related to participant's demographics or disease baseline characteristics.

The association of anti-drug antibodies formation and association to adverse events was analysed. Treatment-emergent ADA responses were observed in 7.7% vs. 2.0% of patients in the dupilumab and placebo group respectively. The number of ADA-positive participants is comparable with the incidence of ADAs in the approved indications AD, asthma and CRSwNP. nAbs were observed in 4 participants in the dupilumab group. Overall, no apparent safety signal can be observed regarding ADA-formation in participants treated with PN.

Overall, these are all known risks and no new safety signals were observed in the PN population. The CHMP concluded that the overall safety profile observed in patients with PN was generally consistent with that observed in patients with AD, asthma and CRSwNP.

3.5. Uncertainties and limitations about unfavourable effects

The safety profile for dupilumab has been characterised in previous studies in the AD, asthma, and CRSwNP indications.

The events of nasopharyngitis were of mild intensity and resolved within 3 to 12 days. None led to permanent treatment discontinuation. One event ("common cold") was considered related to dupilumab. Most of the conjunctivitis events were mild. Two moderate cases are reported in the dupilumab group (placebo: 0). None of the conjunctivitis events led to study discontinuation. All events resolved. Five participants in the dupilumab group versus none in the placebo group with herpes viral infections (HLT: genital herpes simplex, herpes zoster, ophthalmic herpes zoster, and oral herpes). Most of the events were of moderate intensity, except for the event of herpes zoster which was of mild intensity. All participants recovered after treatment within 6-36 days. No clear increase for one specific PT can be observed within the SOC musculoskeletal and connective tissue disorders. The increase in the SOC gastrointestinal disorders appears to be mainly driven PT of diarrhea. No serious event occurred in the dupilumab group. Injection site reactions were generally of short duration and all recovered without corrective treatment and without sequelae. ADA formation did not appear to correlate with any safety findings.

The safety data from the age group ≥65 years and particularly ≥75 years (8 subjects exposed in the dupilumab group) is limited and long-term data in PN is lacking. Pooled data on dupilumab exposure and safety data from patients ≥65 years and ≥75 years from studies in the other indications AD, asthma, CRSwNP and EoE were provided by the MAH. As of 28 March 2022 (DLP of last DSUR), a total of 499 subjects over 65 years of age and 75 patients over 75 years of age have been exposed to dupilumab, across indications. No relevant changes in the incidence of TEAEs can be observed in this enlarged elderly safety population as compared to the total PN population.

Safety data for long-term exposure in the new indication at the intended dose (300 mg, Q2W) are missing.

3.6. Effects Table

Table 50. Effects Table for Dupixent in patients with Prurigo nodularis (data cut-off: EFC16460, 30-Aug-2021; EFC16459, 12-Nov-2021).

Effect	Short description	Unit	DUPI 300 mg Q2W*[1,2]	PCB*[2]	Uncertainties / Strength of evidence	References
Favourable Effects						
WI-NRS	Proportion of participants with reduction by ≥4 points from baseline to Week 12	%	40.5	19.0	p<0001; nominal p-value for study EFC16459 (not part of the hierarchical testing procedure)	Pooled ITT population Study: EFC16460 EFC16459
	Proportion of participants with reduction by ≥4 points from baseline to Week 24	%	58.8	19.0	p<0001; clinically meaningful difference	
	Percent change from baseline to Week 24	P	-53.44	-27.97	p<0001; clinically meaningful difference	
IGA PN-S	Proportion of participants with IGA PN-S 0 or 1 score at Week 24	%	46.4	17.1	p<0001; clinically meaningful difference	
DLQI	Change from baseline at	P	-12.56	-6.27	p<0001; participants with	

Effect	Short description	Unit	DUPI 300 mg Q2W*[1,2]	PCB*[2]	Uncertainties / Strength of evidence	References
	Week 24				clinical meaningful reduction (⩾9 points): (64.7% vs. 22.8%, nominal p<0.0001)	
Skin Pain-NRS	Change from baseline at Week 24	P	-4.28	-2.41	p<0001; (nominal p-value)	
Unfavourable Effects						
TEAE	Nasopharyngitis	%	3.9	1.9	Mild events that resolved.	Pooled Safety Population Study: EFC16460 EFC16459
	Conjunctivitis and conjunctivitis allergic	%	2.0	0.6	Mostly mild, 2 moderate events in dupilumab group, all events resolved except for one participant.	
	Herpes viral infection	%	3.3	0.0	Moderate or mild events. All recovered after treatment.	
	Injection site reactions	%	3.9	5.7	Of short duration; all recovered without sequelae.	
	Treatment-emergent ADAs	%	7.7	2.0	No correlation with safety findings.	

Abbreviations: ADA, anti-drug antibodies; DLQI, Dermatology Life Quality Index; DUPI, dupilumab; IGA, Investigator's Global Assessment, NRS, numeric rating scale, P, points; PCB, placebo, PN; Prurigo nodularis; PN-S, PN-Stage; WI, worst-itch;

Notes: *[1] after an initial loading dose of 600 mg on day 1; *[2] 58.5% participants on stable treatment with topical corticosteroids or topical calcineurin inhibitors

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

The therapy of moderate to severe PN is challenging and of prolonged course. Topical corticosteroids (TCS) and topical calcineurin inhibitors (TCI) are used as first-line therapy alone or in combination. Still, a satisfactory control of disease is often not achieved and topical or systemic immunosuppressive treatment further harbours significant side effects on long-term use. Thus, an important unmet need for new treatment options remains for patients with moderate-to-severe PN that are not adequately controlled with topical therapy and that are candidates for systemic treatment.

Within the pivotal studies EFC16460 and EFC16459, the MAH has demonstrated beneficial treatment effects of dupilumab 300 mg Q2W in patients with moderate-to-severe PN by Week 24. The treatment effect of dupilumab was consistent between both studies. Statistical significance was reached for the primary and key secondary endpoints (reduction in the WI-NRS by ≥4 points; participants reaching IGA PN-S 0 or 1) indicating a clinical meaningful improvement in the severity of pruritus and a reduction in the number of PN lesions. Both symptoms are most relevant in PN. Consequently, significant reduction in health-related quality of life, as measured by DLQI, was observed.

The main uncertainty relates to long-term efficacy and safety for PN, data beyond 24 week of treatment are not available for PN. Based on the similar effect of dupilumab on pruritus reduction in PN

and AD it appears reasonable that the dupilumab 300mg, Q2W is also able to provide long-term improvements in chronic PN. However, this has not been demonstrated for this particular indication and it is not known whether treatment regimens with lower dupilumab doses may provide an improved benefit/risk profile for long-term treatment of PN. Since the MAH didn't plan to generate further clinical data in the long-term use, they have submitted a revised wording to remove the use in long term treatment and added the information that clinical trial data are available for patients treated up to 24 weeks in the SmPC.

Within studies EFC16460 and EFC16459, dupilumab treatment showed a similar safety profile as within the other indications AD, asthma and CRSwNP. The most frequent TEAEs by SOC were infections and infestations and skin and subcutaneous tissue disorders. Nasopharyngitis occurred with a higher frequency after dupilumab treatment. None of the events were serious. Conjunctivitis and conjunctivitis allergic were identified as ADRs for the indication of PN and showed a similar frequency as compared to other indications. A higher occurrence of herpes infection was noted during dupilumab treatment. All events were of moderate or mild intensity and all participants recovered after treatment. ADA-formation was observed after dupilumab treatment with an overall low incidence while a relevant impact on safety and efficacy data was not noted. Occurrence of injection site reactions were low and similar between dupilumab and placebo. None of the reported injection site reactions was serious or severe. Overall, as compared to other indications no new relevant safety signal is apparent based on the current safety data for PN.

3.7.2. Balance of benefits and risks

Based on the data provided on efficacy and safety, and considering the uncertainties in relation to safety and efficacy, the CHMP is of the opinion that the favourable effects outweigh the unfavourable effects in the indication "treatment of adults with moderate-to-severe prurigo nodularis (PN) who are candidates for systemic therapy". The benefit-risk profile of dupilumab in PN appears to be consistent with the profiles already assessed for adult patients with AD, asthma and CRSwNP.

3.8. Conclusions

The overall B/R of Dupilumab is positive in the following indication:

Dupixent is indicated for the treatment of adults with moderate-to-severe prurigo nodularis (PN) who are candidates for systemic therapy.

4. Recommendations

Outcome

Based on the review of the submitted data, the CHMP considers the following variation acceptable and therefore recommends the variation to the terms of the Marketing Authorisation, concerning the following change:

Variation accepted		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I,IIIA and IIIB

Extension of indication to include treatment of adults with moderate to severe prurigo nodularis (PN) who are candidates for systemic therapy, based on results from studies EFC16459 and EFC16460 (PRIME and PRIME2); these are two phase 3, 24-week, randomized, double-blind, placebo-controlled, multi-centre, parallel group studies undertaken to evaluate the efficacy and safety of dupilumab in patients 18 years of age and older with moderate to severe PN, who are inadequately controlled on topical prescription therapies or when those therapies are not advisable. As a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1, 5.2 and 6.1 of the SmPC are updated. The Package Leaflet is updated in accordance. Version 8.1 of the RMP has also been approved. Furthermore, the PI is brought in line with the current excipients guideline.

The variation leads to amendments to the Summary of Product Characteristics, Labelling and Package Leaflet and to the Risk Management Plan (RMP).

Amendments to the marketing authorisation

In view of the data submitted with the variation, amendments to Annexes I, IIIA and IIIB and to the Risk Management Plan are recommended.

Additional market protection

Furthermore, the CHMP reviewed the data submitted by the MAH, taking into account the provisions of Article 14(11) of Regulation (EC) No 726/2004, and considers that the new therapeutic indication brings significant clinical benefit in comparison with existing therapies (see appendix).

5. EPAR changes

The EPAR will be updated following Commission Decision for this variation. In particular the EPAR module 8 "*steps after the authorisation*" will be updated as follows:

Scope

Please refer to the Recommendations section above.

Summary

Please refer to Scientific Discussion ‘Dupixent-H-C-004390-II-63’