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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/P46/017

Note

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

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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	02/12/2024	02/12/2024	☐
☐	CHMP Rapporteur Assessment Report	06/01/2025	06/01/2025	☐
☐	CHMP members comments	20/01/2025	n/a	☐
☐	Updated CHMP Rapporteur Assessment Report	23/01/2025	n/a	☐
☒	CHMP adoption of conclusions	30/01/2025	30/01/2025	☐

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Abbreviations

AD: atopic dermatitis
AE: adverse event
AUC: area under the curve
BMI: body mass index
CDLQI: Children Dermatology Life Questionnaire Index
CSR: clinical study report
EASI: Eczema Area and Severity Index
EMA: European Medicines Agency
EOS CER: Esterified Omega-Hydroxy Fatty Acids And Sphingosine Ceramides
FLG: Filaggrin
IPD: Important Protocol Deviation
ISS: Individual Signs Score
MAH: marketing authorization holder
NRS: Numerical Rating Scale
NS CER: Non-hydroxy Fatty Acid Sphingosine Ceramides
PCA: Pyroglutamic Acid
POEM: Patient Oriented Eczema Measure
PRO: patient reported outcomes
Q2W: every 2 weeks
SC: subcutaneous
SS: Individual Signs Score
STS: skin tape stripping
TEWL: transepidermal water loss
UCA: Urocanic Acid

1. Introduction

On 16 October 2024, the MAH submitted a completed paediatric study report for LPS17244, in accordance with Article 46 of Regulation (EC) No1901/2006, as amended.

A short critical expert overview has also been provided.

2. Scientific discussion

2.1. Information on the development program

The MAH stated that study LPS17244 (PELISTAD China) entitled "Open-label exploratory study to evaluate the effect of dupilumab on skin barrier function in Chinese pediatric patients with moderate-to-severe atopic dermatitis" 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 below:

Table 1 - Investigational medicinal product(s) administered

Intervention label	Dupilumab 200	Dupilumab 300
Intervention name	Dupilumab 200 mg	Dupilumab 300 mg
Intervention description	A 175 mg/mL dupilumab solution in a pre-filled syringe to deliver 200 mg in 1.14 mL	A 150 mg/mL dupilumab solution in a pre-filled syringe to deliver 300 mg in 2 mL
Type	Biological/Vaccine	Biological/Vaccine
Dose formulation	Pre-filled syringe	Pre-filled syringe
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 28 ±2 or 3 days after an initial loading dose of 600 mg
Route of administration	Subcutaneous injection [a]	Subcutaneous injection [a]
Use	Experimental	Experimental
IMP and AxMP	IMP	IMP
Packaging and labeling	Study Intervention was provided in two glass pre-filled syringe packed in a patient kit box. Each box was labeled as required per country requirement.	Study Intervention was provided in two glass pre-filled syringe packed in a patient kit box. Each box was labeled as required per country requirement.
[Current/Former name(s) or alias(es)]	Dupixent	Dupixent

Abbreviations: AxMP, auxiliary medicinal product; IMP, investigational medicinal product.

a. Subcutaneous injection sites were required to alternate between the upper thighs, 4 quadrants of the abdomen, or the upper arms, so that the same site would not be injected twice during consecutive administrations. Injection in the upper arms could only be done by the study site staff and/or by a trained person or health care professional but not the participant themselves.

2.3. Clinical aspects

2.3.1. Introduction

The MAH submitted a final report for:

- LPS17244
- "Open-label exploratory study to evaluate the effect of dupilumab on skin barrier function in Chinese pediatric patients with moderate-to-severe atopic dermatitis"

2.3.2. Clinical study

Description

Study LPS17244 was a Phase 4, open-label exploratory study to evaluate the effect of dupilumab on skin barrier function in Chinese pediatric participants with moderate-to-severe atopic dermatitis (AD) with a healthy volunteer cohort as a reference comparator, and to evaluate the relationship between skin barrier function and disease activity measured by clinical assessments and patient reported outcomes in Chinese pediatric population.

The study design comprised 2 parallel study cohorts: The AD patients' cohort, which received open-label dupilumab treatment for 16 weeks, and the healthy volunteer cohort, which did not receive any treatment and served as a reference comparator group for the skin barrier assessment parameters.

The objective of this study was to assess dupilumab treatment effects on skin barrier function measured as transepidermal water loss (TEWL) and in conjunction with skin tape stripping (STS) in Chinese pediatric participants with moderate-to-severe AD.

TEWL is commonly used for physiologic assessments of skin barrier function. In addition to baseline 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 is possible to follow reactions within the same skin area over time, and to study precisely in which depth of the epidermis the different substances are located. Through these assessments, the study explored the interplay between skin barrier function kinetics and clinical disease severity and therapeutic response. TEWL 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 volunteer cohort assessed at the same time under the same conditions on the same anatomical region with reference thresholds of skin barrier function evaluation indicating pathological relevance.

Methods

Study design and participants

The LPS17244 study was a Phase 4, open-label, exploratory study to evaluate the effect of dupilumab on skin barrier function in Chinese pediatric (aged between ≥6 and <12 years) participants with moderate-to-severe AD, with a healthy volunteer cohort as a reference comparator. Male and female pediatric participants with moderate-to-severe AD were enrolled. Healthy volunteers matched for age

(match on age ±2 years), gender, location of skin served as reference comparators for skin barrier function.

The maximum study duration per participant was 32 weeks. The study comprised:

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

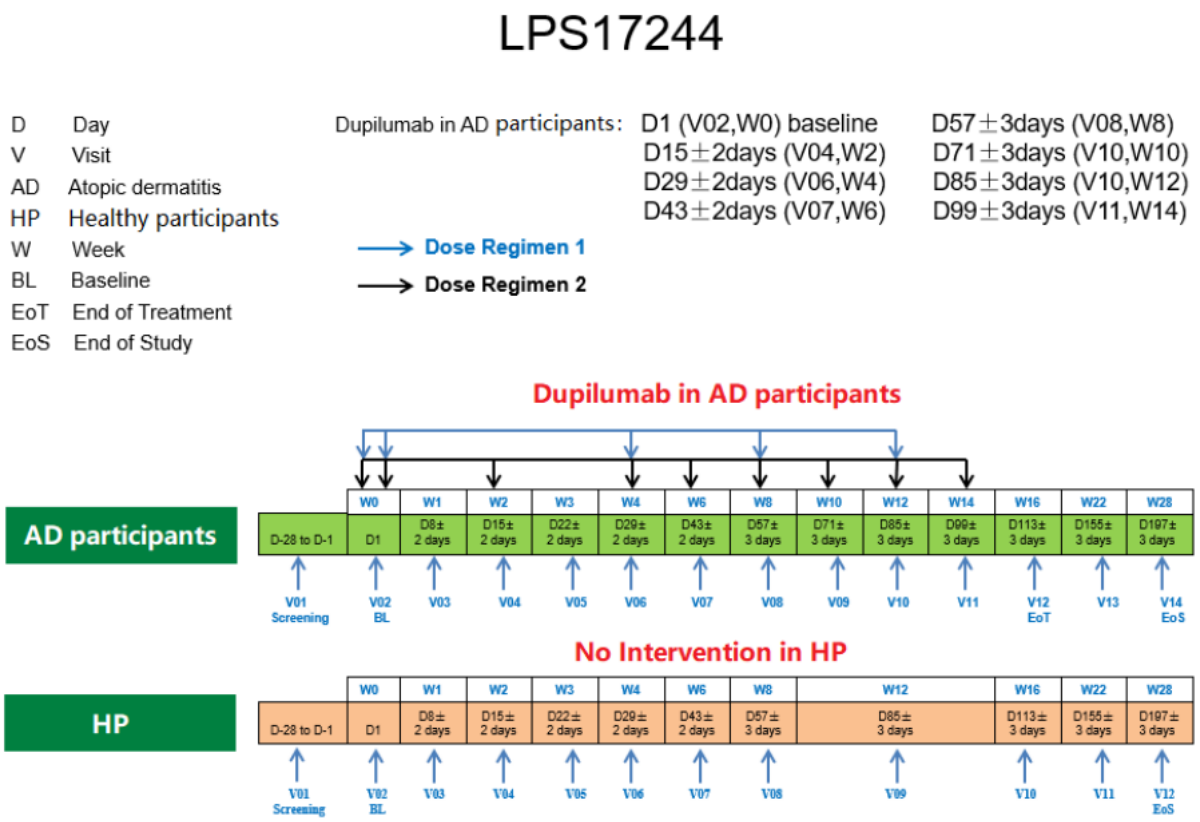
• Baseline Visit (Week 0, Day 1): Participants who remained eligible were enrolled.

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

• A 12-week follow-up period.

Dupilumab was given to pediatric AD patients depending on their body weight. The study intervention included dupilumab 200 mg and 300 mg in a prefilled syringe for subcutaneous (SC) administration. Pediatric AD patients 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 every 4-week SC dosing of dupilumab 300 mg from Week 2 to Week 12. Pediatric AD patients 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.

Figure 1 - Graphical study design



Study population / Sample size

AD patients were enrolled based on the following key criteria:

• Participants must be between ≥6 to <12 years of age inclusive, at the time of signing the informed consent.

• Patients with AD diagnosis according to Hanifin and Rajka criteria (6) at least 1 year before screening.

• Investigator Global Assessment score of ≥3 at screening (on the 0 to 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 must have active lesions on the upper limbs or lower limbs (including trunk, if needed), with severity for lesion erythema or edema/population ≥2 at screening on the 0 to 3 scale of the ISS.

Detailed inclusion and exclusion criteria are provided in the study protocol. Age (match on age ±2 years) and gender were matched to a selected AD patients between the dupilumab cohort and the healthy volunteer cohort.

Treatments

See Table 1 above and Table 2 below.

Table 2 - Arms and associated interventions

Arm title	AD participants	Healthy participants
Arm type	Experimental	No intervention
Arm description	Pediatric patients (≥6 and <12 years of age) with moderate-to-severe AD received a SC injection of dupilumab depending on the body weight. • Regimen 1: children with baseline 15 kg ≤ body weight <30 kg received an SC loading dose of dupilumab 600 mg (2 injections of dupilumab 300 mg) on Day 1 (Week 0), followed by every 4-week SC dosing of dupilumab 300 mg from Week 4 to Week 12. • Regimen 2: children with baseline 30 kg ≤ body weight <60 kg received an SC loading dose of dupilumab 400 mg (2 injections of dupilumab 200 mg) on Day 1 (Week 0), followed by bi-weekly SC dosing of dupilumab 200 mg from Week 2 to Week 14. Dupilumab was administered on-site by study site staff at baseline (Day 1, Week 0), Weeks 4, 8, and 12 for AD participants who received dose regimen 1 and at baseline (Day 1, Week 0), Weeks 2, 4, 6, 8, 10, 12, and 14 for AD participants who received dose regimen 2, after the TEWL assessment had been completed.	Except for IMPs administration, skin barrier function assessments for healthy participants were conducted at the same time and in the same measurement conditions as for AD participants.
Associated Interventions (intervention labels)	Dupilumab 200, Dupilumab 300	Non-treatment healthy participants

Objective(s) and outcomes/endpoints

Study objectives and endpoints are listed in Table 3.

Table 3 - Objectives and endpoints

Objectives	Endpoints
Primary	
• Evaluate changes in skin barrier function with transepidermal water loss (TEWL) assessed after 5 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 Week16 in AD patients.
Secondary	
• Evaluate changes in skin barrier function with TEWL assessed before and after 10, 15, 20 STS in predefined lesional skin in pediatric patients with moderate-to-severe AD treated with dupilumab.	• Change from baseline in TEWL before and after 10, 15, 20 STS assessed on lesional skin in AD patients at Week16.
Tertiary/Exploratory	
• Evaluate changes in skin barrier function with TEWL assessed before and after STS in predefined leasional and non-lesional skin in pediatric patients with moderate-to-severe AD treated with dupilumab in reference to normal skin of healthy volunteers.	• Change from baseline in TEWL before and after 5, 10, 15, 20 STS assessed on non-lesional skin in AD patients and normal skin in healthy volunteers at Week 16.
• 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 in TEWL before STS on lesional/non-lesional skin in AD patients and normal skin in healthy volunteers over time • Change in TEWL after STS assessed on lesional/non-lesional skin in AD patients and normal skin in healthy volunteers over time • Change 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/non-lesional skin in AD patients and normal skin in healthy volunteers over time
• 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 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 ceramides 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 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.

Sample size

Approximately 24 pediatric patients with moderate-to-severe AD were planned to be enrolled to study intervention achieve 20 evaluable patients. Approximately 10 evaluable healthy participants matched for age, gender, location of skin area, and study site should serve as a reference comparator for skin barrier function.

Randomisation and blinding (masking)

The study was conducted from 22 February 2023 (first participant first visit) through 15 March 2024 (last participant last visit) and included 39 pediatric participants (aged ≥6 and <12 years) in China.

This was an open-label study.

Statistical Methods

A detailed description of participant accountability including number of participants by analysis populations, screen failure participants with 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 was generated by cohort.

Continuous variables (age, weight) and qualitative variables (gender, race, and BMI) were summarized by cohort in descriptive statistics. The efficacy evaluation was based on a review of the individual values, descriptive statistics, and where applicable, exploratory statistical analysis.

The satety evaluation was based on a review of vital signs parameters and reported adverse events (AEs). All the safety analyses were performed using the safety population. When applicable, results were reported by cohort and overall.

Results

Participant flow

Participant disposition is shown in Table 4. A total of 39 participants were screened, including 29 participants in the AD cohort and 10 in the healthy participants cohort. A total of 34 participants (87.2%) were successfully screened and enrolled, including 24 participants (82.8%) in the AD cohort and 10 (100%) in the healthy participants cohort. Of the 29 participants screened in the AD cohort, 5 participants (17.2%) were screen failures, including 3 (10.3%) who violated the participant eligibility criteria and 2 (6.9%) with informed consent withdrawal. In the AD cohort, all the 24 participants (100%) completed treatment period and 22 participants (91.7%) completed the study. One participant (4.2%) requested withdrawal from the study, and the other participant (4.2%) discontinued the study due to other reasons (i.e., local recurrence of the rash). The healthy participants did not receive any dupilumab treatment, and all 10 participants (100.0%) completed the study.

Table 4 - Subject distribution (Enrolled population)

Subject distribution	AD participants N=29 n (%)	Healthy participants N=10 n (%)	Total N=39 n (%)
Subjects screened	29	10	39
Subjects screened successfully [a]	24 (82.8)	10 (100.0)	34 (87.2)
Screening failure [a]	5 (17.2)	0	5 (12.8)
Meet any of the Exclusion Criteria or not meet any of the Inclusion Criteria	3 (10.3)	0	3 (7.7)
Subject withdraws informed consent	2 (6.9)	0	2 (5.1)
Subjects completed treatment period successfully [b]	24 (100.0)		
Subjects under treatment period [b]	0		
Subjects with treatment discontinuation [b]	0		
Adverse Event	0		
Lack of Efficacy	0		
Poor Compliance to Protocol	0		
Withdrawal by Subject	0		
Other	0		
Subjects completed study successfully [b]	22 (91.7)	10 (100.0)	32 (94.1)
Subjects under study [b]	0	0	0
Subjects with study discontinuation [b]	2 (8.3)	0	2 (5.9)
Adverse Event	0	0	0
Poor Compliance to Protocol	0	0	0
Patient lost to follow-up	0	0	0
Patient participates in another clinical trial (interventional or observational) during the study	0	0	0
Patient requests withdrawal from the study	1 (4.2)	0	1 (2.9)
Other	1 (4.2)	0	1 (2.9)

a. Denominator was total number of subjects screened.
b. Denominator was total number of subjects successfully screened.
During screening visit, if reason for screening failure was subject withdraws informed consent, subject entered into baseline visit, and the reason for screening failure in baseline visit was described.

Protocol deviations

34 (87.2%) participants of the 39 enrolled participants experienced more than one protocol deviation during the study period.

• All of these 34 participants had protocol deviations related to temperature/humidity exceeding the specified range during TEWL, only one of these participants experienced an important protocol deviation.

• 13 (33.3%) participants had visit-schedules-related protocol deviations, 5 (12.8%) of which related to the investigational medical product (IMP), 8 (20.5%) related to the other (STS sample storage temperature exceeds -80°C).

Recruitment

The study was conducted from 22 February 2023 (first participant first visit) through 15 March 2024 (last participant last visit).

Baseline data

Demographic data

Among the 34 participants, the mean (SD) age was 8.1 (1.86) years. Overall, 17 participants (50.0%) were male and 17 (50.0%) were female. All participants were Asian (N = 34, 100.0%) and 32 (94.1%) were Han ethnicity. Seventeen participants (50.0%) had weight ≥15 kg and <30 kg, 17 participants (50.0%) had weight ≥30 kg and <60 kg. The mean (SD) BMI was 18.1 (3.9) kg/m2.

In the AD cohort (N = 24), the mean (SD) age was 8.0 (1.71) years. Overall, 13 participants (54.2%) were male and 11 (45.8%) were female. All the 24 participants (100.0%) were Asians and 23 (95.8%) were Han ethnicity. Twelve participants (50.0%) had weight ≥15 kg and <30 kg, 12 participants (50.0%) had weight ≥30 kg and <60 kg. The mean (SD) BMI was 18.2 (4.2) kg/m2. The median AD

duration was 40.8 months (range: 13.2 to 125.8 months). In the healthy participants cohort (N = 10), the mean (SD) age was 8.4 (2.27) years. Overall, 4 participants (40.0%) were male and 6 (60.0%) were female. All the 10 participants (100.0%) were Asians and 9 (90.0%) were Han ethnicity. Five participants (50.0%) had weight ≥15 kg and <30 kg, 5 participants (50.0%) had weight ≥30 kg and <60 kg. The mean (SD) BMI was 17.9 (3.3) kg/m2.

Baseline disease characteristics

The baseline disease characteristics showed the clinical and patient-reported outcomes in patients with moderate-to-severe AD. The mean (SD) EASI total score was 18.8 (10.35). Twelve participants (50.0%) had moderate disease and 12 (50.0%) had severe disease according to the IGA score. The mean (SD) POEM score and ISS score was 16.6 (8.22) and 9.0 (2.18), respectively. Average total score of CDLQI (SD) was 8.9 (5.99). The mean (SD) worst itch NRS score was 5.6 (2.64), skin pain NRS score was 3.1 (3.04), and sleep quality NRS score was 6.8 (2.12).

Number analysed

The number of participants included in each analysis population is provided in Table 5. 24 AD participants (82.8%) received IMP and were included into the ITT, mITT, and safety populations. Five participants (17.2%) were screen failures such that they never received IMP and had TEWL/STS assessment. Thus, they were excluded from the ITT, mITT, and safety populations.

No healthy participants were excluded from the populations analyzed.

Table 5 - Number of subjects in each analysis set (Enrolled population)

Analysis Set	AD participants N=29 n (%)	Healthy participants N=10 n (%)	Total N=39 n (%)
Enrolled population	29	10	39
ITT	24 (82.8)	10 (100.0)	34 (87.2)
Reason for exclusion from ITT			
AD participants who never received IMP	5 (17.2)		
Healthy participants who never had TEWL/STS assessment		0	
mITT	24 (82.8)	10 (100.0)	34 (87.2)
Reason for exclusion from mITT			
AD participants who never received IMP	5 (17.2)		
Healthy participants who never had TEWL/STS assessment		0	
Safety population	24 (82.8)	10 (100.0)	34 (87.2)
Reason for exclusion from Safety population			
AD participants who never received IMP or had TEWL/STS assessment	5 (17.2)		
Healthy participants who never had TEWL/STS assessment		0	

Efficacy results

Primary endpoint analysis

The primary endpoint for this study was the percent change from baseline in TEWL after 5 STS assessed on lesional skin at Week 16 in AD patients. Overall, mean (SD) TEWL values after 5 STS assessed on lesional skin were 38.171 (23.1167) g/h/m2 at baseline and 37.849 (22.2341) g/h/m2 at Week 16. The point estimate of absolute change and percent change at Week 16 from baseline in

TEWL values after 5 STS were -0.32 (90% CI: -6.29, 5.65) and -6.73% (90% CI: -23.79%, 7.45%), respectively.

Secondary endpoint analysis

The secondary endpoint for this study was the change from baseline in TEWL before and after 10,

15, 20 STS assessed on lesional skin in AD patients at Week 16. Overall, mean (SD) TEWL value before and after 10, 15, 20 STS assessed on lesional skin was 32.3000 (21.2034) g/h/m2, 45.0579 (27.1362) g/h/m2, 54.8908 (31.1236) g/h/m2, and 63.6721 (33.4040) g/h/m2 among 24 AD patients at baseline, and 32.7819 (20.8285) g/h/m2, 45.4392 (28.9712) g/h/m2, 54.8513 (28.9088) g/h/m2, and 59.1042 (32.0754) g/h/m2 among the 24 participants at Week 16, respectively.

Exploratory endpoints

The mean scores of EASI, ISS, POEM, CDLQI, worst itch NRS, and skin pain NRS decreased from study baseline as early as Week 1 and sustained through Week 28. An increasing trend was displayed in the average score of sleep quality NRS over time as early as Week 1, indicating improvements in sleep with dupilumab treatment in AD patients.

Efficacy conclusions

In this study, the assessments of TEWL-related endpoints were unfulfillable to reflect dupilumab's impact on skin barrier function, due to various factors of protocol deviations including baseline characteristics, disease severity related to inclusion and exclusion criteria and protocol deviations of temperature and humidity during TEWL assessments, reflected in the very high variability of both TEWL and TEWL AUC measures observed during the study.

Safety results

A total of 39 participants were screened in the study, among them 34 participants were screened successfully, including 24 participants with moderate-to-severe AD and 10 healthy volunteers. The safety population in Study LPS17244 included all 34 participants.

Exposure

The exposure and study intervention compliance was analyzed in AD patients of safety population (n=24). Overall, the mean (SD) duration of dupilumab exposure was 112.5 (3.20) days and the median exposure was 112.0 days (range: 119-124 days) (Table 6).

Table 6 - Dupilumab exposure (Safety population)

	AD patients N=24 n
Duration of exposure (days)	
N (Missing)	24 (0)
Mean (SD)	112.5 (3.20)
Median (Q1, Q3)	112.0 (110.5, 113.0)
Min, Max	109, 124

Duration of IMP exposure is defined regardless of unplanned intermittent discontinuations as:
Dose regimen 1: the last dose date - first dose date + 28 days (Injection: 600 mg loading dose + 300 mg q4w)
Dose regimen 2: the last dose date - first dose date + 14 days (Injection: 400 mg loading dose + 200 mg q2w).

Adverse events

In the AD cohort, 15 (62.5%) participants reported a total of 36 AEs, including 15 posttreatment AEs in 9 (37.5%) participants and 21 treatment-emergent adverse events (TEAEs) in 10 (41.7%) participants. No drug withdrawal happened due to TEAEs. The most common TEAEs by preferred term (PT) (≥10.0%) were Dermatitis atopic and Pyrexia (3 [12.5%] participants for both).

In the healthy volunteer's cohort, 5 (50.0%) participants reported a total of 14 AEs, among which the most common AEs by PT was Respiratory tract infection (3 [30.0%] participants).

All reported events were of mild or moderate intensity. None of the participants in either of the cohorts experienced a severe AE. Treatment-emergent adverse events of special interest (AESIs), treatment-emergent serious adverse events (SAEs), and deaths were noted reported in the study.

At all timepoints (baseline, Week 8 and Week 16), the mean values of vital sign parameters (including pulse rate, systolic and diastolic blood pressure [SBP and DBP], body temperature and respiratory rate) and the mean changes from baseline were minimal and similar between the 2 cohorts.

Three (12.5%) participants in the AD cohort had DBP reaching the potentially clinically significant abnormalities (PCSA) criteria during the TE period, while 4 (16.7%) participants in the AD cohort and 3 (30.0%) healthy volunteers had respiratory rate <18 per minutes that reached the PCSA criteria.

Conclusion

Dupilumab was well tolerated in the LPS17244 study population with moderate-to-severe AD. The safety profile was consistent with the established dupilumab safety profile as described in the product information. There were no new safety concerns identified in this study. Overall, 10 (41.7%) participants experienced TEAEs in the AD cohort and 5 (50.0%) healthy volunteers experienced AEs during the study. None of the participants in either of the cohorts experienced a severe AE, and SAE, an AE leading to death, an AE leading to permanent study intervention 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.

2.3.3. Discussion on clinical aspects

The applicant submitted efficacy and safety results from study LPS17244, an open-label exploratory study to evaluate the effect of dupilumab on skin barrier function in Chinese pediatric participants with moderate-to-severe atopic dermatitis (AD) with a healthy volunteer cohort as a reference comparator. Additionally, the relationship between skin barrier function and disease activity measured by clinical assessments and patient reported outcomes were evaluated.

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), skin lipidomics and proteomics, 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.

The objective of this study was to assess dupilumab treatment effects on skin barrier function measured as transepidermal water loss (TEWL) and in conjunction with skin tape stripping (STS) in Chinese pediatric participants aged ≥6 to < 12 years with moderate-to-severe AD.

The maximum study duration per participant was 32 weeks and included a 16-week treatment phase for AD patients and a 16-week observation period for healthy volunteers. Participants were followed up for further 12 weeks. Dupilumab was given to pediatric AD patients according to the labelling.

Participants must have had an AD diagnosis according to Hanifin and Rajka criteria (6) at least 1 year before screening, an IGA score of ≥3 at screening (on the 0 to 4 scale) depending on approved label indication in the country, and must have presented with active lesions on the upper limbs or lower limbs (including trunk, if needed), with severity for lesion erythema or edema/population ≥2 at screening on the 0 to 3 scale of the ISS.

A total of 34 out of 39 participants were enrolled. The intent-to-treat, the modified intent-to-treat, and safety populations included all 34 participants. The demographic characteristics were balanced between the study groups. The baseline disease characteristics were representative for a moderate-to-severe disease grade. Baseline disease characteristics were balanced across the study groups. 24 AD participants (82.8%) received IMP and were included into the ITT, mITT, and safety populations.

As to primary and secondary endpoint analyses, no change in mean (SD) TEWL values after 5, 10, 15, and 20 STS assessed on lesional skin were observed. The vast majority of study participants had protocol violations related to visit schedule, lack of laboratory assessments (temperature and humidity during TEWL assessment), and others, so most of the TEWL assessments are not usable for efficacy analyses. As to exploratory endpoint analysis, dupilumab had a positive effect on clinical and patient-reported outcomes such as EASI, ISS, POEM, SCORAD, and skin pruritus NRS.

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

TEWL assessments are uninformative due to vast protocol violations, however, clinical symptoms slightly improved under dupilumab treatment. 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.