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Human Medicines Division

Assessment report for paediatric studies submitted according to Article 46 of the Regulation (EC) No 1901/2006

Dupixent

dupilumab

Procedure no: EMEA/H/C/004390/P46/012

Note

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

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us
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Status of this report and steps taken for the assessment				
Current step[1]	**Description**	**Planned date**	**Actual Date**	**Need for discussion[2]**
☐	Start of procedure	22/05/2023	22/05/2023	☐
☐	CHMP Rapporteur Assessment Report	26/06/2023	26/06/2023	☐
☐	CHMP members comments	10/07/2023	n/a	☐
☐	Updated CHMP Rapporteur Assessment Report	13/07/2023	n/a	☐
☒	CHMP adoption of conclusions	20/07/2023	20/07/2023	☐

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Abbreviations

AESI: adverse event of special interest
AUC: area under the curve
CDLQI: children dermatology life qualigy index
CER: ceramides
CSR: clinical study report
EASI: eczema area and severity index
EC: European Commission
EOS: E for esterified/O for omega-hydroxy/S for sphingosin
FDA: Food and Drug Administration
FLG: filaggrin
FTIR: fourier transform infrared spectroscopy
ISS: individual signs score
ITT: intent-to-treat
MAH: marketing authorization holder
mITT: modified intent-to-treat
NRS: numerical rating scale
NS: non-hydroxy fatty acid sphingosine
OCT: optical coherence tomography
PCA: pyrrolidone carboxylic acid
PIP: pediatric investigational plan
POEM: patient oriented eczema measure
PRO: patient reported outcome
SAE: serious adverse event
SC: subcutaneous
SD: standard deviation
STS: skin tape stripping
TEAE: treatment-emergent adverse event
TEWL: transepidermal water loss
TIVI: tissue visibility
UCA: urocanic acid

1. Introduction

On 27 April 2023, the MAH submitted a completed paediatric study for Study No. LPS16764, in accordance with Article 46 of Regulation (EC) No 1901/2006, as amended.

A short critical expert overview has been provided.

2. Scientific discussion

2.1. Information on the development program

The MAH stated that the Phase 4 study entitled 'Open-label exploratory study to evaluate the effect of dupilumab on skin barrier function in pediatric patients with moderate-to-severe atopic dermatitis', Study No. LPS16764/PELISTAD is a stand-alone study. It was not conducted as part of the approved PIP.

2.2. Information on the pharmaceutical formulation used in the study

An overview on administered study interventions including the pharmaceutical formulations is shown in Table 1: Overview of study intervention(s) administered:

Table 1: Overview of study intervention(s) administered

Intervention label	Dupilumab 200 mg	Dupilumab 300 mg
Intervention name	Dupilumab 200 mg	Dupilumab 300 mg
Intervention description	An initial loading dose of 400 mg on Day 1 (Week 0), followed by bi-weekly dosing of 200 mg from Week 2 to Week 14	An initial loading dose of 600 mg on Day 1 (week 0), followed by every 4-week dosing of 300 mg from Week 4 to Week 12
Type	Biological/Vaccine	Biological/Vaccine
Dose formulation	A 175 mg/mL dupilumab solution in a prefilled syringe to deliver 200 mg in 1.14 mL	A 150 mg/mL dupilumab solution in a prefilled syringe to deliver 300 mg in 2 mL
Unit dose strength(s)	200 mg	300 mg
Dosage level(s)	200 mg every 14 ±2 or 3 days after an initial loading dose of 400 mg	300 mg every 14 ±2 or 3 days after an initial loading dose of 600 mg
Route of administration	Subcutaneous[a]	Subcutaneous[a]
Use	Experimental	Experimental
IMP and AxMP	IMP	IMP
Packaging and labeling	One glass prefilled syringe packed in a patient kit box. Both the glass prefilled syringe and the box were labeled as required per country requirement.	One glass prefilled syringe packed in a patient kit box. Both the glass prefilled syringe and the box were labeled as required per country requirement.
Current/Former name(s) or alias(es)	Dupixent®	Dupixent®

a Subcutaneous injection sites alternated between the upper thighs, 4 quadrants of the abdomen or the upper arms, so that the same site was not injected twice during consecutive administrations. Injection in the upper arms was only done by a trained person (parent/legally authorized representative/caregiver trained by Investigator or Delegate) or health care professional but not the participant themselves.

IMP: investigational medicinal product; NIMP: noninvestigational medicinal product

2.3. Clinical aspects

2.3.1. Introduction

The MAH submitted a final report for:

Study number: LPS16764

Study title: Open-label exploratory study to evaluate the effect of dupilumab on skin barrier function in pediatric patients with moderate-to-severe atopic dermatitis

Brief title: Dupilumab-PEdiatric skin barrier function and Lipidomics Study in patients with Atopic Dermatitis - PELISTAD

Study initiation date: 19 February 2021 (first participant first visit)

Study completion date: 30 November 2022 (last participant last visit)

The analyses presented in this report are based on a database lock date of 23 December 2022.

2.3.2. Clinical study

Open-label exploratory study to evaluate the effect of dupilumab on skin barrier function in pediatric patients with moderate-to-severe atopic dermatitis - LPS16764

Description

Study LPS16764 (PELISTAD) was a phase 4, open-label, exploratory study to evaluate the effect of dupilumab on skin barrier function in pediatric patients aged between ≥6 and <12 years old with moderate-to-severe AD with a healthy participant cohort as a reference comparator. It was conducted in 2 sites in the United States and 1 site in United Kingdom from 26 February 2021 (first participant first visit) through 30 November 2022 (last participant last visit).

Methods

Study participants

Atopic dermatitis participants were enrolled based on the following criteria:

• Patients with AD diagnosis according to Hanifin and Rajka criteria (4) at least 1 year before screening.

• Investigator global assessment (IGA) score of ≥3 (for US patients) or IGA ≥4 (for EU patients) at screening (on the 0-4 scale) depending on approved label indication in the country.

• Patients with moderate-to-severe AD eligible to be treated with dupilumab according to product label.

• Patients with AD had active lesions on the upper limbs or lower limbs, with severity for lesion erythema or edema/papulation ≥2 at screening on the 0-3 scale of the Individual Signs Score (ISS).

• Atopic dermatitis participants had a non-lesional (normal looking) skin area 4 cm from the edge of the lesional area. If unable to identify non-lesional skin 4 cm from the lesional area, it was acceptable to identify normal looking skin as close to the lesion as possible. Age, gender, and other demography and participant characteristics at baseline were matched between the AD participant cohort and the

healthy participant cohort for the safety population. A total of 48 participants (24 participants in the AD participant cohort and 24 participants in the healthy participant cohort) were planned to be enrolled to achieve 40 evaluable participants. A total of 43 participants were enrolled in the study, among them 41 participants were screened successfully, including 23 participants with moderate to severe AD and 18 healthy participants. The intent-to-treat (ITT), the modified intent-to-treat (mITT) and safety populations included all 41 participants.

In the AD participant cohort, the median age of the participants at baseline was 7.0 years, and ranged from 6 to 11 years. More than half of the participants (15 [65.2%]) were male. The majority of the participants (16 [69.6%]) were white. The mean (SD) BMI of the participants at baseline was 19.60 (3.71) kg/m^2. In the healthy participant cohort, the median age of the participants at baseline was 8.0 years, and ranged from 6 to 11 years. More than half of the participants (10 [55.6%]) were male. Half of the participants (9 [50%]) were white. The mean (SD) BMI of the participants at baseline was 18.44 (3.14) kg/m^2.

Study design

Study LPS16764 was a Phase 4, open-label, exploratory study to evaluate the effect of dupilumab on skin barrier function in pediatric participants aged between ≥6 and <12 years old with moderate-to-severe AD with a healthy participant cohort not receiving any drug or placebo as a reference comparator.

Male and female participants with moderate-to-severe AD were enrolled. Healthy participants matched for age, gender, location of skin area, and study site served as reference comparators for skin barrier function.

The study intervention included dupilumab 200 mg and 300 mg in a prefilled syringe for subcutaneous administration. AD participants with baseline 15 kg ≤ body weight <30 kg received a SC loading dose of dupilumab 600 mg (2 injections of dupilumab 300 mg) on Day 1 (Week 0), followed by Q4W SC dosing of dupilumab 300 mg from Week 4 to Week 12. AD participants with baseline 30 kg ≤ body weight <60 kg received a SC loading dose of dupilumab 400 mg (2 injections of dupilumab 200 mg) on Day 1 (Week 0), followed by Q2W SC dosing of dupilumab 200 mg from Week 2 to Week 14.

The duration of the treatment period was 16 weeks. The maximum study duration per participant was 32 weeks.

The study comprised:

• Screening period 1 (Day -28 to Day -1): Participants were evaluated according to inclusion and exclusion criteria.

• Baseline visit (Week 0, Day 1): Participants who remain eligible were enrolled.

• A 16-week treatment phase for participants with AD and a 16-week observation period for healthy volunteers.

• A 12-week follow-up period.

Treatments

See Table 1 above.

Objectives and outcomes

The objectives of this study (see Table 2) were to assess the effect of dupilumab treatment on skin barrier function measured by transepidermal water loss (TEWL) and measurement of lipids, proteins, and gene expression associated with skin barrier function from skin tape stripping (STS) in participants with moderate to severe AD. In addition, this study evaluated the relationship between skin barrier function and disease activity measured by clinical assessments and patient-reported outcomes, as well as high-definition standard photography from the targeted lesional and non-lesional areas. Transepidermal water loss is commonly used for physiologic assessments of skin barrier function. In addition to basal TEWL to assess the undisturbed permeability of the skin barrier, TEWL measurements were combined with skin barrier perturbation using STS to measure skin barrier function and integrity. The STS technique uses a standardized tape for removing the epidermis layer by layer. The advantages of this technique are as follows: it is noninvasive, causes no pain in participants, and leaves no scars. With this technique, it was possible to follow reactions within the same skin area over time and to study precisely in which depth of the epidermis the different cellular and molecular cutaneous markers were located. Through these assessments, the study explored the interplay between skin barrier function kinetics, clinical disease severity, and therapeutic response.

Transepidermal water loss is the loss of water that passes from inside a body through the epidermis. A higher value of TEWL means more water is passing through the skin, such as in AD patients. It is influenced by many environmental and individual factors, including age, gender, race, anatomical region, skin temperature, environmental conditions, season, smoking status, measurement technique, and many others. Therefore, it was important to include a 'normal' TEWL from an age-, gender-, targeted lesion area-, and study site-matched healthy participant cohort assessed at the same time under the same measurement conditions on the same anatomical region with reference thresholds of skin barrier function evaluation indicating pathological relevance.

Table 2: Objectives and endpoints of Study LPS16764

Objectives	Endpoints
Primary	
• Evaluate changes in skin barrier function with transepidermal water loss (TEWL) assessed after skin tape stripping (STS) in predefined lesional skin in pediatric patients with moderate-to-severe atopic dermatitis (AD) treated with dupilumab.	• Percent change from baseline in TEWL after 5 STS assessed on lesional skin at Week 16 in AD patients.
Secondary	
• Evaluate changes in skin barrier function with TEWL assessed after STS in predefined lesional and non-lesional skin in pediatric patients with moderate-to-severe AD treated with dupilumab in reference to normal skin of healthy volunteers.	• Change (percent and absolute) from baseline in TEWL after 20 STS assessed on lesional skin at Week 16 in AD patients. • Change (percent and absolute) from baseline in TEWL after 20 STS assessed on non-lesional skin at Week 16 in AD patients. • Change (percent and absolute) from baseline in TEWL after 20 STS assessed on normal skin at Week 16 in healthy volunteers. • Change (percent and absolute) from baseline in TEWL after 15 STS assessed on lesional skin at Week 16 in AD patients. • Change (percent and absolute) from baseline in TEWL after 15 STS assessed on non-lesional skin at Week 16 in AD patients. • Change (percent and absolute) from baseline in TEWL after 15 STS assessed on normal skin at Week 16 in healthy volunteers. • Change (percent and absolute) from baseline in TEWL after 10 STS assessed on lesional skin at Week 16 in AD patients. • Change (percent and absolute) from baseline in TEWL after 10 STS assessed on non-lesional skin at Week 16 in AD patients. • Change (percent and absolute) from baseline in TEWL after 10 STS assessed on normal skin at Week 16 in healthy volunteers. • Change (percent and absolute) from baseline in TEWL after 5 STS assessed on non-lesional skin at Week 16 in AD patients. • Change (percent and absolute) from baseline in TEWL after 5 STS assessed on normal skin at Week 16 in healthy volunteers.
• Evaluate time course of change in skin barrier function with TEWL assessed before and after STS in predefined lesional and non-lesional skin in pediatric patients with moderate-to-severe AD during dupilumab treatment phase and follow-up period in reference to normal skin of healthy volunteers.	• Change (percent and absolute) in TEWL before STS on lesional skin in AD patients over time. • Change (percent and absolute) in TEWL before STS on non-lesional skin in AD patients over time. • Change (percent and absolute) in TEWL before STS on normal skin in healthy volunteers over time.

Objectives	Endpoints
	• Change (percent and absolute) in TEWL area under the curve (TEWL AUC: a composite measure before and after 5, 10, 15, and 20 STS) for skin barrier function in lesional skin in AD patients over time. • Change (percent and absolute) in TEWL AUC (a composite measure before and after 5, 10, 15, and 20 STS) for skin barrier function in non-lesional skin in AD patients over time. • Change (percent and absolute) in TEWL AUC (a composite measure before and after 5, 10, 15, and 20 STS) for skin barrier function in normal skin in healthy volunteers over time. • Change (percent and absolute) in TEWL after STS assessed on lesional skin in AD patients over time. • Change (percent and absolute) in TEWL after STS assessed on non-lesional skin in AD patients over time. • Change (percent and absolute) in TEWL after STS assessed on normal skin in healthy volunteers over time.
Tertiary/exploratory	
• Evaluate dupilumab treatment effect on skin lipidomics using STS samples in both predefined lesional and non-lesional skin in pediatric patients with moderate-to-severe AD during dupilumab treatment phase and follow-up period in reference to normal skin of healthy volunteers.	• Changes (percent and absolute) in lipidomics parameters in lesional and non-lesional skin including the ratio of highly hydrophobic omega-esterified fatty acid sphingosine ceramides (EOS CER) and non-hydroxy fatty acid sphingosine ceramides (NS CER), and filaggrin (FLG) breakdown products of urocanic acid (UCA) and pyroglutamic acid (PCA) concentrations over time. • Global characterization of protein-bound CER over time.
• Evaluate dupilumab treatment effect on skin proteomics using STS samples in both predefined lesional and non-lesional skin in pediatric patients with moderate-to-severe AD during dupilumab treatment phase and follow-up period in reference to normal skin of healthy volunteers.	• Changes (percent and absolute) in the expression of proteins associated with skin barrier function including keratin intermediate filaments, proteins associated with inflammatory response, and glycolysis and oxidative stress response proteins in STS protein extracts over time.
• Evaluate dupilumab treatment effect on epidermal hypertrophy and structure of skin barrier changes measured by Optical Coherence Tomography (OCT) and Fourier-Transform Infrared (FTIR) spectroscopy in both predefined lesional and non-lesional skin in pediatric patients with moderate-to-severe AD during dupilumab treatment phase and follow-up period in reference to normal skin of healthy volunteers.	• Change (percent and absolute) in epidermal hypertrophy parameters including epidermal thickness (µm), superficial plexus depth (µm), blood vessel diameter (µm) and density (segments/mm^2) measured by OCT over time. • Change (percent and absolute) in stratum corneum lipid structure measured by FTIR spectroscopy in conjunction with tape-stripping over time.

Sample size

Sample size for this exploratory study was based on medical/clinical judgment and is consistent with the sample size from similar studies in the literature (Danby et al., 2011). No formal sample size calculation was performed. TEWL data collected in similar settings as planned for this study were not available, i.e., TEWL values after 5 STS, and pre- and post-dupilumab treatment are unknown. Allowing for drop-out rate of 15%, a total of approximately 24 pediatric patients with moderate-to-severe AD will be enrolled to achieve 20 evaluable patients, ie, patients with no major or critical deviations related to IMP and/or TEWL measurements, for whom the TEWL data for primary analysis: ie, TEWL at baseline and Week 16, are considered sufficient and interpretable. An approximately equal number of age, gender, location of targeted lesion area and site matched healthy volunteers serving as

a reference comparator cohort will be enrolled. Drop-out rate in healthy volunteers is expected to be minimal. Any drop-out healthy volunteer for whom the matched patient is considered as evaluable will not be replaced.

Randomisation and blinding (masking)

This was an open-label study.

Changes to the conduct of the study

There were no changes in the conduct of the study.

Statistical Methods

A detailed description of participant accountability including number of participants by analysis population, screen failure of participants with the reasons for screen failure, participants who did not complete the study observation period along with the main reason for permanent treatment discontinuation, and participants who requested permanent treatment discontinuation were generated by cohort. Continuous variables (age, weight) and qualitative variables (gender, race, and body mass index) were summarized by cohort and by descriptive statistics (summary tables). The efficacy evaluation was based on a review of the individual values (graphics), descriptive statistics (summary tables, graphics), and where applicable, exploratory statistical analysis. All efficacy analyses were performed using the ITT and mITT population. The safety evaluation was based on a review of vital signs parameters and reported adverse events. All the safety analyses were performed using the safety population. When applicable, results were reported by cohort and overall.

Results

Participant disposition

A total of 43 participants were enrolled in the study, among them 41 participants were screened including 23 participants with moderate to severe AD and 18 healthy participants. All 23 AD participants completed the study treatment period and 21 AD participants completed the study period, 1 AD participant discontinued from the study period due to withdrawal by participants and 1 AD participant was lost to follow up and didn’t perform end of study visit. All 18 healthy participants completed the study period. The details of the participant disposition are provided in Table 3.

Table 3: Participant disposition

n	Healthy Participant	AD Participant	All
Enrolled[a]	19	24	43
Screen failures[a]	1	1	2
Exposed	na	23	23
Completed the study treatment period	na	23	23
Did not complete the study treatment period	na	0	0
Completed the study period	18	21	39
Did not complete the study period	0	2	2
Reason for study discontinuation			
Adverse event	0	0	0
Poor compliance to protocol	0	0	0
Withdrawal by representative	0	1	1
Other[b]	0	1	1

na: not applicable, AD: Atopic dermatitis

a Enrolled set is all participants who sign the ICF. Screen failures are included in the enrolled set but no treatment arm was assigned to them. However, the planned group was used for reporting, regardless of screen failure status

b Verbatim terms for these discontinuations are provided in the "Listing of participants with premature end of study"

Study initiation date: 2021-02-19 Study completion date: 2022-11-30 Study date of last available information: 2022-11-30 ¶

Baseline data

Demographic data

Age, sex, and other demographics and participant characteristics at baseline were matched between the AD participant cohort and the healthy participant cohort for the mITT population. In the AD participant cohort, the median age of the participants at baseline was 7.0 years, and ranged from 6 to 11 years. More than half of the participants (15 [65.2%]) were male. The majority of the participants (16 [69.6%]) were white. The mean (SD) BMI of the participants at baseline was 19.60 (3.71) kg/m^2. In the healthy participant cohort, the median age of the participants at baseline was 8.0 years, and ranged from 6 to 11 years. More than half of the participants (10 [55.6%]) were male. Half of the participants (9 [50.0%]) were white. The mean (SD) BMI of the participants at baseline was 18.44 (3.14) kg/m^2.

Table 4: Demographics and participant characteristics at baseline – mITT population

	Healthy Participant (N=18)	AD Participant (N=23)	All (N=41)
Age (years)			
Number	18	23	41
Mean (SD)	8.2 (1.8)	7.8 (1.6)	8.0 (1.7)
Median	8.0	7.0	7.0
Min ; Max	6 ; 11	6 ; 11	6 ; 11
Age group (years) [n (%)]			
Number	18	23	41
Children (2-11 years)	18 (100)	23 (100)	41 (100)
Sex [n (%)]			
Number	18	23	41
Male	10 (55.6)	15 (65.2)	25 (61.0)
Female	8 (44.4)	8 (34.8)	16 (39.0)
Race [n (%)]			
Number	18	23	41
White	9 (50.0)	16 (69.6)	25 (61.0)
Black or african american	2 (11.1)	2 (8.7)	4 (9.8)
Asian	6 (33.3)	3 (13.0)	9 (22.0)
Multiple	0	1 (4.3)	1 (2.4)
Black or african american/White	0	1 (100)	1 (100)
Not reported	1 (5.6)	1 (4.3)	2 (4.9)
Ethnicity [n (%)]			
Number	18	23	41
Hispanic or Latino	3 (16.7)	2 (8.7)	5 (12.2)
Not Hispanic or Latino	15 (83.3)	21 (91.3)	36 (87.8)
Baseline Weight (kg)			
Number	18	23	41
Mean (SD)	34.46 (13.10)	31.92 (9.22)	33.03 (11.01)
Median	33.55	29.00	30.10
Min ; Max	21.4 ; 72.0	20.5 ; 56.5	20.5 ; 72.0
Baseline BMI (kg/m2)			
Number	17	23	40
Mean (SD)	18.44 (3.14)	19.60 (3.71)	19.11 (3.49)
Median	18.42	19.17	18.65
Min ; Max	14.6 ; 27.8	14.5 ; 30.5	14.5 ; 30.5

BMI: Body mass index, AD: Atopic dermatitis
PGM = dem_demo_m_t.sas OUT = dem_demo_m_t_i.rtf (19JAN2023 11:07)

Baseline disease characteristics

In the AD participant cohort, the median (range) duration since diagnosis of AD was 7.1 (3 to 12) years in the mITT population (Table 5).

Table 5: Disease duration at baseline – mITT population – AD participants

	AD Participant (N=23)
Years since atopic dermatitis diagnosis	
Number	23
Mean (SD)	7.1 (2.0)
Median	7.1
Min ; Max	3 ; 12

AD: Atopic dermatitis
PGM = dem_disea_m_t.sas OUT = dem_disea_m_t_i.rtf (06JAN2023 15:56)

Prior and concomitant medications

The prior medications used in this study are summarized for the safety population in Table 6. Eighteen (78.3%) participants in the AD participant cohort and 1 (5.6%) participant in the healthy participants

cohort were reported to have taken prior medications. Prior medications in the AD participant cohort are mainly corticosteroids, dermatological preparation.

Table 6: Prior medications – Number of participants by anatomic class and therapeutic class – Safety population

Anatomic class Therapeutic class n (%)	Healthy Participant (N=18)	AD Participant (N=23)	Overall (N=41)
Any prior medications	1 (5.6)	18 (78.3)	19 (46.3)
Dermatologicals	1 (5.6)	18 (78.3)	19 (46.3)
Corticosteroids, dermatological preparations	0	17 (73.9)	17 (41.5)
Other dermatological preparations	0	4 (17.4)	4 (9.8)
Emollients and protectives	0	3 (13.0)	3 (7.3)
Antifungals for dermatological use	0	2 (8.7)	2 (4.9)
Antibiotics and chemotherapeutics for dermatological use	0	1 (4.3)	1 (2.4)
Antipruritics, incl. antihistamines, anesthetics, etc.	1 (5.6)	0	1 (2.4)
Sensory organs	1 (5.6)	17 (73.9)	18 (43.9)
Ophthalmologicals	1 (5.6)	17 (73.9)	18 (43.9)
Otologicals	0	10 (43.5)	10 (24.4)
Ophthalmological and otological preparations	0	3 (13.0)	3 (7.3)
Alimentary tract and metabolism	1 (5.6)	15 (65.2)	16 (39.0)
Stomatological preparations	0	13 (56.5)	13 (31.7)
Antidiarrheals, intestinal antiinflammatory/antiinfective agents	0	10 (43.5)	10 (24.4)
Antiemetics and antinauseants	1 (5.6)	0	1 (2.4)
Cardiovascular system	0	14 (60.9)	14 (34.1)
Vasoprotectives	0	14 (60.9)	14 (34.1)
Respiratory system	1 (5.6)	13 (56.5)	14 (34.1)
Drugs for obstructive airway diseases	0	13 (56.5)	13 (31.7)
Nasal preparations	0	13 (56.5)	13 (31.7)
Antihistamines for systemic use	1 (5.6)	0	1 (2.4)
Systemic hormonal preparations, excl. sex hormones and insulins	0	14 (60.9)	14 (34.1)
Corticosteroids for systemic use	0	14 (60.9)	14 (34.1)
Antineoplastic and immunomodulating agents	0	4 (17.4)	4 (9.8)
Immunosuppressants	0	4 (17.4)	4 (9.8)
Antiinfectives for systemic use	0	1 (4.3)	1 (2.4)
Antimycotics for systemic use	0	1 (4.3)	1 (2.4)
Genito urinary system and sex hormones	0	1 (4.3)	1 (2.4)
Gynecological antiinfectives and antiseptics	0	1 (4.3)	1 (2.4)
Nervous system	1 (5.6)	0	1 (2.4)
Anti-parkinson drugs	1 (5.6)	0	1 (2.4)
Psycholeptics	1 (5.6)	0	1 (2.4)
Various	0	1 (4.3)	1 (2.4)
Unspecified herbal and traditional medicine	0	1 (4.3)	1 (2.4)

The concomitant medications used in this study are summarized for the safety population in Table 7.

Table 7: Concomitant medications – Number of participants by anatomic class and therapeutic class – Safety population

Anatomic class Therapeutic class n (%)	Healthy Participant (N=18)	AD Participant (N=23)
Any concomitant medications	12 (66.7)	23 (100)
Dermatologicals	7 (38.9)	22 (95.7)
Antipruritics, incl. antihistamines, anesthetics, etc.	1 (5.6)	18 (78.3)
Emollients and protectives	1 (5.6)	16 (69.6)
Corticosteroids, dermatological preparations	1 (5.6)	11 (47.8)
Other dermatological preparations	4 (22.2)	6 (26.1)
Anti-acne preparations	4 (22.2)	5 (21.7)
Antibiotics and chemotherapeutics for dermatological use	0	3 (13.0)
Respiratory system	7 (38.9)	22 (95.7)
Antihistamines for systemic use	1 (5.6)	18 (78.3)
Drugs for obstructive airway diseases	1 (5.6)	16 (69.6)
Nasal preparations	1 (5.6)	13 (56.5)
Throat preparations	4 (22.2)	4 (17.4)
Cough and cold preparations	1 (5.6)	1 (4.3)
Sensory organs	1 (5.6)	22 (95.7)
Ophthalmologicals	1 (5.6)	22 (95.7)
Otologicals	0	7 (30.4)
Ophthalmological and otological preparations	0	3 (13.0)
Alimentary tract and metabolism	6 (33.3)	14 (60.9)
Antidiarrheals, intestinal antiinflammatory/antiinfective agents	0	7 (30.4)
Stomatological preparations	0	7 (30.4)
Vitamins	5 (27.8)	2 (8.7)
Antiemetics and antinauseants	0	5 (21.7)
Drugs for constipation	0	3 (13.0)
Drugs for acid related disorders	1 (5.6)	1 (4.3)
Mineral supplements	1 (5.6)	0
Tonics	1 (5.6)	0
Genito urinary system and sex hormones	4 (22.2)	13 (56.5)
Other gynecologicals	4 (22.2)	13 (56.5)
Gynecological antiinfectives and antiseptics	0	1 (4.3)
Urologicals	0	1 (4.3)

Anatomic class Therapeutic class n (%)	Healthy Participant (N=18)	AD Participant (N=23)
Cardiovascular system	4 (22.2)	12 (52.2)
Cardiac therapy	4 (22.2)	8 (34.8)
Vasoprotectives	0	5 (21.7)
Nervous system	2 (11.1)	14 (60.9)
Analgesics	1 (5.6)	10 (43.5)
Psycholeptics	1 (5.6)	8 (34.8)
Anti-parkinson drugs	0	3 (13.0)
Blood and blood forming organs	5 (27.8)	7 (30.4)
Blood substitutes and perfusion solutions	5 (27.8)	3 (13.0)
Antihemorrhagics	0	5 (21.7)
Antianemic preparations	1 (5.6)	0
Various	1 (5.6)	9 (39.1)
Homeopathic preparation	0	6 (26.1)
Unspecified herbal and traditional medicine	0	2 (8.7)
All other non-therapeutic products	0	1 (4.3)
General nutrients	1 (5.6)	0
Musculo-skeletal system	4 (22.2)	4 (17.4)
Antiinflammatory and antirheumatic products	4 (22.2)	4 (17.4)
Topical products for joint and muscular pain	4 (22.2)	4 (17.4)
Antiinfectives for systemic use	2 (11.1)	5 (21.7)
Antibacterials for systemic use	2 (11.1)	4 (17.4)
Vaccines	1 (5.6)	1 (4.3)
Systemic hormonal preparations, excl. sex hormones and insulins	0	3 (13.0)
Corticosteroids for systemic use	0	3 (13.0)

AD: Atopic dermatitis
WHO-DDE 2022 SEPTEMBER 1
n (%) = number and percentage of participants with at least one concomitant medication
Note: Concomitant medications are those the participant used at any time during the treatment-emergent period (from the IMP administration up to the end of treatment (included)) for AD participants and during the observational period (period of 16 week following collection of the first skin biopsy) for healthy participants.
A medication can be counted in several ATC classes.
Anatomic classes are sorted by decreasing frequency in AD Participant group.
Therapeutic classes are sorted by decreasing frequency in AD Participant group within each anatomic class.
PGM = dem_concmed_s_t.sas OUT = dem_concmed_s_t_i.rtf (05JAN2023 15:17)

Number analysed

41 participants were included in the efficacy population and safety population. Two participants (1 AD participant and 1 healthy participant) were excluded from the efficacy and safety population due to screen failures. The number of participants included in each analysis population is provided in Table 8.

Table 8: Analysis populations

	Healthy Participant	AD Participant	All
Enrolled population[a]	19	24	43
Efficacy population			
Intent-To-Treat population (ITT)	18	23	41
Modified Intent-To-Treat (mITT) population	18	23	41
Safety population	18	23	41

AD: Atopic dermatitis
a Screen failures are included in the enrolled set but no treatment group was assigned to them
PGM = dis_ana_pop_a_t.sas OUT = dis_ana_pop_a_t_i.rtf (06JAN2023 15:56)

Efficacy results

Primary endpoint

Transepidermal water loss is a widely used objective measurement for physiologic assessments of skin barrier function. In addition to basal TEWL to assess the undisturbed permeability of the skin barrier, TEWL measurements were combined with skin barrier perturbation using STS to measure skin barrier

function and integrity. The primary endpoint for this study was the change from baseline in TEWL after 5 STS assessed on lesional skin at Week 16 in AD participants. The primary endpoint of percent change from baseline in TEWL after 5 STS on lesional skin in AD participants demonstrated a clinically significant improvement at Week 16 for the ITT population, representing a 37.5% reduction in TEWL.

Table 9: Summary of percent change from baseline in TEWL (g/m^2/hour) at Week 16 by groups and number of STS – ITT population

	Percent change from baseline						
	N	Mean	SD	SEM	Median	Min	Max
AD Participant - Lesional Skin Area							
Before / Without STS							
D113 - Before STS - Spot 1	23	-36.0022	32.4856	6.7737	-41.6407	-86.626	56.038
D113 - Before STS - Spot 2	23	-35.1507	28.9709	6.0408	-34.5738	-87.852	27.672
D113 - Before STS - Spot 3	23	-28.6460	30.6542	6.3918	-30.9331	-75.913	31.860
After 5 STS							
D113 - Spot 1	23	-37.4892	26.7174	5.5710	-34.8843	-85.077	4.580
After 10 STS							
D113 - Spot 1	22	-33.2244	32.2862	6.8834	-37.1061	-81.836	40.971
After 15 STS							
D113 - Spot 1	22	-32.7769	31.7544	6.7701	-41.7736	-76.339	33.181
After 20 STS							
D113 - Spot 1	21	-29.9602	29.8447	6.5127	-40.1565	-65.156	36.831

D113: End of Treatment (Week 16), AD: Atopic dermatitis
N corresponds to the count of participants with available data
Baseline is defined as the Day 1 value
Percent change from baseline is calculated according to spots
Participants with a change in spot anatomical location changed versus Day 1 are excluded from the analysis
PGM = eff_twl_descp_w16_i_t.sas OUT = eff_twl_descp_w16_i_t_i.rtf (02FEB2023 10:27)

Secondary endpoints

The median TEWL before STS (spot 1) on lesional and non-lesional skin area were 48.1500 and 25.3400 g/m^2/hour, respectively, at baseline, versus 28.1000 and 17.2500 g/m^2/hour on lesional and non-lesional skin area, respectively at Week 16. The median TEWL after 20 STS on lesional and non-lesional skin area were 92.7600 and 82.3100 g/m^2/hour, respectively at baseline, versus 55.7450 and 68.8400 g/m^2/hour on lesional and non-lesional skin area, respectively at Week 16. The results of the secondary endpoints of TEWL before and after 5, 10, 15, and 20 STS demonstrated a clinically significant improvement at Week 16 versus baseline on lesional and non-lesional skin for the ITT population. There were no observed changes at Week 16 on healthy skin.

The median TEWL AUC on lesional and non-lesional skin area were 1447.9250 and 1106.9500 g*nsts/m^2/hour at baseline, respectively, versus 815.2000 and 826.1000 g*nsts/m^2/hour at Week 16, respectively. The results of the secondary endpoints of TEWL AUC demonstrated a significant improvement at Week 16 versus baseline on lesional skin area and non-lesional skin area for ITT population. The secondary endpoints of the absolute change from baseline in the AUC of TEWL at Week 16 for the ITT population assessed on lesional, non-lesional, and healthy skin are provided in 5.3.5.1

Table 10: Summary of percent change from baseline in TEWL (g/m²/hour) at Week 16 by groups and number of STS – ITT population (AD Participant – Non-Lesional Skin Area)

	Percent change from baseline						
	N	Mean	SD	SEM	Median	Min	Max
AD Participant - Non-Lesional Skin Area							
Before / Without STS							
D113 - Before STS - Spot 1	22	-17.7649	40.5295	8.6409	-26.0755	-68.782	93.476
D113 - Before STS - Spot 2	21	-23.7095	38.0986	8.3138	-30.3185	-74.444	71.642
D113 - Before STS - Spot 3	22	-24.9380	34.3756	7.3289	-33.2435	-71.967	49.793
After 5 STS							
D113 - Spot 1	22	-9.8059	63.4911	13.5363	-29.8137	-67.150	170.439
After 10 STS							
D113 - Spot 1	22	-9.0071	66.3832	14.1529	-29.7909	-67.768	193.570
After 15 STS							
D113 - Spot 1	22	-10.8166	49.5722	10.5688	-20.8826	-66.785	169.932

Table 11: Summary of percent change from baseline in TEWL (g/m²/hour) at Week 16 by groups and number of STS – ITT population (Healthy Participant)

	Percent change from baseline						
	N	Mean	SD	SEM	Median	Min	Max
Healthy Participant							
Before / Without STS							
D113 - Before STS - Spot 1	11	2.6054	26.2241	7.9069	-4.4098	-22.590	72.826
D113 - Before STS - Spot 2	11	9.4234	24.1533	7.2825	3.8944	-22.897	56.806
D113 - Before STS - Spot 3	11	17.0905	16.4596	4.9627	14.1236	-3.505	46.154
After 5 STS							
D113 - Spot 1	11	1.4464	26.7257	8.0581	-6.4960	-24.814	57.068
After 10 STS							
D113 - Spot 1	11	0.7091	25.0615	7.5563	1.9271	-37.722	44.360
After 15 STS							
D113 - Spot 1	11	4.5364	42.7525	12.8904	6.6351	-47.848	107.319
After 20 STS							
D113 - Spot 1	11	13.2578	64.3880	19.4137	-4.0509	-44.980	179.386

D113: End of Treatment (Week 16), AD: Atopic dermatitis
N corresponds to the count of participants with available data
Baseline is defined as the Day 1 value
Percent change from baseline is calculated according to spots
Participants with a change in spot anatomical location changed versus Day 1 are excluded from the analysis
PGM = eff_twl_descp_w16_i_t.sas OUT = eff_twl_descp_w16_i_t_i.rtf (02FEB2023 10:27)

Table 12: Comparison in TEWL betwen Day 1 and Week 16 by skin group and number of STS – ITT population (AD Participant – Non-Lesional Skin Area)

	Test Statistics	p-value
AD Participant - Non-Lesional Skin Area		
Before STS		
D113 vs D1 - Spot 1	-70.5	0.0182
D113 vs D1 - Spot 2	-84.5	0.0013
D113 vs D1 - Spot 3	-93.5	0.0008
After 5 STS		
D113 vs D1 - Spot 1	-66.5	0.0271
After 10 STS		
D113 vs D1 - Spot 1	-62.5	0.0392
After 15 STS		
D113 vs D1 - Spot 1	-74.5	0.0118
After 20 STS		
D113 vs D1 - Spot 1	-98.5	0.0003

D113: End of Treatment (Week 16)
The comparison Week 16 versus Day 1 is performed using the non-parametric Wilcoxon signed-rank test.
Participants with a change in spot anatomical location changed versus Day 1 are excluded from the analysis.
PGM = eff_twl_compD1W16_t.sas OUT = eff_twl_compD1W16_t_i.rtf (18JAN2023 09:50)

Table 13: Comparison in TEWL AUC between Day 1 and Week 16 by skin group- ITT population (AD Participant – Lesional Skin Area)

	Test Statistics	p-value
AD Participant - Lesional Skin Area		
D113 vs D1 - Spot 1	-107	0.0003

D113: End of Treatment (Week 16)
The comparison Week 16 versus Day 1 is performed using the non-parametric Wilcoxon signed-rank test.
Area under the curve is calculated using the trapezoidal method over the 20 STS (measurement at every 5 STS and all other unplanned number of STS) at each visit.
Participants with a change in spot anatomical location changed versus Day 1 are excluded from the analysis.
PGM = eff_auc_compD1W16_t.sas OUT = eff_auc_compD1W16_t_i.rtf (18JAN2023 09:52)

Table 14: Comparison in TEWL AUC between Day 1 and Week 16 by skin group- ITT population (AD Participant – Non-Lesional Skin Area)

	Test Statistics	p-value
AD Participant - Non-Lesional Skin Area		
D113 vs D1 - Spot 1	-76.5	0.0094

D113: End of Treatment (Week 16)
The comparison Week 16 versus Day 1 is performed using the non-parametric Wilcoxon signed-rank test.
Area under the curve is calculated using the trapezoidal method over the 20 STS (measurement at every 5 STS and all other unplanned number of STS) at each visit.
Participants with a change in spot anatomical location changed versus Day 1 are excluded from the analysis.
PGM = eff_auc_compD1W16_t.sas OUT = eff_auc_compD1W16_t_i.rtf (18JAN2023 09:52)

Safety results

Exposure

The mean (SD) exposure was 191.8 (41.8) days. All participants with AD were treated for more than 112 days.

Adverse events

Overview

In the safety population, 21 (91.3%) participants with AD treated with dupilumab and 6 (33.3%) participants in the healthy participant cohort experienced at least 1 TEAE (Table 15 and Table 16). None of the participants in either of the cohorts experienced a severe AE, an SAE, an AE leading to permanent study intervention discontinuation, an AE leading to permanent study discontinuation, or an AESI. Overall, no clinically meaningful findings were reported in vital sign measurements, physical examination assessments, or other observations related to safety in this study.

Table 15: Overview of adverse event profile: Treatment-emergent adverse events – Safety population – AD participants

n (%)	AD Participant (N=23)
Participants with any TEAE	21 (91.3)
Participants with any severe TEAE	0
Participants with any treatment emergent SAE	0
Participants with any TEAE leading to permanent study intervention discontinuation	0
Participants with any TEAE leading to permanent study discontinuation	0
Participants with any treatment emergent AESI	0

TEAE: Treatment emergent adverse event, SAE: Serious adverse event, AESI: Adverse event of special interest, AD: Atopic dermatitis
n (%) = number and percentage of participants with at least one TEAE
Note: An adverse event is considered as treatment emergent if it occurred from the time of the first investigational medicinal product (IMP) administration up to the end of treatment visit (EoT included).
PGM = ae_overview_s_t.sas OUT = ae_overview_s_t_i.rtf (03JAN2023 11:36)

Table 16: Overview of adverse event profile: Adverse events – Safety population – Healthy participants

n (%)	Healthy Participant (N=18)
Participants with any AE	6 (33.3)
Participants with any severe AE	0
Participants with any SAE	0
Participants with any AE leading to permanent study intervention discontinuation	0
Participants with any AE leading to permanent study discontinuation	0
Participants with any AESI	0

AE: Adverse event, SAE: Serious adverse event, AESI: Adverse event of special interest
n (%) = number and percentage of participants with at least one AE
PGM = ae_overviewae_s_t.sas OUT = ae_overviewae_s_t_i.rtf (03JAN2023 11:37)

Treatment-emergent adverse events

In the AD participant cohort, the most common TEAE SOCs (≥15% participants) reported were infections and infestations (11 [47.8%] participants), skin and subcutaneous tissue disorders (11 [47.8%] participants), general disorders and administration site conditions (6 [26.1%] participants), eye disorders (5 [21.7%] participants), and nervous system disorders (4 [17.4%] participants) (Table 17). In the healthy participant cohort, the most common AE SOCs reported were infection and infestations (2 [11.1%] participants) and general disorders and administration site conditions (2 [11.1%] participants); all other SOCs were reported in 1 (5.6%) participant each (Table 18).

In the AD participant cohort, the most common TEAE PTs reported were dermatitis atopic (9 [39.1%] participants), medical device site haemorrhage (skin bleeding at skin tape stripping site, 6 [26.1%] participants), upper respiratory tract infection (4 [17.4%] participants), headache (3 [13%] participants), urticaria (3 [13%] participants) and eye pruritus (2 [8.7%] participants); all other PTs were reported in 1 (4.3%) participant each (Table 17). In the healthy participants cohort, the most common AE PT was pyrexia (2 [11.1%] participants), all other PTs were reported in 1 (5.6%) participant each (Table 18).

Table 17: Number (%) of participants with TEAE(s) by primary SOC and PT – Safety population – AD participants

PRIMARY SYSTEM ORGAN CLASS Preferred Term [n (%)]	AD Participant (N=23) n (%)	E
Any event	21 (91.3)	62
INFECTIONS AND INFESTATIONS	11 (47.8)	17
Upper respiratory tract infection	4 (17.4)	5
Covid-19	1 (4.3)	1
Cellulitis	1 (4.3)	1
Dermatitis infected	1 (4.3)	1
Gastroenteritis	1 (4.3)	1
Gastrointestinal viral infection	1 (4.3)	1
Impetigo	1 (4.3)	1
Molluscum contagiosum	1 (4.3)	1
Otitis media chronic	1 (4.3)	1
Pneumonia	1 (4.3)	1
Suspected covid-19	1 (4.3)	1
Tonsillitis	1 (4.3)	1
Urinary tract infection	1 (4.3)	1
IMMUNE SYSTEM DISORDERS	1 (4.3)	1
Food allergy	1 (4.3)	1
NERVOUS SYSTEM DISORDERS	4 (17.4)	5
Headache	3 (13.0)	4
Lethargy	1 (4.3)	1
EYE DISORDERS	5 (21.7)	7
Eye pruritus	2 (8.7)	2
Dry eye	1 (4.3)	1
Eye irritation	1 (4.3)	1
Eye pain	1 (4.3)	1
Ocular hyperaemia	1 (4.3)	1
Vision blurred	1 (4.3)	1
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	2 (8.7)	2
Cough	1 (4.3)	1
Oropharyngeal pain	1 (4.3)	1
GASTROINTESTINAL DISORDERS	2 (8.7)	4
Abdominal pain upper	1 (4.3)	2
Nausea	1 (4.3)	1
Vomiting	1 (4.3)	1
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	11 (47.8)	15
Dermatitis atopic	9 (39.1)	10
Urticaria	3 (13.0)	3
Erythema	1 (4.3)	1
Rash erythematous	1 (4.3)	1
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	1 (4.3)	1
Pain in extremity	1 (4.3)	1
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	6 (26.1)	7
Medical device site haemorrhage	6 (26.1)	7
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	3 (13.0)	3
Arthropod sting	1 (4.3)	1
Tendon injury	1 (4.3)	1
Wound	1 (4.3)	1

TEAE: Treatment emergent adverse event, SOC: System organ class, PT: Preferred term, AD: Atopic dermatitis
MedDRA 25.1
n (%) = number and percentage of participants with at least one TEAE
E = number of events
Note: Table sorted by SOC internationally agreed order and by decreasing frequency of PT in AD Participant group.
An adverse event is considered as treatment emergent if it occurred from the time of the first investigational medicinal product (IMP) administration up to the end of treatment visit (EoT included).
PGM = ae_socpt_s_t.sas OUT = ae_socpt_s_t_i.rtf (03JAN2023 11:37)

Table 18: Number (%) of participants with AE(s) by primary SOC and PT – Safety population- Healthy participants

PRIMARY SYSTEM ORGAN CLASS Preferred Term [n (%)]	Healthy Participant (N=18) n (%)	E
Any event	6 (33.3)	8
INFECTIONS AND INFESTATIONS	2 (11.1)	2
Covid-19	1 (5.6)	1
Skin bacterial infection	1 (5.6)	1
BLOOD AND LYMPHATIC SYSTEM DISORDERS	1 (5.6)	1
Lymphadenopathy	1 (5.6)	1
IMMUNE SYSTEM DISORDERS	1 (5.6)	1
Seasonal allergy	1 (5.6)	1
NERVOUS SYSTEM DISORDERS	1 (5.6)	1
Headache	1 (5.6)	1
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	1 (5.6)	1
Cough	1 (5.6)	1
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	2 (11.1)	2
Pyrexia	2 (11.1)	2

TEAE: Treatment emergent adverse event, SOC: System organ class, PT: Preferred term.
MedDRA 25.1
n (%) = number and percentage of participants with at least one TEAE

Deaths

No deaths were reported during the study.

Serious adverse events (SAEs)

No treatment-emergent SAE were reported during the study.

Discontinuations and/or dose modifications due to adverse events

None of the AEs led to permanent discontinuation of the study intervention.

Adverse events of special interest

No AESI were reported during the study.

Other significant adverse events

No other significant adverse events were reported during the study.

Evaluation of clinical laboratory tests

There were no participants with positive urine pregnancy test.

Other safety evaluations

There were no clinically meaningful findings in the vital signs' measurements, physical examination assessments, or other observations related to safety in this study.

2.3.3. Discussion on clinical aspects

The applicant submitted efficacy and safety results from study LPS16764, a phase 4, open-label, exploratory study to evaluate the effect of dupilumab on skin barrier function in pediatric patients aged between ≥6 and <12 years old with moderate-to-severe atopic dermatitis (AD). Atopic dermatitis is associated with skin barrier defects, which has, amongst others, implications for the immune function of the skin. The purpose of this phase 4 study was the analysis of the effect of dupilumab treatment on skin-barrier function in adolescent and adult AD patients, i.e. on (patho-)physiological features such as

transepidermal water loss (TEWL), epidermal activation, epidermal lipids and proteins, etc. using skin rape stripping (STS) to measure skin barrier function and integrity. In addition, disease activity was measured by clinical assessments and patient-reported outcomes, as well as high-definition standard photography from the targeted lesional and non-lesional areas.

Overall, 43 children were enrolled in the study, two of the participants were excluded from the efficacy and safety population due to screen failures, thus 41 subjects were treated; 23 patients were assigned to the dupilumab group, and 18 healthy volunteers (HV) to the control group which served as reference comparator for the skin barrier assessment parameters. The participants were enrolled if they had an AD diagnosis according to Hanifin and Rajka criteria at least 1 year before screening, moderate-to-severe symptoms, and active lesions on the upper limbs or lower limbs with Individual Signs Score ≥2 at screening. The demographic characteristics were balanced between both groups. The median age was 7 years in the AD group with a median disease duration of 7 years. Accordingly, most patients in the AD participant cohort had prior medications such as topical corticosteroids and other dermatological preparations, systemic corticosteroids and immunosuppressants. Further medications included ophthalmologicals, drugs for the treatment of obstructive airway disease, and nasal preparations indicating concomitant type 2 inflammatory diseases. To establish similar conditions for the subsequent analysis of dupilumab's treatment effect on the skin barrier, individuals were matched with AD patients for age, gender, examined skin area and study site. Study subjects must have had a treatment gap of at least 6 months or must have been treatment-naïve.

The patients assigned to the dupilumab group were treated according to product label. The duration of the open-label treatment or observation period was 16 weeks, and the maximum study duration per participant was 32 weeks.

The objectives of this study were to assess the effect of dupilumab treatment on skin barrier function measured by TEWL and measurement of lipids, proteins, and gene expression associated with skin barrier function from STS in the participants. In addition, this study evaluated the relationship between skin barrier function, integrity and disease activity measured by clinical assessments and patient-reported outcomes. The measurement of TEWL to quantify the skin barrier functionality as well as non-invasive techniques such as STS to determine TEWL are commonly used in clinical trials. Here, 5-20 STS over a period of 16 weeks were performed in lesional and non-lesional skin areas in AD patients under dupilumab treatment and for comparison in HV. The STS time points are acceptable as the onset of dupilumab's effect was observed after 2 treatment weeks in clinical trials.

41 participants were included in the efficacy population (ITT) and safety population. TEWL measurements were combined with skin barrier perturbation using STS to measure skin barrier function and integrity. The primary endpoint for this study was the change from baseline in TEWL after 5 STS assessed on lesional skin at Week 16 in AD participants. After 5 STS on lesional skin in AD participants the TEWL was reduced by 37.5% at week 16, and also on non-lesional skin of AD patients as demonstrated by results of the secondary endpoints. In contrast, no changes were observed on healthy skin. As demonstrated before, dupilumab had a positive effect on further clinical and patient-reported outcomes EASI, ISS, POEM, skin pain NRS, sleep disturbance NRS, worst itch NRS, and CDLQ total scores. Major protocol deviations that are deemed to have impacted efficacy analyses were reported in 31 participants (20 participants in the AD participant cohort, and 11 participants in the healthy participant cohort) due to used prohibited therapies or missing TEWL assessment not performed as defined in the protocol. It is unclear if adolescent patients were involved. To what extent these medications have influenced TEWL measurements, is not discussed by the MAH.

The safety results are consistent with the known safety profile of dupilumab. Overall, no new safety findings were identified in this study. No amendments of the product information were introduced by the applicant which is supported.

3. Rapporteur’s overall conclusion and recommendation

The efficacy results indicate that TEWL of lesional skin was gradually reduced for the total AD ITT population over a period of 16 treatment weeks compared with the TEWL of healthy volunteers suggesting an improved skin barrier. Treatment benefits also included improvements in quality of life. However, the relatively high amount of concomitant AD medication and major protocol deviations are supposed to have influenced the results. Regarding the limited analysed patient number, the generated data are considered to be supportive information. The collected safety data are consistent with the known safety profile. It is concurred that no amendment of the PI is indicated.

☒ Fulfilled:

No regulatory action required.

4. Request for supplementary information

None.