Dupilumab (prurigo nodularis)

Addendum to Project A23-24 (dossier assessment)[1]

ADDENDUM

Project: A23-82 Version: 1.0 Status: 14 September 2023

[1] Translation of addendum A23-82 *Dupilumab (Prurigo nodularis) – Addendum zum Projekt A23-24 (Dossierbewertung)*. Please note: This translation is provided as a service by IQWiG to English-language readers. However, solely the German original text is absolutely authoritative and legally binding.

Publishing details

Publisher

Institute for Quality and Efficiency in Health Care

Topic

Dupilumab (prurigo nodularis) – Addendum to Project A23-24

Commissioning agency

Federal Joint Committee

Commission awarded on

8 August 2023

Internal Project No.

A23-82

Address of publisher

Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen
Im Mediapark 8
50670 Köln
Germany

Phone: +49 221 35685-0
Fax: +49 221 35685-1
E-mail: berichte@iqwig.de
Internet: www.iqwig.de

IQWiG employees involved in the addendum

- Jana Göbel
- Erika Baumbach
- Benjamin Becker
- Petra Kohlepp
- Daniela Preukschat

Keywords

Dupilumab, Prurigo, Benefit Assessment, NCT04183335, NCT04202679

Table of contents

List of tables

Page

List of figures

Page

List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
AE	adverse event
BSC	best supportive care
CMQ	Custom MedDRA Query
DLQI	Dermatology Life Quality Index
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
HADS	Hospital Anxiety and Depression Scale
IGA PN-S	Investigator Global Assessment for Prurigo Nodularis-Stage
IPD	individual patient data
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
MedDRA	Medical Dictionary for Regulatory Activities
MI	multiple imputation
NRI	non-responder imputation
NRS	Numeric Rating Scale
PAS	Prurigo Activity Score
Peto OR	Peto odds ratio
PGIC	Patient Global Impression of Change
PGIS	Patient Global Impression of Severity
PT	Preferred Term
SAE	serious adverse event
SGB	Sozialgesetzbuch (Social Code Book)
SOC	System Organ Class
TCI	topical calcineurin inhibitor
TCS	topical corticosteroids
UVB	ultraviolet B radiation
VAS	visual analogue scale
WI-NRS	Worst Itch Numeric Rating Scale

1 Background

On 8 August 2023, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to conduct supplementary assessments for Project A23-24 (Dupilumab – Benefit assessment according to § 35a Social Code Book V) [1].

The commission comprises the assessment of the data of the PRIME and PRIME2 studies presented in the dossier, taking into account the information provided in the dossier [2].

The responsibility for the present assessment and the assessment result lies exclusively with IQWiG. The assessment is forwarded to the G-BA. The G-BA decides on the added benefit.

2 Assessment

As explained in detail in dossier assessment A23-24 [1], the studies PRIME and PRIME2 on dupilumab in comparison with the appropriate comparator therapy (ACT) presented by the pharmaceutical company (hereinafter referred to as "the company") were not included in the benefit assessment because they did not implement the ACT best supportive care (BSC). The reasons for the lack of implementation of the ACT were as follows:

- **Restriction of treatment with topical corticosteroids (TCS):** High potency to superpotent TCS could not be used outside rescue therapy, and dose adjustment of an already existing TCS therapy was also not allowed. High potency to superpotent TCS dosage even had to be decreased before the study, as background therapy with TCS was restricted to low to medium-potency preparations. In addition, treatment with TCS could only be continued during the study if it was used with stable dosing.
- **Prohibition of UVB phototherapy:** The use of ultraviolet B (UVB) phototherapy was prohibited in both studies for the entire study duration.
- **Stable use of emollients:** In both studies, patients were to continue their basic therapy with emollients, but initiating therapy with prescription emollients or switching emollients was not allowed.

According to the G-BA, however, it is assumed in the present therapeutic indication that topical basic skin care therapy, TCS, and UVB phototherapy can be used as part of BSC. Furthermore, treatment should be adjusted (e.g. different dosages of TCS) if this was indicated for the patient. Thus, key components of the ACT BSC were not allowed in the studies, or their use was restricted (for detailed justification of the study exclusion, see dossier assessment A23-24 [1]).

Overall, the listed points of criticism were not resolved in the comments of the company [3] or in the oral hearing [4]. Therefore, the dossier assessment's conclusion that the ACT specified by the G-BA had been inadequately implemented remains unchanged. Irrespective of this, the company was also unable to provide any information in the oral hearing on how many patients had to reduce their high potency to superpotent TCS before the study.

In accordance with the commission, the following Sections 2.1 to 2.3 describe the studies PRIME and PRIME2 and present the results.

Table 1: Study pool of the company – RCT, direct comparison: dupilumab vs. placebo

Study	Study category			Available sources		
	Study for the approval of the drug to be assessed (yes/no)	Sponsored study[a] (yes/no)	Third-party study (yes/no)	CSR (yes/no [citation])	Registry entries[b] (yes/no [citation])	Publication (yes/no [citation])
LIBERTY-PN PRIME (PRIME[c])	Yes	Yes	No	Yes [5,6]	Yes [7,8]	Yes [9]
LIBERTY-PN PRIME2 (PRIME2[c])	Yes	Yes	No	Yes [10,11]	Yes [12,13]	Yes [9]

a. Study sponsored by the company.
b. References of trial registry entries and any available reports on the study design and/or results listed in the trial registries.
c. In the tables below, the study will be referred to using this acronym.

CSR: clinical study report; RCT: randomized controlled trial

2.1 Study characteristics

Table 2 and Table 3 describe the studies PRIME and PRIME2.

Table 2: Characteristics of the studies included by the company – RCT, direct comparison: dupilumab vs. placebo

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[a]
PRIME	RCT, double-blind, parallel	Adults (18–80 years) with moderate to severe PN (PN lesions ≥ 20; worst itch score ≥ 7)[b], diagnosed ≥ 3 months before enrolment, and with inadequate response[c] to medium to superpotent TCS	Dupilumab + background therapy (N = 75) Placebo + background therapy (N = 76)	▪ Screening: 2 to 4 weeks ▪ Treatment: 24 weeks ▪ Follow-up: 12 weeks[d]	58 study centres in Argentina, China, France, Japan, Korea, Mexico, Russia and USA 12/2019–11/2021[e]	Primary: WI-NRS improvement ≥ 4 points at week 24 Secondary: morbidity, health-related quality of life, AEs
PRIME2	RCT, double-blind, parallel	Adults (18–80 years) with moderate to severe PN (PN lesions ≥ 20; worst itch score ≥ 7)[b], diagnosed ≥ 3 months before enrolment, and with inadequate response[c] to medium to superpotent TCS	Dupilumab + background therapy (N = 78) Placebo + background therapy (N = 82)	▪ Screening: 2 to 4 weeks ▪ Treatment: 24 weeks ▪ Follow-up: 12 weeks[d]	55 study centres in Canada, Chile, France, Hungary, Italy, Portugal, South Korea, Spain, Taiwan, United Kingdom, and USA 1/2020–8/2021[e]	Primary: WI-NRS improvement ≥ 4 points at week 12 Secondary: morbidity, health-related quality of life, AEs

a. Primary outcomes include information without consideration of the relevance for this benefit assessment. Secondary outcomes comprise exclusively data only the basis of the information provided by the company's Module 4 G.
b. According to the study protocol, patients had to have an average score of at least 7 on the WI-NRS in the 7 days prior to treatment start. 4 daily scores out of the 7 days were required to calculate the average score. Furthermore, patients had to have a minimum of 20 PN lesions in total on both legs, and/or both arms and/or trunk, at screening visit and on day 1.
c. Inadequate response to TCS is defined as a history of failing a 2-week course of medium to superpotent TCS (± TCIs if required) or when TCS were not medically advisable. Remission or low disease activity (similar to IGA PN-S score of ≤ 2 [≤ 19 lesions]) was neither achieved nor maintained despite this treatment.
d. Follow-up observation of AEs was up to 98 days.
e. According to the CSR, first visit of the first patient and last visit at the end of treatment after 24 weeks. According to the addendum to the CSR, the last visit of the last patient at the end of the study took place in 2/2022 for the PRIME study and in 11/2021 for the PRIME2 study. The addenda include the follow-up data from week 24 to 36.

AE: adverse event; CSR: clinical study report; IGA PN-S: Investigator Global Assessment for PN Stage; N: number of randomized patients; PN: prurigo nodularis; RCT: randomized controlled trial; TCI: topical calcineurin inhibitor; TCS: topical corticosteroids; WI-NRS: Worst Itch Numeric Rating Scale

Table 3: Characteristics of the intervention – RCT, direct comparison: dupilumab vs. placebo

Study	Intervention	Comparison
PRIME	Dupilumab 600 mg SC on day 1, followed by 300 mg SC every 2 weeks	Placebo SC on day 1, then every 2 weeks
	Individual dose adjustments were not allowed[a]	
	Background therapy ▪ Optional continuation of stable treatment (once or twice daily) with low to medium-potency TCS or TCIs from 2 weeks prior to screening: ▫ If patients were treated with high potency to superpotent TCS, the dosage had to be decreased before the study. ▫ No initiation of TCS or TCI therapy during the screening phase; no change in the preparation used, the dosage or the frequency; only if lesions had already resolved, the application of the TCS to those sites could be stopped. ▪ Mandatory use of emollients once or twice daily for at least 5 out of the 7 consecutive days before treatment start until the end of the study[b]; but initiation of a prescription emollient or switching emollients was not allowed during the study. ▪ Rescue therapy with high potency and superpotent TCS or TCIs was indicated in case of intolerable symptoms, for example, and should be started, if possible, at least 14 days after initiation of treatment. Continuation of the study treatment was allowed. **Disallowed pretreatment (4 weeks before screening) and concomitant treatment** ▪ systemic immunosuppressive/immunomodulating drugs (e.g. systemic corticosteroids, ciclosporin, interferon gamma, methotrexate) ▪ intralesional corticosteroid injections, cryotherapy ▪ phototherapy, including tanning beds ▪ naltrexone or other opioid antagonists ▪ gabapentin, pregabalin, thalidomide ▪ exclusively related to pretreatment: biologics[c] and live vaccines ▪ exclusively related to concomitant treatment: other monoclonal antibodies **Allowed concomitant treatment** ▪ antihistamines, in stable dosage (except for treatment of AD or PN) ▪ in stable dosage from ≥ 3 months before screening: paroxetine, fluvoxamine, or other SSRIs, SNRIs, amitriptyline or other tricyclic or tetracyclic antidepressants	
PRIME2	see PRIME study	

a. The study medication could be interrupted because of suspected adverse events. If more than 2 consecutive doses had been missed, the study treatment was permanently discontinued.
b. Discrepant information in the study protocol: According to the study protocol, emollients and other products with itch-relieving effect were not allowed to be continued or applied. Prescription emollients and emollients containing certain additives (such as ceramide, hyaluronic acid, urea, menthol, polidocanol, or filaggrin degradation products, for example) could be used if already used at stable doses before screening, however.
c. Any cell-depleting agents including (but not limited to) rituximab within 6 months before screening, omalizumab within 5 months before screening, other immunomodulatory biologics within 5 half-lives (if known) or 16 weeks before screening (whichever was longer).

AD: atopic dermatitis; PN: prurigo nodularis; RCT: randomized controlled trial; SNRI: serotonin-norepinephrine reuptake inhibitor; SSRI: selective serotonin reuptake inhibitor; TCI: topical calcineurin inhibitor; TCS: topical corticosteroids

Detailed characteristics of the 2 double-blind randomized studies PRIME and PRIME2 as well as a detailed description of the lack of implementation of the ACT BSC (restriction of background therapy, prohibition of UVB phototherapy and stable use of emollients) can be found in dossier assessment A23-24 [1].

Patient characteristics

Table 4 presents the characteristics of patients in the PRIME and PRIME2 studies.

Table 4: Characteristics of the study populations as well as study/treatment discontinuation – RCT, direct comparison: dupilumab vs. placebo (multipage table)

Study Characteristic Category	PRIME		PRIME2	
	Dupilumab	Placebo	Dupilumab	Placebo
	N[a] = 75	N[a] = 76	N[a] = 78	N[a] = 82
Age [years], mean (SD)	49 (17)	51 (16)	51 (16)	47 (15)
Sex [F/M], %	69/31	63/37	67/33	62/38
Disease duration: time since diagnosis [years]				
Mean (SD)	6.0 (7.6)	5.4 (6.2)	5.4 (6.9)	5.5 (7.0)
Disease duration: time since diagnosis, n (%)				
< 3 years	32 (43)	37 (49)	40 (51)	40 (49)
≥ 3 years	43 (57)	39 (51)	38 (49)	42 (51)
Region, n (%)				
Asia	27 (36)	23 (30)	20 (26)	23 (28)
Latin America	19 (25)	22 (29)	6 (8)	8 (10)
Eastern Europe	11 (15)	11 (14)	6 (8)	5 (6)
Western countries	18 (24)	20 (26)	46 (59)	46 (56)
Family origin, n (%)				
White	35 (47)	45 (59)	48 (62)	48 (59)
Black or African American	8 (11)	3 (4)	3 (4)	5 (6)
Asian	29 (39)	25 (33)	25 (32)	27 (33)
Other	3 (4)[b]	3 (4)[b]	2 (3)[b]	2 (2)[b]
Prior topical therapy, n (%)				
TCS	74 (99)	75 (99)	77 (99)	80 (98)
TCI	9 (12)	12 (16)	6 (8)	8 (10)
TCS/TCIs at baseline, n (%)				
Yes	47 (63)	45 (59)	44 (56)	46 (56)
No	28 (37)	31 (41)	34 (44)	36 (44)
Atopic comorbidities, n (%)				
Any atopic comorbidity	33 (44)	28 (37)	34 (44)	40 (49)
Atopic dermatitis	7 (9)	6 (8)	13 (17)	15 (18)
Allergic rhinitis	19 (25)	16 (21)	22 (28)	18 (22)
Allergic rhinoconjunctivits	8 (11)	9 (12)	2 (3)	4 (5)
Asthma	13 (17)	9 (12)	13 (17)	10 (12)
Food allergy	2 (3)	4 (5)	7 (9)	5 (6)
Treatment discontinuation, n (%)[c]	1 (1)	16 (21)	2 (3)	25 (30)
Study discontinuation, n (%)[d]	3 (4)	11 (14)	5 (6)	24 (29)

Table 4: Characteristics of the study populations as well as study/treatment discontinuation – RCT, direct comparison: dupilumab vs. placebo (multipage table)

Study Characteristic Category	PRIME		PRIME2	
	Dupilumab	Placebo	Dupilumab	Placebo
	N[a] = 75	N[a] = 76	N[a] = 78	N[a] = 82

a. Number of randomized patients. Values that are based on other patient numbers are marked in the corresponding line if the deviation is relevant.
b. Institute's calculation.
c. Common reasons for treatment discontinuation in the intervention vs. control arm were, in the PRIME study: withdrawal of consent (0% vs. 11%), lack of efficacy (0% vs. 7%), AEs (0% vs. 4%); and in the PRIME2 study: lack of efficacy (1% vs. 13%), withdrawal of consent (1% vs. 12%), AEs (0% vs. 2%).
d. Common reasons for study discontinuation in the intervention vs. control arm were, in the PRIME study: withdrawal of consent (4% vs. 13%), AEs (0% vs. 1%); and in the PRIME2 study: withdrawal of consent (6% vs. 26%), AEs (0% vs. 2%).

AE: adverse event; F: female; M: male; n: number of patients in the category; N: number of randomized (or included) patients; RCT: randomized controlled trial; SD: standard deviation; TCI: topical calcineurin inhibitor; TCS: topical glucocorticoids

Demographic and disease-specific characteristics are largely comparable between the PRIME and PRIME2 studies as well as between their study arms. Only the proportion of white patients differs slightly between the study arms of the PRIME study (47% versus 59% in the intervention versus control arm). In addition, more than twice as many patients from Western countries were included in the PRIME2 study compared with the PRIME study. Almost all patients in both studies had received prior therapy with TCS, and about 10% with topical calcineurin inhibitors (TCIs). However, only about 60% of patients in the PRIME study and 56% in the PRIME2 study were on this topical therapy with TCS/TCI at baseline.

In both studies, the proportion of patients who discontinued therapy was notably higher in the control arm (21% in the PRIME study and 30% in the PRIME2 study) than in the intervention arm (1% and 3% respectively). The 2 most common reasons for treatment discontinuation in the control arms were withdrawal of consent and lack of efficacy. The proportions of patients who discontinued the study were also notably higher in the comparator arms than in the intervention arms in both studies.

Risk of bias across outcomes (study level)

Table 5 shows the risk of bias across outcomes (risk of bias at study level).

Table 5: Risk of bias across outcomes (study level) – RCT, direct comparison: dupilumab vs. placebo

Study	Adequate random sequence generation	Allocation concealment	Blinding		Reporting independent of the results	No additional aspects	Risk of bias at study level
			Patients	Treating staff			
PRIME	Yes	Yes	Yes	Yes	Yes	Yes	Low
PRIME2	Yes	Yes	Yes	Yes	Yes	Yes	Low
RCT: randomized controlled trial							

The risk of bias across outcomes is rated as low for both studies.

2.2 Results

2.2.1 Outcomes included

The following patient-relevant outcomes were to be included in the assessment:

- Mortality
  - all-cause mortality
- Morbidity
  - symptoms – itching (recorded using Worst Itch Numeric Rating Scale [WI-NRS])
  - symptoms – pain (recorded using Skin Pain NRS)
  - symptoms – pain (recorded using Sleep Quality NRS)
  - symptoms – lesions (recorded as a component of the Prurigo Activity Score [PAS])
  - anxiety and depression symptoms (recorded using the Hospital Anxiety and Depression Scale [HADS])
  - health status
    - Patient Global Impression of Change (PGIC)
    - Patient Global Impression of Severity (PGIS)
    - EQ-5D visual analogue scale (VAS)
- Health-related quality of life
  - recorded using the Dermatology Life Quality Index (DLQI)
- Side effects

- serious adverse events (SAEs)
- discontinuation due to adverse events (AEs)
- eye disorders (System Organ Class [SOC], AEs)
- further specific AEs, if any

The choice of patient-relevant outcomes deviates from that of the company, which used further outcomes in the dossier (Module 4 G).

Table 6 shows the outcomes for which data were available in the studies included.

Table 6: Matrix of outcomes – RCT, direct comparison: dupilumab vs. placebo

Study	Outcomes												
	All-cause mortality[a]	Symptoms – itching (WI-NRS)	Symptoms – pain (Skin Pain NRS)	Symptoms – sleep quality (Sleep Quality NRS)	Symptoms – lesions[b]	Anxiety and depression symptoms (HADS)	Health status (PGIC, EQ-5D VAS)	Health status (PGIS)	Health-related quality of life (DLQI)	SAEs[c]	Discontinuation due to AEs	Eye disorders (SOC, AEs)	Further specific AEs
PRIME	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No[d]
PRIME2	No[e]	No[f]	No[f]	No[f]	No[e]	No[e]	No[e]	Yes	No[e]	No[e]	No[e]	No[e]	No[d]

a. Deaths were recorded within the framework of AEs.
b. Operationalized as 100% healed lesions; proportion of healed lesions is recorded as 1 item by the physician as part of the Prurigo Activity Score (PAS).
c. According to the company, without events assigned to the PT neurodermatitis, which includes the LLT prurigo nodularis and the LLT prurigo nodularis flare.
d. No further specific AEs were identified based on the AEs occurring in the relevant studies.
e. No suitable data for PRIME2; however, there are sufficient suitable data at the level of the IPD meta-analysis; see text below as well as Section 2.2.2.
f. No suitable data for PRIME2 and for the IPD meta-analysis, see text below and Section 2.2.2.

AE: adverse event; DLQI: Dermatology Life Quality Index; HADS: Hospital Anxiety and Depression Scale; LLT: Lowest Level Term; NRS: numeric rating scale; PGIC: Patient Global Impression of Change; PGIS: Patient Global Impression of Severity; PT: Preferred Term, RCT: randomized controlled trial; SAE: serious adverse event; SOC: System Organ Class; VAS: visual analogue scale; WI: Worst Itch

Notes on outcomes

Symptoms – itching (WI-NRS), symptoms – skin pain (Skin Pain NRS), and symptoms – sleep quality (Sleep Quality NRS)

WI-NRS, Skin Pain NRS and Sleep Quality NRS are self-assessment instruments to determine the worst itch, the maximum pain and the worst possible sleep quality within the last 24 hours. Data are recorded using a numerical scale from 0 to 10. For the WI-NRS and Skin Pain NRS, 0 means no itch or pain, while 10 means worst imaginable itch or pain. For the Sleep Quality NRS, however, 0 means worst possible sleep, while 10 means best possible sleep. In the PRIME and PRIME2 studies, all 3 scales were recorded daily via an electronic patient diary beyond the end of treatment (week 24) until the end of the study (week 36). The weekly mean values of the respective instruments were included in the analyses of the company up to week 24.

The present assessment uses the prespecified responder analysis with an improvement of ≥ 4 points at week 24. For the Skin Pain NRS and for the Sleep Quality NRS, the post hoc responder analyses with an improvement of ≥ 1.5 points at week 24 presented by the company in the dossier are used. As explained in the *General Methods* of the Institute [14], for a response criterion to reflect with sufficient certainty a patient-noticeable change, it should correspond to at least 15% of the scale range of an instrument if prespecified (in post-hoc analyses exactly 15% of the scale range). The response criteria presented by the company thus meet the requirements.

Symptoms – lesions

The PAS is a 5-item instrument for the medical assessment of PN lesions. With this instrument, the physician assesses the type of lesions (item 1), the estimated number of lesions (item 2), the distribution of lesions over the body areas (item 3), the exact number of lesions in a representative body area (item 4), as well as crusting (item 5a) and healing of the lesions (item 5b). Recordings were at weeks 0, 4, 8, 12, 24 and at week 36. The company provided analyses for the proportion of patients with ≥ 75% and with 100% healed lesions at week 24 (item 5b) as well as the change in the number of lesions in a representative body area (item 4) at week 24.

The proportion of patients with 100% healed lesions at week 24 (end of treatment) is used for the present assessment. This means complete healing of the external signs (i.e. 100% compared with baseline) and is a patient-relevant outcome.

Anxiety symptoms (HADS-A) and depression symptoms (HADS-D)

The HADS is a patient-reported instrument to assess the severity of anxiety and of depression symptoms during the past week [15-17]. The instrument is used in different therapeutic indications associated with these symptoms. The 14 questions of the scale are grouped into 2 subscales (anxiety symptoms [HADS-A] and depression symptoms [HADS-D]) with 7 items

each. The questions on the 2 subscales alternate in the questionnaire. All questions are answered on Likert scales from 0 to 3, with 0 indicating normal and 3 indicating the highest level of anxiety or depression. Possible scores range from 0 to 21 for each HADS subscale. A score of 0 to 7 points is interpreted as normal, 8 to 10 points indicate anxiety or depression, and scores ≥ 11 indicate the probable presence of these disorders [16]. The questionnaire was recorded at week 0, 12, 24 (end of treatment) and week 36 (end of study).

The responder analysis defined post hoc with an improvement of ≥ 3.15 points at week 24 presented by the company in the dossier is used for each of the 2 subscales, HADS-A and HADS-D. This response criterion corresponds to 15% of the subscales' scale range.

Health status (PGIC)

The PGIC consists of a single question that asks patients to provide the overall self-assessment of change in their disease since starting treatment on a 7-point scale (from "very much better" to "very much worse"). The PGIC was recorded at weeks 4, 8, 12 and 24. In its dossier, the company presented, among other things, responder analyses showing the best assessment of change ("very much better" [0]), the 2 best assessments of change ("better" [1] or "very much better" [0]), or the 2 worst assessments of change ("worse" [5] or "very much worse" [6]). The present assessment uses the results on the proportion of patients who assessed their health status at week 24 as "very much better" or "much better" compared with the start of treatment.

Health status (PGIS)

The PGIS consists of a single question that asks patients to provide an assessment of their disease severity on a 4-point scale (from 1 = "none" to 4 = "severe") for the past week. The PGIS was recorded at screening and at weeks 0, 4, 8, 12 and 24. In its dossier, the company presented analyses for the proportion of patients with a PGIS of 1 (none) or with a PGIS of 1 or 2 (none or mild) at week 24 as well as the change in PGIS at week 24 compared with baseline. Since the aim of treatment in the present therapeutic indication is an improvement in health status, the change in the PGIS at week 24 is used instead of the proportions with a defined health status.

Notes on the analyses presented

Planned duration of follow-up after treatment and study discontinuation

Patients who discontinued treatment prematurely (prior to completing the 24-week treatment period) performed an early termination visit as soon as possible after treatment discontinuation. Analogous to the actual end-of-study visit, all outcomes on morbidity, health-related quality of life and adverse events (AEs) were recorded at this visit. In addition, the patients were asked to participate in all remaining study visits and recordings (especially the recording of AEs) according to the plan.

Analogous to the procedure in case of treatment discontinuation, patients who discontinued not only treatment, but also the study performed an early termination visit as soon as possible after study discontinuation. In addition, the value of their participation in the study was emphasized to the patients, and attempts were made to convince them to participate in further recordings of the study.

For the analyses in Module 4 G, the company considered all data, including data recorded after study discontinuation and/or use of prohibited medication or rescue therapy. Missing values at week 24 were imputed by means of multiple imputation (MI) for the analysis of continuous outcomes and rated as non-responders for the analysis of dichotomous outcomes (non-responder imputation [NRI]). This analysis was prespecified as one of 3 supplementary analyses in the statistical analysis plan.

Large proportion of missing values with discrepancy between study arms

The information provided by the company shows that values for morbidity and health-related quality of life outcomes at the analysis date of 24 weeks were missing to a relevant extent and were imputed. For the PRIME2 study, the proportion is so high in each case that, with the exception of the PGIS, no usable data are available (for explanation, see Section 2.2.2). At the level of the meta-analysis of individual patient data (IPD), however, there is sufficient suitable data (except for the 3 outcomes of itching, skin pain and sleep quality [NRS]) (see Section 2.2.2).

No information on observation period

As described in Section 2.1, a relevant proportion of patients in both studies discontinued treatment and the study, with notably more discontinuations in the control arms than in the intervention arms. Data are available on treatment durations, but not on observation durations (overall and outcome-specific). For the PRIME2 study in particular, however, the difference in the proportion of treatment discontinuations between the study arms is so high (23%) that it is unclear whether the observation durations do not also differ to a relevant extent. The analyses of AEs are therefore not usable for the PRIME2 study. At the level of the IPD meta-analysis, however, there are sufficient suitable data (see Section 2.2.2).

2.2.2 Risk of bias

Table 7 describes the risk of bias for the results of the relevant outcomes.

Table 7: Risk of bias across outcomes and outcome-specific risk of bias – RCT, direct comparison: dupilumab versus placebo

Study	Study level	Outcomes												
		All-cause mortality[a]	Symptoms – itching (WI-NRS)	Symptoms – pain (Skin Pain NRS)	Symptoms – sleep quality (Sleep Quality NRS)	Symptoms – lesions[b]	Anxiety and depression symptoms (HADS)	Health status (PGIC, EQ-5D VAS)	Health status (PGIS)	Health-related quality of life (DLQI)	SAEs[c]	Discontinuation due to AEs	Eye disorders (SOC, AEs)	Further specific AEs
PRIME	L	H[d]	H[e]	H[e]	H[e]	H[e]	H[e]	H[e]	H[e]	H[e]	H[d]	H[d]	H[d]	–
PRIME2	L	–[f]	–[g]	–[g]	–[g]	–[g]	–[g]	–[g]	H[e]	–[g]	–[f]	–[f]	–[f]	–
IPD meta-analysis	L	H[d]	–[g]	–[g]	–[g]	H[e]	H[e]	H[e]	H[e]	H[e]	H[d]	H[d]	H[d]	–

a. Deaths were recorded within the framework of AEs.
b. Operationalized as 100% healed lesions; proportion of healed lesions is recorded as 1 item by the physician as part of the Prurigo Activity Score (PAS).
c. According to the company, without events assigned to the PT neurodermatitis, which includes the LLT prurigo nodularis and the LLT prurigo nodularis flare.
d. Potentially informative censoring due to different proportions of study discontinuations and reasons for study discontinuation.
e. Large difference in the proportions of imputed values between the 2 arms.
f. No usable data due to potentially informative censoring due to different proportions of study discontinuations and reasons for study discontinuation.
g. No usable data because the difference in the proportions of imputed values between the 2 arms is too large.

AE: adverse event; DLQI: Dermatology Life Quality Index; H: high; HADS: Hospital Anxiety and Depression Scale; IPD: individual patient data; L: low; LLT: Lowest Level Term; NRS: numeric rating scale; PGIC: Patient Global Impression of Change; PGIS: Patient Global Impression of Severity; PT: Preferred Term, RCT: randomized controlled trial; SAE: serious adverse event; SOC: System Organ Class; VAS: visual analogue scale; WI: Worst Itch

In the PRIME study, the risk of bias for the results on all outcomes is rated as high. For the morbidity and health-related quality of life outcomes, this is due to the high proportions of imputed values that are discrepant between the treatment arms (1.3% in the intervention arm versus 14.5% to 21.1% in the control arm). For the outcome of all-cause mortality, captured via the recording of AEs, and the side effects outcomes, the risk of bias of the results is rated as high due to incomplete observations for potentially informative reasons.

In the PRIME2 study, no usable data are available for all outcomes except for the outcome of health status (PGIS), as the difference in the proportions of imputed values between the 2 arms (3.8% in the intervention arm vs. 24.4% to 29.3% in the control arm) or the difference in the proportion of study discontinuations between the treatment arms is too high, and it is unclear whether the observation periods do not also differ to a relevant extent. For the results of the outcome of health status (PGIS), for which the continuous analysis (change in PGIS at week 24) with multiple imputation is used, the risk of bias is rated as high due to the high proportions of imputed values that differed between the treatment arms (3.8% in the intervention arm versus 24.4% in the control arm).

Due to the identical study design of the 2 studies PRIME and PRIME2 and since there are no other aspects of bias beyond the large difference in the proportions of missing and imputed values, the risk of bias in the present situation can be determined not only at the individual study level, but additionally for the results of the IPD meta-analysis. Instead of the proportions of missing and imputed values of the individual studies, those of the pooled meta-analysis are considered to assess the risk of bias. This results in the following constellations: In the IPD meta-analysis, the risk of bias for the results on all outcomes is rated as high. For the morbidity and health-related quality of life outcomes, this is due to the high proportions of imputed values that are discrepant between the treatment arms (2.6% in the intervention arm versus 19.6% to 20.3% in the control arm). For the outcome of all-cause mortality and the side effects outcomes, the risk of bias of the results is rated high due to incomplete observations for potentially informative reasons. However, the data for the outcomes of itching, skin pain and sleep quality are still not usable in the meta-analysis because the difference in the proportions of missing values between the 2 arms is too high (2.6% in the intervention arm versus 25.3% in the control arm).

2.2.3 Results

Table 8 and Table 9 summarize the results on the comparison of dupilumab with placebo in adult patients with moderate to severe prurigo nodularis who are candidates for systemic therapy. Where necessary, calculations conducted by the Institute are provided in addition to the data from the company's dossier.

Forest plots of the presented meta-analyses can be found in Appendix A. The results on common AEs, common SAEs and discontinuations due to AEs are presented in Appendix B.

Table 8: Results (mortality, morbidity, health-related quality of life, and side effects, dichotomous) – RCT, direct comparison: dupilumab vs. placebo (multipage table)

Outcome category Outcome Study	Dupilumab N	Dupilumab Patients with event n (%)	Placebo N	Placebo Patients with event n (%)	Dupilumab vs. placebo RR [95% CI]; p-value[a]
Mortality					
All-cause mortality[b]					
PRIME	75	0 (0)	76	0 (0)	–
PRIME 2	78	0 (0)	82	0 (0)	–[c]
Morbidity					
Symptoms					
Itching (improvement by ≥ 4 points)[d, e]					
PRIME	75	48 (64.0)	76	19 (25.0)	2.77 [1.71; 4.48]; < 0.001
PRIME2				No usable data[c]	
Total					–[c]
Skin pain (improvement by ≥ 1.5 points)[f, e]					
PRIME	75	63 (84.0)	76	39 (51.3)	1.62 [1.25; 2.09]; < 0.001
PRIME2				No usable data[c]	
Total					–[c]
Sleep quality (improvement by ≥ 1.5 points)[g, e]					
PRIME	75	45 (60.0)	76	24 (31.6)	2.12 [1.41; 3.19]; < 0.001
PRIME2				No usable data[c]	
Total					–[c]
Lesions[h, e]					
PRIME	75	11 (14.7)	76	2 (2.6)	6.03 [1.24; 29.34]; 0.026
PRIME2	78	17 (21.8)	82	3 (3.7)	–[c]
Total	153	28 (18.3)	158	5 (3.2)	6.69 [2.22; 20.17]; < 0.001
Anxiety symptoms (HADS-A, improvement by ≥ 3.15 points)[i, e]					
PRIME	75	29 (38.7)	76	16 (21.1)	2.02 [1.17; 3.50]; 0.0121
PRIME2	78	36 (46.2)	82	17 (20.7)	–[c]
Total	153	65 (42.5)	158	33 (20.9)	2.08 [1.44; 3.00]; < 0.001
Depression symptoms (HADS-D, improvement by ≥ 3.15 points)[i, e]					
PRIME	75	21 (28)	76	12 (15.8)	1.86 [0.93; 3.74]; 0.081
PRIME2	78	24 (30.8)	82	12 (14.6)	–[c]
Total	153	45 (29.4)	158	24 (15.2)	2.12 [1.32; 3.40]; 0.002

Table 8: Results (mortality, morbidity, health-related quality of life, and side effects, dichotomous) – RCT, direct comparison: dupilumab vs. placebo (multipage table)

Outcome category Outcome Study	Dupilumab N	Dupilumab Patients with event n (%)	Placebo N	Placebo Patients with event n (%)	Dupilumab vs. placebo RR [95% CI]; p-value[a]
Health status					
PGIC[j, d]					
PRIME	75	64 (85.3)	76	28 (36.8)	2.25 [1.66; 3.04]; < 0.001
PRIME2	78	61 (78.2)	82	31 (37.8)	–[c]
Total	153	125 (81.7)	158	59 (37.3)	2.28 [1.82; 2.86]; < 0.001
EQ-5D VAS (improvement by ≥ 15 points)[k, e]					
PRIME	75	31 (41.3)	76	13 (17.1)	2.50 [1.30; 4.82]; 0.006
PRIME2	78	35 (44.9)	82	23 (28.0)	–[c]
Total	153	66 (43.1)	158	36 (22.8)	2.01 [1.39; 2.92]; < 0.001
Health-related quality of life					
DLQI (0 or 1)[l, e]					
PRIME	75	20 (26.7)	76	13 (17.1)	1.52 [0.78; 2.96]; 0.219
PRIME2	78	17 (21.8)	82	4 (4.9)	–[c]
Total	153	37 (24.2)	158	17 (10.8)	2.39 [1.31; 4.34]; 0.004
Side effects					
AEs (supplementary information)[m]					
PRIME	75	52 (69.3)	75	44 (58.7)	–
PRIME2	77	47 (61)	82	44 (53.7)	–
SAEs[m]					
PRIME	75	5 (6.7)	75	7 (9.3)	0.71 [0.24; 2.17]; 0.551
PRIME2	77	2 (2.6)	82	4 (4.9)	–[c]
Total	152	7 (4.6)	157	11 (7)	0.65 [0.26; 1.64]; 0.361
Discontinuation due to AEs					
PRIME	75	0 (0)	75	3 (4)	0.13[n] [0.01; 1.29]; 0.081
PRIME2	77	0 (0)	82	1 (1.2)	–[c]
Total	152	0 (0)	157	4 (2.5)	0.14[n] [0.02; 0.98]; 0.048
Eye disorders (SOC, AEs)					
PRIME	75	2 (2.7)	75	3 (4.0)	0.67 [0.11; 3.88]; 0.652[o]
PRIME2	77	6 (7.8)	82	2 (2.4)	–[c]
Total	152	8 (5.3)	157	5 (3.2)	1.66 [0.55; 4.94]; 0.363[o]

Table 8: Results (mortality, morbidity, health-related quality of life, and side effects, dichotomous) – RCT, direct comparison: dupilumab vs. placebo (multipage table)

Outcome category Outcome Study	Dupilumab N	Dupilumab Patients with event n (%)	Placebo N	Placebo Patients with event n (%)	Dupilumab vs. placebo RR [95% CI]; p-value[a]
Supplementary: conjunctivitis (broad CMQ)[p]					
PRIME	*75*	*3 (4.0)*	*75*	*3 (4.0)*	*1.00 [0.21; 4.80]; > 0.999[o]*
PRIME2	*77*	*5 (6.5)*	*82*	*0 (0)*	*–[c]*
Total	*152*	*8 (5.3)*	*157*	*3 (1.9)*	*2.49 [0.74; 8.42]; 0.143[o]*

a. RR [95% CI], p-value for the individual studies from Cochran-Mantel-Haenszel test stratified by atopic history (atopic or non-atopic), TCS/TCI treatment (yes or no), region, antidepressants at baseline (yes or no); for the IPD meta-analysis, same model with study (PRIME or PRIME2) as additional stratification factor.
b. Deaths were recorded within the framework of AEs.
c. No usable data for the PRIME2 study or for the IPD meta-analysis of the 2 studies PRIME and PRIME2 (for explanation, see Section 2.2.2).
d. Proportion of patients with a score decrease by ≥ 4 points from baseline to week 24, at a scale range of 0 to 10. Lower (decreasing) values indicate an improvement in symptoms.
e. For the time point of end of treatment (week 24), missing observations were imputed by non-responder imputation (NRI).
f. Proportion of patients with a score decrease by ≥ 1.5 points from baseline to week 24, at a scale range of 0 to 10. Lower (decreasing) values indicate an improvement in symptoms.
g. Proportion of patients with a score increase by ≥ 1.5 points from baseline to week 24, at a scale range of 0 to 10. Higher (increasing) values indicate an improvement in symptoms.
h. Proportion of patients with 100% healed lesions at week 24.
i. Proportion of patients with decrease (of the anxiety score [HADS-A] and the depression score [HADS-D]) by ≥ 3.15 points from baseline to week 24, at a scale range of 0 to 21. Lower (decreasing) values indicate an improvement in symptoms.
j. Proportion of patients who assessed their health as much better or better at week 24 compared with baseline.
k. Proportion of patients with a score increase by ≥ 15 points from baseline to week 24, at a scale range of 0 to 100. Higher (increasing) values indicate an improvement in health status.
l. Proportion of patients achieving a DLQI of 0 or 1 (no impairment in quality of life) at week 24.
m. Without the following disease-related events: LLT prurigo nodularis and LLT prurigo nodularis flare.
n. Peto OR as estimator for the relative risk; the p-value was determined via a normal approximation.
o. RR [95% CI], p-value: Institute's calculation, Cochran-Mantel-Haenszel test stratified by study only. In case of 0 events in one study arm, the correction factor 0.5 was used for the calculation of effect and CI in both study arms.
p. Prespecified operationalization for conjunctivitis with 16 PTs (broad conjunctivitis CMQ).

AE: adverse event; CI: confidence interval; CMQ: Custom MedDRA Query; DLQI: Dermatology Life Quality Index; HADS: Hospital Anxiety and Depression Scale; IPD: individual patient data; LLT: Lowest Level Term; n: number of patients with (at least one) event; N: number of analysed patients; OR: odds ratio; PGIC: Patient Global Impression of Change; PT: Preferred Term; RCT: randomized controlled trial; RR: relative risk; SAE: serious adverse event; SOC: System Organ Class; TCI: topical calcineurin inhibitor; TCS: topical corticosteroids; VAS: visual analogue scale

Table 9: Results (morbidity, continuous) – RCT, direct comparison: dupilumab vs. placebo

Outcome category Outcome Study	Dupilumab			Placebo			Dupilumab vs. placebo
	N[a]	Values at baseline mean (SD)	Change at week 24 N[b]; mean[c] (SE)	N[a]	Values at baseline mean (SD)	Change at week 24 N[b]; mean[c] (SE)	MD[c] [95% CI]; p-value
Morbidity							
Health status							
PGIS[d]							
PRIME	75	3.28 (0.45)	74; –1.64 (0.17)	76	3.29 (0.46)	65; –0.78 (0.18)	–0.75 [–0.99; –0.50]; < 0.001
PRIME2	78	3.74 (0.55)	75; –1.63 (0.18)	82	3.72 (0.48)	62; –0.89 (0.17)	–0.74 [–1.03; –0.44]; < 0.001
Total	153	3.71 (0.52)	149; –1.64 (0.1)	158	3.65 (0.49)	127; –0.93 (0.1)	–0.71 [–0.90; –0.52] < 0.001 SMD: -0.88 [-1.12; -0.65]

a. Number of patients taken into account in the analysis for calculating the effect estimate at week 24 may rest on different patient numbers.
b. Number of patients with values at week 24.
c. ANCOVA analysis of the ITT population with baseline value, treatment group, atopic history (atopic or non-atopic), TCS/TCI treatment (yes or no), region, antidepressants at baseline (yes or no) and study indicator (PRIME or PRIME2) as covariates. Missing values were imputed using multiple imputation (MI).
d. Lower (decreasing) values indicate improved health status; negative effects (intervention minus control) indicate an advantage for the intervention (scale range of 1 to 4).

ANCOVA: analysis of covariance; CI: confidence interval; ITT: intention to treat; MD: adjusted mean difference; N: number of analysed patients; RCT: randomized controlled trial; SD: standard deviation; SE: standard error; SMD: standardized mean difference; TCI: topical calcineurin inhibitor; TCS: topical corticosteroids

Mortality

No deaths occurred during the PRIME and PRIME2 studies.

Morbidity

Symptoms – itching, symptoms – skin pain, and symptoms – sleep quality

No usable data are available for the meta-analysis for the outcomes of itching (WI-NRS, improvement by ≥ 4 points), skin pain (Skin Pain NRS, improvement by ≥ 1,5 points), and sleep quality (Sleep Quality NRS, improvement by ≥ 1,5 points). Considering the PRIME study alone, there was a statistically significant difference in favour of dupilumab compared with placebo for all 3 outcomes listed above.

Symptoms – lesions

For the outcome of lesions (100% healed lesions), the meta-analysis of the studies PRIME and PRIME2 showed a statistically significant difference in favour of dupilumab over placebo.

Anxiety and depression symptoms

For each of the outcomes of anxiety symptoms (HADS-A, improvement by ≥ 3.15 points) and depression symptoms (HADS-D, improvement by ≥ 3.15 points), the meta-analysis of the studies PRIME and PRIME2 showed a statistically significant difference in favour of dupilumab over placebo.

Health status (PGIC and EQ-5D VAS)

For the outcomes of PGIC (0 or 1) and EQ-5D VAS (improvement by 15 points), the meta-analysis of the studies PRIME and PRIME2 showed a statistically significant difference in favour of dupilumab over placebo.

Health status (PGIS)

For the outcome of PGIS (change at week 24), the meta-analysis of the studies PRIME and PRIME2 showed a statistically significant and relevant difference in favour of dupilumab over placebo.

Health-related quality of life

DLQI

For the DLQI (0 or 1), the meta-analysis of the studies PRIME and PRIME2 showed a statistically significant difference in favour of dupilumab over placebo, but there is an effect modification by sex (see Section 2.2.4).

Side effects

SAEs and eye disorders (SOC, AEs)

For the outcomes of SAEs and eye disorders (SOC, AEs), the meta-analysis of the studies PRIME and PRIME2 showed no statistically significant difference between treatment groups.

Discontinuation due to AEs

For the outcome of discontinuation due to AEs, the meta-analysis of the studies PRIME and PRIME2 showed a statistically significant difference in favour of dupilumab over placebo.

2.2.4 Subgroups and other effect modifiers

The following subgroup characteristics are relevant for the present analysis:

- Age (< 65 years versus ≥ 65 years)

- Sex (male versus female)
- Disease severity (Investigator Global Assessment for Prurigo Nodularis-Stage [IGA PN-S] 3 versus IGA PN-S 4)

Interaction tests are performed when at least 10 patients per subgroup are included in the analysis. Moreover, for binary data, there have to be at least 10 events in at least one subgroup.

Only the results with an effect modification with a statistically significant interaction between treatment and subgroup characteristic (p-value < 0.05) are presented. In addition, subgroup results are presented only if there is a statistically significant and relevant effect in at least one subgroup. Subgroup results where the extent does not differ between subgroups are not presented.

Table 10 presents the subgroup results of dupilumab in comparison with placebo.

Table 10: Subgroups (health-related quality of life, dichotomous) – RCT, direct comparison: dupilumab vs. placebo

Outcome Characteristic Study Subgroup	Dupilumab N	Dupilumab Patients with event n (%)	Placebo N	Placebo Patients with event n (%)	Dupilumab vs. placebo RR [95% CI][a]	Dupilumab vs. placebo p-value[a]
DLQI (0 or 1)[b, c]						
Sex						
PRIME						
Men	23	12 (52.2)	28	4 (14.3)	2.86 [0.96; 8.54]	0.060
Women	52	8 (15.4)	48	9 (18.8)	0.99 [0.42; 2.34]	0.979
PRIME2						
Men	26	9 (34.6)	31	2 (6.5)	–[d]	
Women	52	8 (15.4)	51	2 (3.9)	–[d]	
Total					Interaction:	0.034[e]
Men	49	21 (42.9)	59	6 (10.2)	3.89 [1.44; 10.52]	0.008
Women	104	16 (15.4)	99	11 (11.1)	1.61 [0.75; 3.46]	0.220

a. RR [95% CI], p-value for the individual studies from Cochran-Mantel-Haenszel test stratified by atopic history (atopic or non-atopic), TCS/TCI treatment (yes or no), region, antidepressants at baseline (yes or no); for the IPD meta-analysis, same model with study (PRIME or PRIME2) as additional stratification factor.
b. Proportion of patients achieving a DLQI of 0 or 1 (no impairment in quality of life) at week 24.
c. For the time point of end of treatment (week 24), missing observations were imputed by non-responder imputation (NRI).
d. No usable data due to the large difference in the proportions of imputed values between the 2 treatment arms (for explanation, see Section 2.2.2).
e. p-value for the interaction test based on logistic regression with atopic history (atopic or non-atopic), TCS/TCI treatment (yes or no), region, antidepressants at baseline (yes or no) sex and interaction as fixed factors; for the IPD meta-analysis, same model with study (PRIME or PRIME2) as additional fixed factor.

CI: confidence interval; DLQI: Dermatology Life Quality Index; IPD: individual patient data; n: number of patients with (at least one) event; N: number of analysed patients; RCT: randomized controlled trial; RR: relative risk; TCI: topical calcineurin inhibitor; TCS: topical corticosteroids

There was an effect modification by the characteristic of sex for the outcome of DLQI (0 or 1) in the meta-analysis. For male patients, a statistically significant difference was shown in favour of dupilumab versus placebo. For female patients, in contrast, there was no statistically significant difference between treatment groups.

2.2.5 Summary of the results

Overall, the meta-analysis showed advantages of dupilumab for the following outcomes: lesions, anxiety and depression symptoms, health status (PGIC, PGIS and EQ-5D VAS), health-related quality of life (DLQI, subgroup of men), and discontinuation due to AEs. Due to the large differences in the proportions of imputed values between the treatment arms, the data

of the meta-analysis are not usable for the outcomes of itching, skin pain, and sleep quality. Considering the PRIME study alone, there is an advantage of dupilumab compared with placebo for all of these 3 outcomes.

2.3 Summary

Overall, there is no change to the conclusion on the added benefit of dupilumab drawn in dossier assessment A23-24 [1].

The following Table 11 shows the result of the benefit assessment of dupilumab under consideration of dossier assessment A23-24 and the present addendum.

Table 11: Dupilumab – probability and extent of added benefit

Therapeutic indication	**ACT[a]**	**Probability and extent of added benefit**
Moderate-to-severe prurigo nodularis in adults who are candidates for systemic therapy	BSC[b, c]	Added benefit not proven

a. Presented is the ACT specified by the G-BA.
b. BSC refers to the therapy that provides the patient with the best possible, individually optimized, supportive treatment to alleviate symptoms and improve the quality of life. BSC may include the use of topical basic skin care therapy, topical glucocorticoids, and UVB phototherapy. If treatment needs to be adjusted for the patients (e.g. different dosages of topical glucocorticoids), such adjustments should be made.
c. In the present case, the drugs recommended in guidelines or used in clinical practice, that have no or no explicit approval for the present therapeutic indication, cannot be considered as ACT in the narrower sense within the meaning of §2 para 1 S. 3, §12 SGB V (BSG judgment of 22 February 2023, reference number: B 3 KR 14/21 R).

ACT: appropriate comparator therapy; BSC: best supportive care; BSG: Federal Social Court; G-BA: Federal Joint Committee.; SGB: Social Code Book; UVB: ultraviolet B radiation

The G-BA decides on the added benefit.

3 References

The reference list contains citations provided by the company in which bibliographical information may be missing.

1. Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen. Dupilumab (Prurigo nodularis); Nutzenbewertung gemäß § 35a SGB V; Dossierbewertung [online]. 2023 [Accessed: 11.07.2023]. URL: https://www.iqwig.de/download/a23-24_dupilumab_nutzenbewertung-35a-sgb-v_v1-0.pdf.

2. Sanofi-Aventis Deutschland. Dupilumab (Dupixent); Dossier zur Nutzenbewertung gemäß § 35a SGB V [online]. 2023 [Accessed: 10.08.2023]. URL: https://www.g-ba.de/bewertungsverfahren/nutzenbewertung/944/#dossier.

3. Sanofi-Aventis Deutschland. Stellungnahme zum IQWiG-Bericht Nr. 1589: Dupilumab (Prurigo nodularis); Nutzenbewertung gemäß § 35a SGB V; Dossierbewertung. [Demnächst verfügbar unter: https://www.g-ba.de/bewertungsverfahren/nutzenbewertung/944/#beschluesse im Dokument "Zusammenfassende Dokumentation"].

4. Gemeinsamer Bundesausschuss. Mündliche Anhörung gemäß 5. Kapitel § 19 Abs. 2 Verfahrensordnung des Gemeinsamen Bundesausschusses; hier: Wirkstoff Dupilumab (D-915) - stenografisches Wortprotokoll [online]. 2023 [Accessed: 25.08.2023]. URL: https://www.g-ba.de/downloads/91-1031-944/2023-08-08_Wortprotokoll_Dupilumab_D-915.pdf.

5. Sanofi-Aventis. A randomized, double blind, placebo-controlled, multi-center, parallel group study to evaluate the efficacy and safety of dupilumab in patients with prurigo nodularis who are inadequately controlled on topical prescription therapies or when those therapies are not advisable (LIBERTY-PN PRIME); study EFC16459; Clinical Study Report [unpublished]. 2022.

6. Sanofi-Aventis. A randomized, double blind, placebo-controlled, multi-center, parallel group study to evaluate the efficacy and safety of dupilumab in patients with prurigo nodularis who are inadequately controlled on topical prescription therapies or when those therapies are not advisable (LIBERTY-PN PRIME); study EFC16459; Clinical Study Report Addendum [unpublished]. 2022.

7. Sanofi. Study of Dupilumab for the Treatment of Patients With Prurigo Nodularis, Inadequately Controlled on Topical Prescription Therapies or When Those Therapies Are Not Advisable (LIBERTY-PN PRIME) [online]. 2022 [Accessed: 24.04.2023]. URL: https://ClinicalTrials.gov/show/NCT04183335.

8. Sanofi-aventis Recherche & Développement. A randomized, double blind, placebo-controlled, multi-center, parallel group study to evaluate the efficacy and safety of dupilumab in patients with prurigo nodularis who are inadequately controlled on topical prescription therapies or when those therapies are not advisable [online]. [Accessed: 24.04.2023]. URL: https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2019-003774-41.

9. Yosipovitch G, Mollanazar N, Stander S et al. Dupilumab in patients with prurigo nodularis: two randomized, double-blind, placebo-controlled phase 3 trials. Nat Med 2023; 29(5): 1180-1190. https://dx.doi.org/10.1038/s41591-023-02320-9.

10. Sanofi-Aventis. A randomized, double blind, placebo-controlled, multi-center, parallel group study to evaluate the efficacy and safety of dupilumab in patients with prurigo nodularis who are inadequately controlled on topical prescription therapies or when those therapies are not advisable (LIBERTY-PN PRIME2); study EFC16460; Clinical Study Report [unpublished]. 2022.

11. Sanofi-Aventis. A randomized, double blind, placebo-controlled, multi-center, parallel group study to evaluate the efficacy and safety of dupilumab in patients with prurigo nodularis who are inadequately controlled on topical prescription therapies or when those therapies are not advisable (LIBERTY-PN PRIME2); study EFC16460; Clinical Study Report Addendum [unpublished]. 2022.

12. Sanofi. Study of Dupilumab for the Treatment of Patients With Prurigo Nodularis, Inadequately Controlled on Topical Prescription Therapies or When Those Therapies Are Not Advisable (PRIME2) [online]. 2022 [Accessed: 24.04.2023]. URL: https://ClinicalTrials.gov/show/NCT04202679.

13. Sanofi-aventis Recherche & Développement. A randomized, double blind, placebo-controlled, multi-center, parallel group study to evaluate the efficacy and safety of dupilumab in patients with prurigo nodularis who are inadequately controlled on topical prescription therapies or when those therapies are not advisable [online]. [Accessed: 24.04.2023]. URL: https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2019-003801-90.

14. Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen. Allgemeine Methoden; Version 6.1 [online]. 2022 [Accessed: 27.01.2022]. URL: https://www.iqwig.de/methoden/allgemeine-methoden-v6-1.pdf.

15. Herrmann C. International experiences with the Hospital Anxiety and Depression Scale--a review of validation data and clinical results. J Psychosom Res 1997; 42(1): 17-41. https://dx.doi.org/10.1016/s0022-3999(96)00216-4.

16. Snaith RP. The Hospital Anxiety And Depression Scale. Health Qual Life Outcomes 2003; 1: 29. https://dx.doi.org/10.1186/1477-7525-1-29.

17. Zigmond AS, Snaith RP. The hospital anxiety and depression scale. Acta Psychiatr Scand 1983; 67(6): 361-370. https://dx.doi.org/10.1111/j.1600-0447.1983.tb09716.x.

Appendix A Figures on meta-analyses (forest plots)

A.1 Morbidity

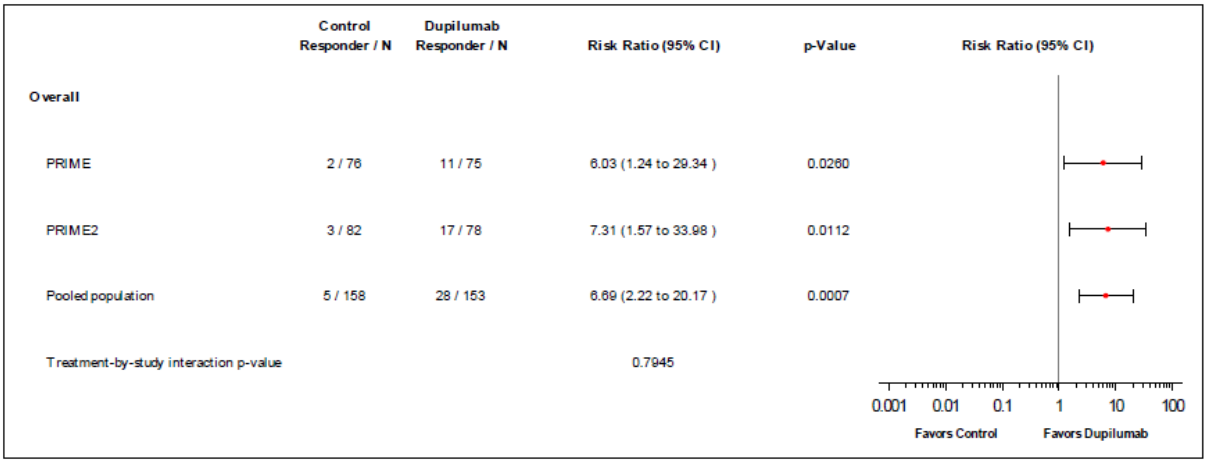

Figure 1: IPD meta-analysis for the outcome of lesions; effect measure: RR; PRIME and PRIME2 studies: dupilumab vs. placebo

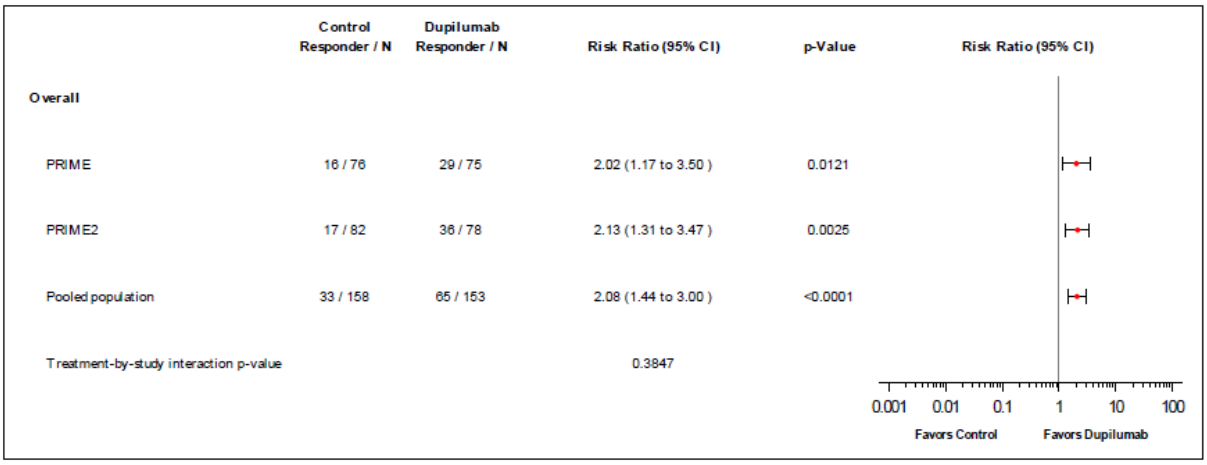

Figure 2: IPD meta-analysis for the outcome of anxiety symptoms (HADS-A); effect measure: RR; PRIME and PRIME2 studies: dupilumab vs. placebo

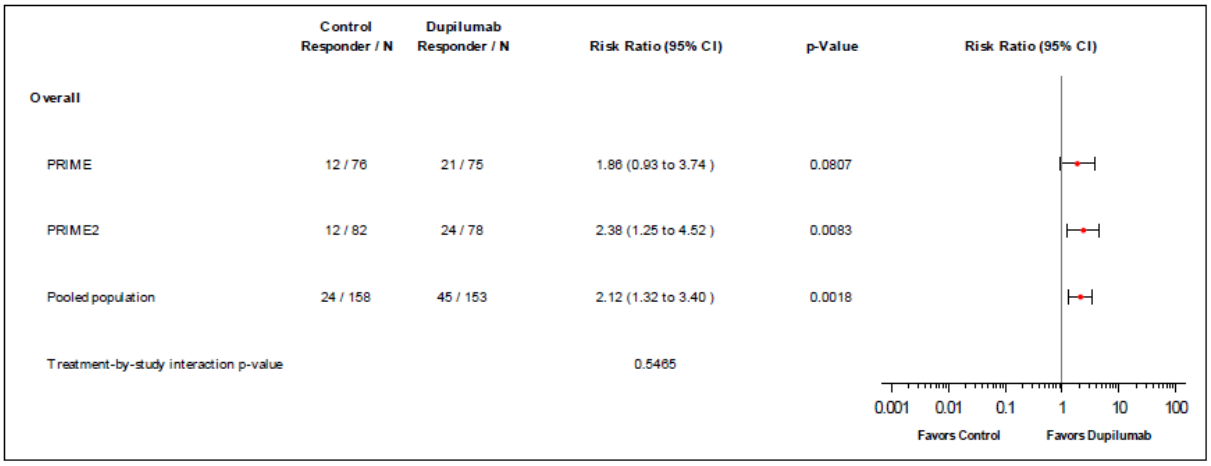

Figure 3: IPD meta-analysis for the outcome of depression symptoms (HADS-D); effect measure: RR; PRIME and PRIME2 studies: dupilumab vs. placebo

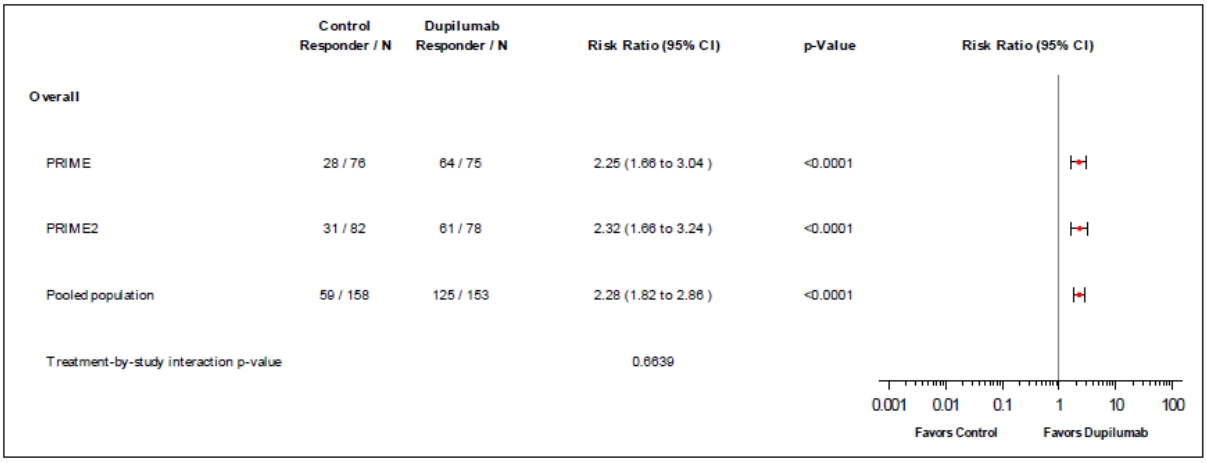

Figure 4: IPD meta-analysis for the outcome of health status (PGIC); effect measure: RR; PRIME and PRIME2 studies: dupilumab vs. placebo

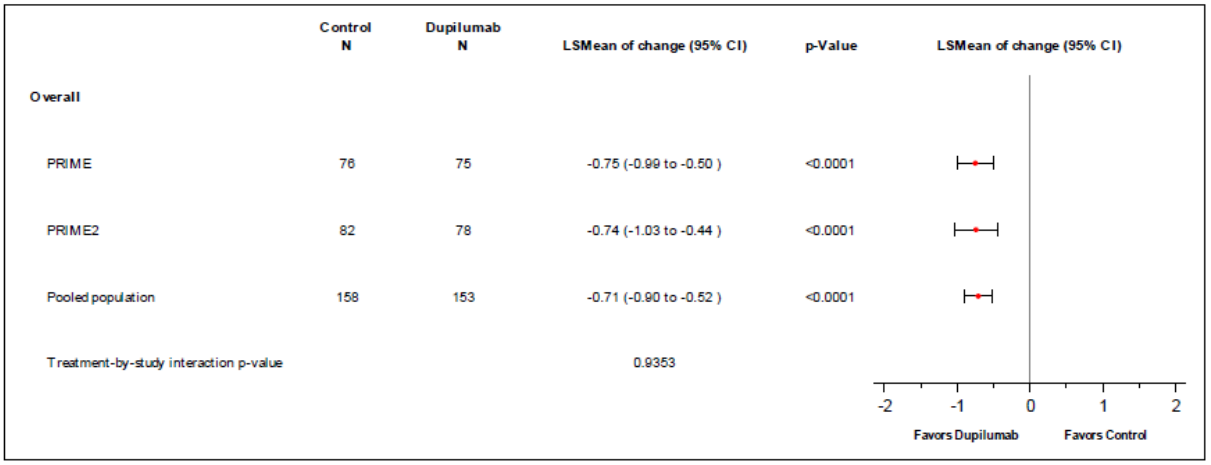

Figure 5: IPD meta-analysis for the outcome of health status (PGIS); effect measure: mean difference; PRIME and PRIME2 studies: dupilumab vs. placebo

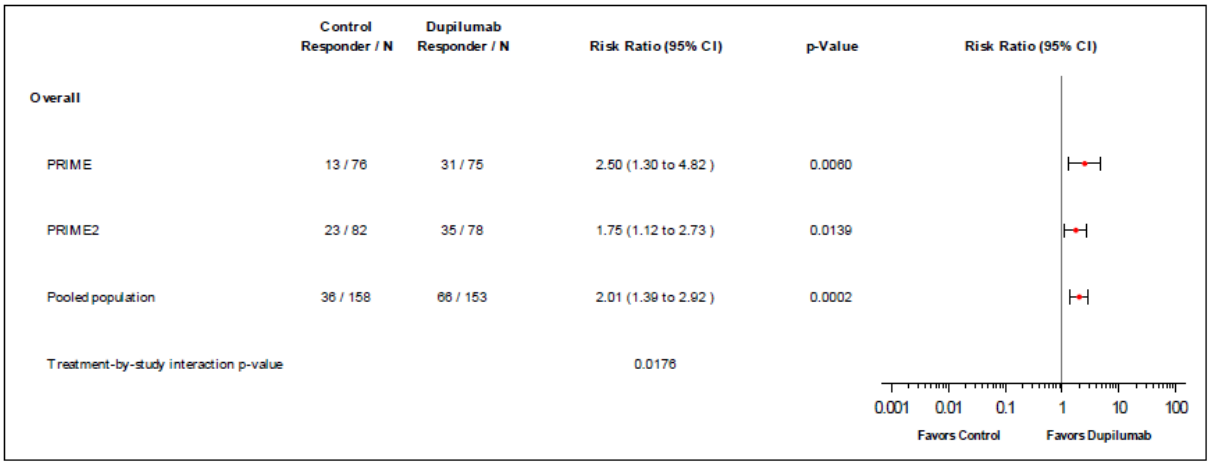

Figure 6: IPD meta-analysis for the outcome of health status (EQ-5D VAS); effect measure: RR; PRIME and PRIME2 studies: dupilumab vs. placebo

A.2 Health-related quality of life

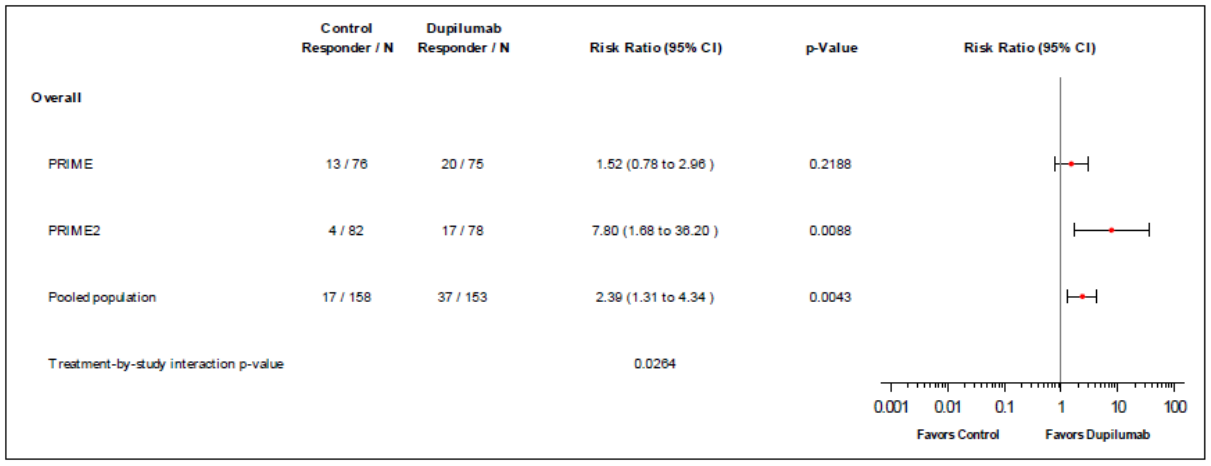

Figure 7: IPD meta-analysis for the outcome of DLQI; effect measure: RR; PRIME and PRIME2 studies: dupilumab vs. placebo

A.3 Side effects

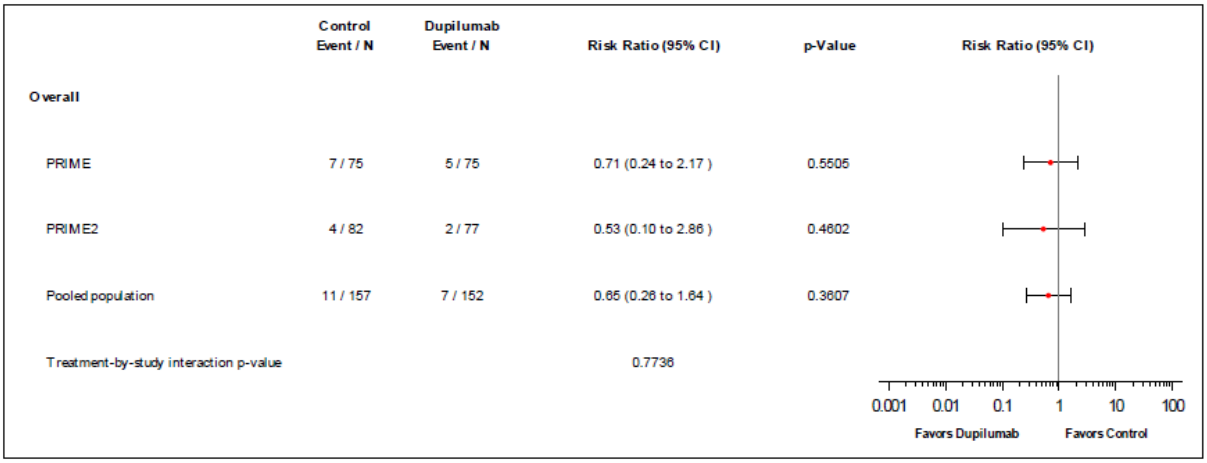

Figure 8: IPD meta-analysis for the outcome of SAEs; effect measure: RR; PRIME and PRIME2 studies: dupilumab vs. placebo

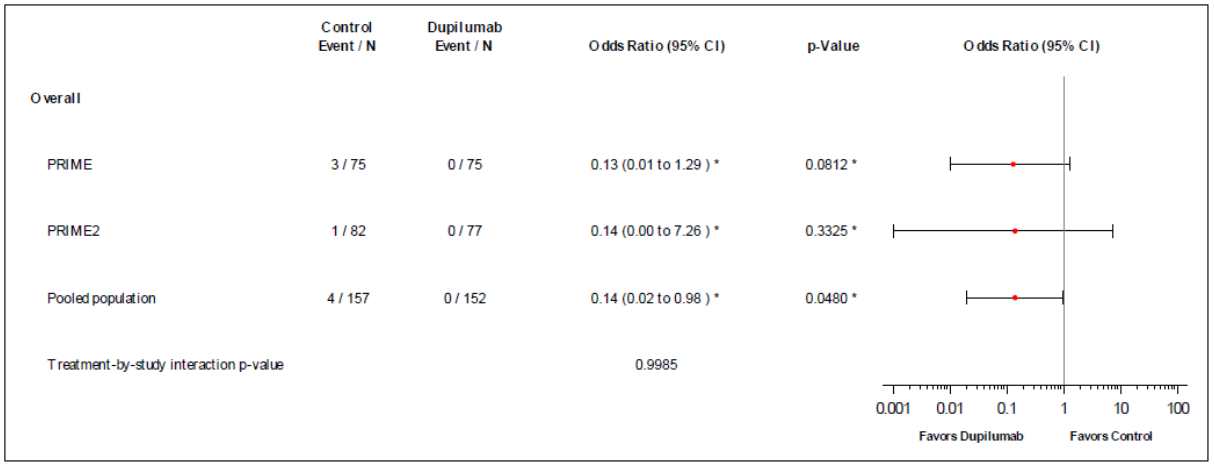

Figure 9: IPD meta-analysis for the outcome of discontinuation due to AEs; effect measure: Peto OR; PRIME and PRIME2 studies: dupilumab vs. placebo

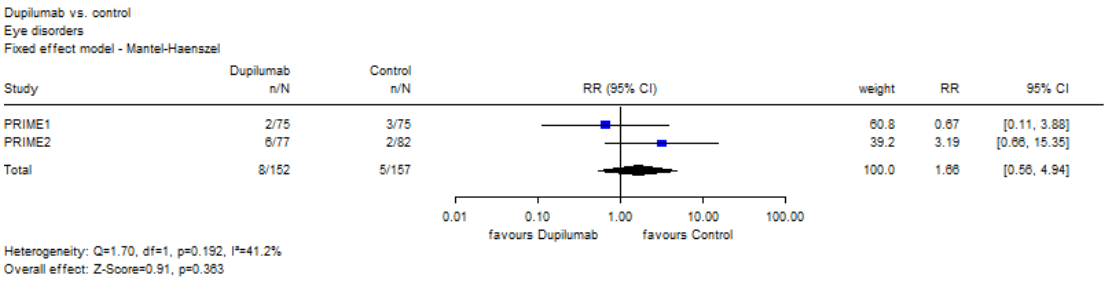

Figure 10: Meta-analysis for the outcome of eye disorders (SOC, AEs); effect measure: RR (Institute's calculation); PRIME and PRIME2 studies: dupilumab vs. placebo

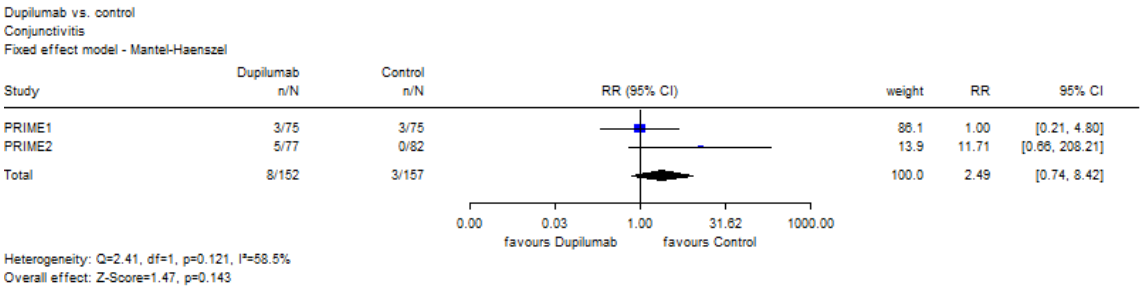

Figure 11: Meta-analysis for the outcome of conjunctivitis (broad CMQ) presented as supplementary information; effect measure: RR (Institute's calculation); PRIME and PRIME2 studies: dupilumab vs. placebo

A.4 Meta-analyses by subgroups

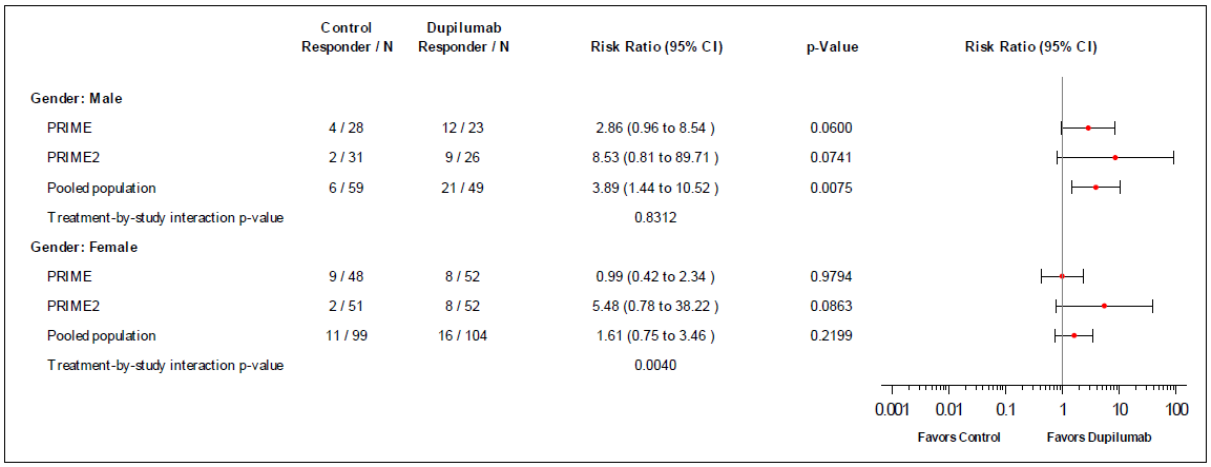

Figure 12: IPD meta-analysis for the outcome of DLQI; subgroup characteristic: sex (men and women); effect measure: RR; PRIME and PRIME2 studies: dupilumab vs. placebo

Appendix B Results on side effects

For the overall rates of AEs and SAEs, the tables below present events for System Organ Classes (SOCs) and Preferred Terms (PTs) according to the Medical Dictionary for Regulatory Activities (MedDRA), each on the basis of the following criteria:

- overall rate of AEs (irrespective of severity): events that occurred in at least 10% of patients in one study arm
- overall rates of SAEs: events that occurred in at least 5% of patients in one study arm
- in addition, for all events irrespective of severity grade: events that occurred in at least 10 patients and in at least 1% of patients in one study arm

For the outcome of discontinuation due to AEs, a complete presentation of all events (SOCs/PTs) that resulted in discontinuation is provided.

Study PRIME

Table 12: Common AEs[a] – RCT, direct comparison: dupilumab vs. placebo (PRIME study)

Study	**Patients with event n (%)**	
SOC[b] **PT[b]**	**Dupilumab** **N = 75**	**Placebo** **N = 75**
PRIME		
Overall rate of AEs[c]	53 (71)	47 (63)
Infections and infestations	18 (24)	22 (29)
Injury, poisoning and procedural complications	9 (12)	5 (7)
Musculoskeletal and connective tissue disorders	8 (11)	4 (5)
Nervous system disorders	10 (13)	7 (9)
Skin and subcutaneous tissue disorders	15 (20)	13 (17)

a. Events that occurred in ≥ 10% of the patients in at least one study arm.
b. MedDRA version 24.1; SOCs taken from Module 4 G.
c. Overall rate of AEs including disease-related events.

AE: adverse event; MedDRA: Medical Dictionary for Regulatory Activities; n: number of patients with at least one event; N: number of analysed patients; PT: Preferred Term; RCT: randomized controlled trial; SOC: System Organ Class

Table 13: Common SAEs[a] – RCT, direct comparison: dupilumab vs. placebo (PRIME study)

Study	**Patients with event n (%)**	
SOC **PT**	**Dupilumab** **N = 75**	**Placebo** **N = 75**
PRIME		
Overall rate of SAEs[b, c]	5 (7)	8 (11)

a. Events that occurred in ≥ 5% of the patients in at least one study arm.
b. For SAEs, no MedDRA SOCs and PTs met the criterion for presentation.
c. Overall rate of SAEs including disease-related events.

MedDRA: Medical Dictionary for Regulatory Activities; n: number of patients with at least one event; N: number of analysed patients; PT: Preferred Term; RCT: randomized controlled trial; SAE: serious adverse event; SOC: System Organ Class

Table 14: Discontinuations due to AEs – RCT, direct comparison: dupilumab vs. placebo (PRIME study)

Study	**Patients with event n (%)**	
SOC[a] **PT[a]**	**Dupilumab** **N = 75**	**Placebo** **N = 75**
PRIME		
Overall rate of discontinuations due to AEs	0 (0)	3 (4)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	0 (0)	1 (1)
Hodgkin's disease	0 (0)	1 (1)
Gastrointestinal disorders	0 (0)	1 (1)
Duodenal ulcer perforation	0 (0)	1 (1)
Skin and subcutaneous tissue disorders	0 (0)	1 (1)
Neurodermatitis	0 (0)	1 (1)

a. MedDRA version 24.1; SOCs and PTs taken from Module 4 G.

AE: adverse event; MedDRA: Medical Dictionary for Regulatory Activities; n: number of patients with at least one event; N: number of analysed patients; PT: Preferred Term; RCT: randomized controlled trial; SOC: System Organ Class

Study PRIME2

Table 15: Common AEs[a] – RCT, direct comparison: dupilumab vs. placebo (PRIME2 study)

Study	Patients with event n (%)	
SOC[b] **PT[b]**	**Dupilumab** **N = 77**	**Placebo** **N = 82**
PRIME2		
Overall rate of AEs[c]	47 (61)	47 (57)
Gastrointestinal disorders	8 (10)	3 (4)
Infections and infestations	23 (30)	16 (20)
Injury, poisoning and procedural complications	5 (7)	9 (11)
Nervous system disorders	9 (12)	9 (11)
Skin and subcutaneous tissue disorders	11 (14)	12 (15)

a. Events that occurred in ≥ 10% of the patients in at least one study arm.
b. MedDRA version 24.1; SOCs taken from Module 4 G.
c. Overall rate of AEs including disease-related events.

AE: adverse event; MedDRA: Medical Dictionary for Regulatory Activities; n: number of patients with at least one event; N: number of analysed patients; PT: Preferred Term; RCT: randomized controlled trial; SOC: System Organ Class

Table 16: Common SAEs[a] – RCT, direct comparison: dupilumab vs. placebo (PRIME2 study)

Study	Patients with event n (%)	
SOC **PT**	**Dupilumab** **N = 77**	**Placebo** **N = 82**
PRIME2		
Overall rate of SAEs[b, c]	2 (3)	4 (5)

a. Events that occurred in ≥ 5% of the patients in at least one study arm.
b. For SAEs, no MedDRA SOCs and PTs met the criterion for presentation.
c. Overall rate of SAEs including disease-related events.

MedDRA: Medical Dictionary for Regulatory Activities; n: number of patients with at least one event; N: number of analysed patients; PT: Preferred Term; RCT: randomized controlled trial; SAE: serious adverse event; SOC: System Organ Class

Table 17: Discontinuations due to AEs – RCT, direct comparison: dupilumab vs. placebo (PRIME2 study)

Study	**Patients with event n (%)**	
SOC[a] **PT[a]**	**Dupilumab** **N = 77**	**Placebo** **N = 82**
PRIME2		
Overall rate of discontinuations due to AEs	0 (0)	1 (1)
Skin and subcutaneous tissue disorders	0 (0)	1 (1)
Urticaria	0 (0)	1 (1)

a. MedDRA version 24.1; SOCs and PTs taken from Module 4 G.

AE: adverse event; MedDRA: Medical Dictionary for Regulatory Activities; n: number of patients with at least one event; N: number of analysed patients; PT: Preferred Term; RCT: randomized controlled trial; SOC: System Organ Class