19 September 2024
EMA/456929/2024
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/P46/016

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
Send us a question Go to www.ema.europa.eu/contact **Telephone** +31 (0)88 781 6000 An agency of the European Union

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	22/07/2024	22/07/2024	☐
☐	CHMP Rapporteur Assessment Report	26/08/2024	26/08/2024	☐
☐	CHMP members comments	09/09/2024	n/a	☐
☐	Updated CHMP Rapporteur Assessment Report	12/09/2024	n/a	☐
☒	CHMP adoption of conclusions:	19/09/2024	19/09/2024	☐

Table of contents

Abbreviations **4**

1. Introduction **5**

2. Scientific discussion **5**

2.1. Information on the development program 5

2.2. Information on the pharmaceutical formulation used in the study 5

2.3. Clinical aspects 6

2.3.1. Introduction 6

Description 6

Methods 6

Results 11

2.3.2. Discussion on clinical aspects 15

3. Rapporteur's overall conclusion and recommendation **16**

☒ Fulfilled: 16

Abbreviations

AE: adverse event
AESI: adverse event of special interest
AUC: area under the curve
CDLQI: Children Dermatology Life Quality Index
DLQI: Dermatology Life Quality Index
EASI: Eczema Area And Severity Index
EOS CER: esterified omega-hydroxy fatty acids and sphingosine ceramides
FLG: filaggrin
IGA: Investigator Global Assessment
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 outcome
PT: preferred term
SAE: serious adverse event
SC: subcutaneous
SCORAD: Scoring Atopic Dermatitis
STS: skin tape stripping
TEAE: treatment-emergent adverse event
TEWL: transepidermal water loss
UCA: urocanic acid

1. Introduction

On 8 July 2024, the MAH submitted a completed paediatric study report for LPS17250, 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 LPS17250 entitled 'Open-label exploratory study to evaluate the effect of dupilumab on skin barrier function in Chinese 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.

Table 1 - Study Intervention(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	biologic	biologic
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 14 ±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 NIMP	IMP	IMP
Packaging and labeling	Study Intervention will be provided in two glass pre-filled syringes packed in a patient kit box. Each box will be labeled as required per country requirement.	Study Intervention will be provided in two glass pre-filled syringes packed in a patient kit box. Each box will be labeled as required per country requirement.
[Current/former name(s) or alias(es)]	Dupixent®	Dupixent®

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

2.3. Clinical aspects

2.3.1. Introduction

The MAH submitted a final report for:

- Study number: LPS17250
- Title: Open-label exploratory study to evaluate the effect of dupilumab on skin barrier function in Chinese patients with moderate to severe atopic dermatitis

Study LPS17250, Open-label exploratory study to evaluate the effect of dupilumab on skin barrier function in Chinese patients with moderate to severe atopic dermatitis

Description

Study LPS17250 (BALISTAD China) was a Phase 4, open-label exploratory study to evaluate the effect of dupilumab on skin barrier function in adolescent (aged 12 to 17 years) and adult (aged 18 to 65 years) Chinese participants with moderate-to-severe 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 population.

Methods

Study design and participants

The LPS17250 study was a Phase 4, open-label, exploratory study to evaluate the effect of dupilumab on skin barrier function in adolescent (aged 12 to 17 years) and adult (aged 18 to 65 years) Chinese participants with moderate-to-severe AD, with a healthy volunteer cohort as a reference comparator.

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

The maximum study duration per participant was 24 weeks.

The study comprised (see Fig. 1):

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

• Baseline Visit (Day 1): Eligible participants were enrolled.

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

• A 4-week safety follow-up period.

Atopic dermatitis participants were enrolled based on the following key criteria:

• Participant must be between 12 to 65 years of age (inclusive), at the time of signing the informed consent.

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

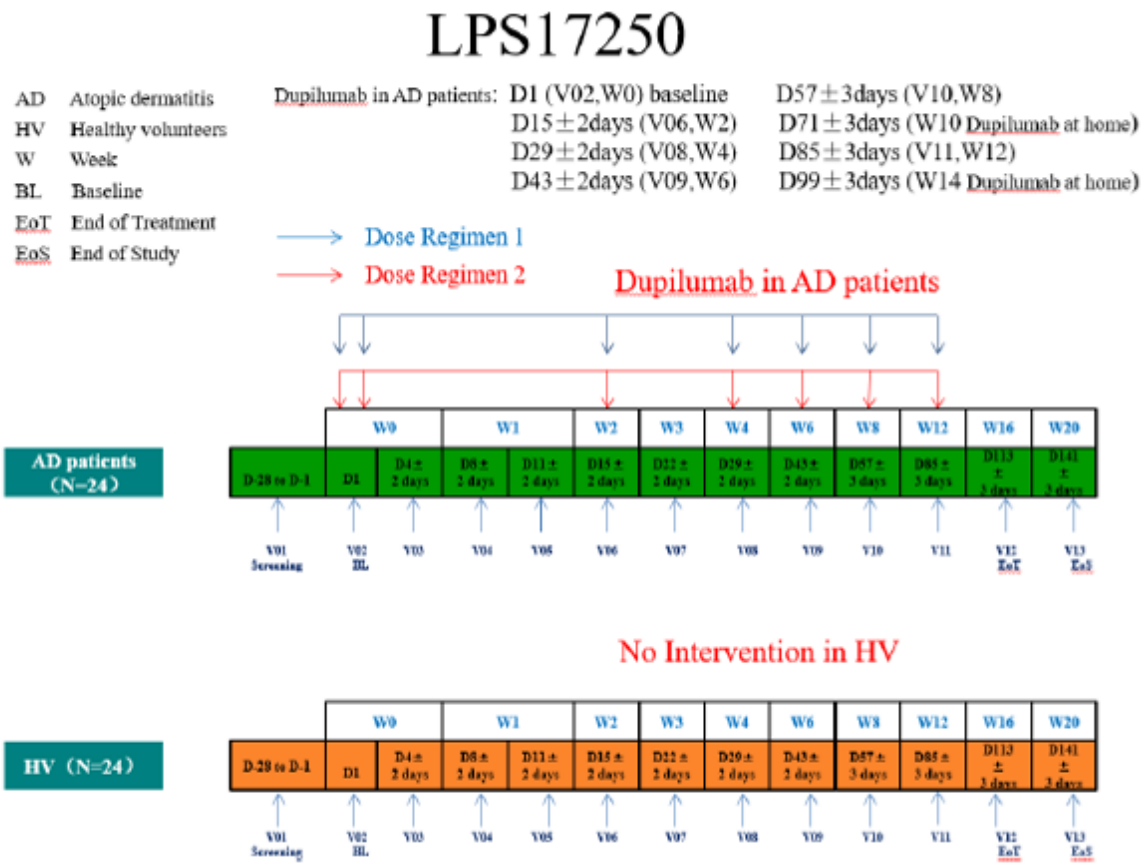
• IGA score of ≥3 at screening (on the 0 to 4 scale).

• Patients with AD must have 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 ISS.

Detailed inclusion and exclusion criteria are provided in the study protocol.

Age and gender were matched to a selected AD patient between the dupilumab cohort and the healthy volunteer cohort. Adolescents (aged ≥12 to <18 years) were matched by post puberty status.

Figure 1 - Graphical study design



Treatments

Dupilumab was given to AD patients depending on their age and body weight. The study intervention included dupilumab 200 mg and 300 mg in a prefilled syringe for subcutaneous administration. AD participants aged ≥12 to <18 years with baseline 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. AD participants with baseline body weight ≥60 kg received a SC loading dose of dupilumab 600 mg (2 injections of dupilumab 300 mg) on Day 1 (Week 0), followed by Q2W SC dosing of dupilumab 300 mg from Week 2 to Week 14.

No change in dosing was made when body weight increased or decreased during the study. AD patients aged 18 years and older received a SC loading dose of 600 mg on Day 1, followed by 300 mg Q2W SC through Week 14. Dupilumab was administered by study site staff at baseline, Week, 2, 4, 6, 8 and 12. Dupilumab was self-administered by AD patients at home at Week 10 and 14.

Objective(s)

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 TEWL and on skin lipidomics in conjunction with STS in Chinese AD population. 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 (3). 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 (4, 5). Through these assessments, the study will explore 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.

Key objectives, endpoints, and estimands are shown in Table 2 and Table 3.

Table 2 - 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 pre-defined lesional skin in 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 and 20 STS in pre-defined lesional skin in patients with moderate to severe AD treated with dupilumab	• Change from baseline in TEWL before and after 10, 15 and 20 STS respectively assessed on lesional skin at Week16 in AD patients.
Tertiary/exploratory	
• Evaluate changes in skin barrier function with TEWL assessed after STS in pre-defined non-lesional skin in patients with moderate to severe AD treated with dupilumab and in normal skin in healthy volunteers	• Change (percent and absolute) from baseline in TEWL before and after 5,10, 15 and 20 STS assessed on non-lesional skin at Week16 in AD patients and on normal skin at Week16 in healthy volunteers respectively.
• Evaluate time course of skin barrier function with TEWL assessed before and after STS in pre-defined lesional and non-lesional skin in patients with moderate to severe AD treated with dupilumab in reference to normal skin of healthy volunteers.	• 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 and non-lesional skin in AD patients and normal skin in healthy volunteers over time. • Change (percent and absolute) in TEWL before and after 5, 10, 15 and 20 STS assessed on lesional and 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 pre-defined lesional and non-lesional skin in patients with moderate to severe AD 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 ω-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 at Week 8 and Week 16, respectively. • 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 patients with moderate-to-severe AD 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.

Table 3 - Summary of primary estimands for main endpoints

Endpoint Category (estimand)	Estimands			
	Endpoint	Population	Intercurrent event(s) handling strategy	Population-level summary (Analysis and missing data handling)
Primary objective: To evaluate changes in skin barrier function with TEWL assessed after STS in pre-defined lesional skin in patients with moderate to severe AD treated with dupilumab.				
Primary endpoint (primary estimand)	Percent change from baseline in TEWL after 5 STS assessed on lesional skin at Week16 in AD patients	Modified Intent-to-treat (mITT) and intent-to-treat (ITT)	Had rescue medication not been initiated (hypothetical strategy), regardless of IMP discontinuation (treatment policy strategy)	Percent change from baseline to Week 16. Missing data will not be imputed due to the small sample size and the exploratory characteristics of the study. In case an important number of patients using rescue therapy is observed, visit values removed due to use of rescue therapy will be imputed.
Secondary objective: To evaluate changes in skin barrier function with TEWL assessed after STS in pre-defined lesional in patients with moderate to severe AD treated with dupilumab.				
Secondary endpoint (estimand 2)	Change from baseline in TEWL before and after 10, 15 and 20 STS respectively assessed on lesional skin at Week16 in AD patients.	mITT	Had rescue medication not been initiated (hypothetical strategy), regardless of IMP discontinuation (treatment policy strategy)	Change from baseline to Week 16. Missing data will not be imputed due to the small sample size and the exploratory characteristics of the study. In case an important number of patients using rescue therapy is observed, visit values removed due to use of rescue therapy will be imputed.

Sample size

Approximately 24 patients with moderate to severe AD were planned to be enrolled to study intervention to achieve 20 evaluable patients.

Approximately 20 evaluable healthy volunteers matched for age, gender, location of skin area, and study site will serve as a reference comparator for skin barrier function.

Sample size for this exploratory study in Asian population was based on medical/clinical judgement and is consistent with the sample size from similar studies in the literature (39). No formal sample size calculation was performed.

Allowing for drop-out rate of 15%, a total of approximately 24 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 Week16, 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 zero. Any drop-out healthy volunteer for whom the matched patient is considered as evaluable will not be replaced.

Randomisation and Blinding

The study was conducted from 25 November 2022 (first participant first visit) through 25 January 2024 (last participant last visit) and included 11 pediatric participants (aged ≥12 and <18 years) in China.

This was an open-label study.

Statistical Methods

A detailed description of participant accountability including number of participants by analysis population, 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 body mass index) were summarized by cohort in 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.

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

Results

Recruitment

The study was conducted from 25 November 2022 (first participant first visit) through 25 January 2024 (last participant last visit) and included 11 pediatric participants (aged ≥12 and <18 years) in China.

Baseline data

A total of 44 participants (24 participants in the dupilumab cohort [AD cohort] and 20 participants in the healthy volunteer cohort) were screened and enrolled in the study. There was no screening failure and no participants were excluded from the populations analyzed. The intent-to-treat (ITT), modified intent-to-treat (mITT) and safety populations included 44 participants). Of the 44 participants enrolled, 33 participants (17 participants in the AD cohort and 16 participants in the healthy volunteer cohort) were adults and 11 participants (7 participants in the AD cohort and 4 participants in the healthy volunteer cohort) were adolescents. Detailed demographics of age, gender, ethnicity, and weight for AD patients and healthy volunteers are presented in the LPS17250 CSR [Section 4.4.1]. Demographics for the adolescent participants in the AD cohort are presented in Table 4.

Table 4 - Participant demographics for AD patients aged <18 years (ITT)

	AD participants N=7 n (%)
Weight group	
Baseline body weight <60 kg	5 (71.4)
Baseline body weight ≥60 kg	2 (28.6)
Weight (kg)	
N (Missing)	7 (0)
Mean (SD)	54.14 (7.983)
Median (Q1, Q3)	57.00 (46.50, 63.00)
Min, Max	44.5, 63.0
Body Mass Index (kg/m^2)	
N (Missing)	7 (0)
Mean (SD)	20.4 (2.9)
Median (Q1, Q3)	19.0 (18.6, 23.1)
Min, Max	16.5, 24.5
Course of disease (months)*	
N(Missing)	7 (0)
Mean (SD)	48.6 (14.7)
Median (Q1, Q3)	55.3 (28.0, 60.6)
Min, Max	27.9, 60.8

* Course of disease (months) = (ICF signature date - Date of first diagnosis of AD + 1)/30.4375, rounding to one decimal place.

Generated datetime: 2024-03-18 10:04

In the AD cohort, 23 participants (95.8%) completed the treatment period and the study. One adult participant discontinued dupilumab treatment and the study. In the healthy participant cohort, 20 participants (100.0%) completed the study.

Number analysed

A detailed description of participant accountability including number of participants by analysis population, 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 body mass index) were summarized by cohort in 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. The safety evaluation was based on a review of vital signs parameters and reported AEs. All the safety analyses were performed using the safety population. When applicable, results were reported by cohort and overall.

Efficacy results

Primary endpoint analysis

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 patients.

Overall, mean TEWL values after 5 STS assessed on lesional skin at baseline and Week 16 were 63.073 ±19.1351 g/h/m² and 36.018 ±18.4224 g/h/m², respectively. The mean (SD) absolute change from

baseline was -25.641 (26.0180), and the corresponding mean percent change was -36.8510% (37.1486%), both representing significant decrease with 1 sided p-value p<0.0001. Results in detail are presented in the LPS17250 CSR [Section 5.1.2]. In both ITT and mITT populations, 17 patients were adults (aged ≥18 years) and 7 were adolescents (aged ≥12 to <18 years). Subgroup analysis was conducted for adolescents and adults on the primary endpoint in both ITT and mITT populations. The subgroup analysis results were generally consistent with results of the primary analysis.

Compared with the baseline value, the mean TEWL value after 5 STS assessed on lesional skin in in adolescent participants at Week 16 was significantly reduced, similar to the results found in all AD patients.

Secondary endpoint analysis

Secondary endpoint analysis was performed on the ITT population.

Subgroup analysis of the secondary endpoint was performed based on the ITT and mITT populations with same age categories as in the primary endpoint (aged <18 years, and ≥18 years). Overall, mean TEWL values before and after 10, 15, 20 STS assessed on lesional skin were 51.2028 ±14.1574 g/h/m², 73.2146 ±20.6552 g/h/m², 81.6246 ±21.7895 g/h/m² and 84.6833 ±19.9446 g/h/m² among 24 participants at baseline, and 27.5163 ±9.7373 g/h/m², 50.5209 ±23.6596 g/h/m², 62.4013 ±24.5885 g/h/m², 77.7839 ±23.0836 g/h/m² at Week 16, respectively among 23 AD participants.

A significant decrease of TEWL was observed after 10 and 15 STS but not after 20 STS. Reduction trends observed in adolescent were similar to the trends seen in all AD patients. Results in detail are presented in the LPS17250 CSR [Section 5.1.3].

Tertiary/exploratory endpoints

The mean scores of EASI, ISS, POEM, SCORAD, DLQI (among 20 patients aged ≥16 years), and peak pruritus NRS decreased from study baseline as early as Week 1 and sustained through Week 16. Among four AD patients (aged ≥12 and <16 years), the average score of CDLQI reduced from baseline over time, with similar extent of reduction at different timepoints (eg, Week 8 and Week 16). The CDLQI assessment in adolescents are presented in Appendix 16.2.6 Efficacy response data [Table 14.2.3.2.6] of the LPS17250 CSR. An increasing trend was displayed in average score of sleep quality NRS over time as early as Week 1, indicating improvements in sleep with dupilumab treatment in AD patients. Similar results were also found in changes (percent and absolute) from baseline in EASI, ISS, POEM, SCORAD, DLQI / CDLQI, peak pruritus NRS and sleep quality NRS over time. Detailed results of tertiary/exploratory endpoints including TEWL assessments, are presented in Section 5.1.4 of the LPS17250 CSR.

Safety results

Brief description and objectives of LPS17250 are provided in Section 3.1 and the details of study design, study population, evaluation criteria and statistical methods are provided in Section 3.2. The statistical method of safety evaluation is detailed in Section 3.2.4.

DEFINITION OF STUDY PARTICIPANT POPULATIONS

The population for safety analyses is described in Section 3.2.2. A total of 44 participants (24 participants in the dupilumab cohort and 20 participants in the healthy volunteer cohort) were enrolled in the study. The safety population in LPS17250 included all 44 participants.

EXTENT OF EXPOSURE

The exposure and study intervention compliance was analyzed in AD participants of safety population (n=24). Overall, the mean (SD) duration of dupilumab exposure was 110.7 ±18.12 days and the median exposure was 114.5 days (range: 112.0-117.0 days). For adolescent AD participants (n=7), mean duration of exposure was 113.6 ±3.41 days and the median exposure was 113.0 days (range: 112.0-115.0 days) (Table 5).

Table 5 - Dupilumab Exposure and compliance for AD patients aged <18 years (safety population)

	AD participants < 18 years of age N=7 n (%)
Duration of exposure (days)	
N (Missing)	7 (0)
Mean (SD)	113.6 (3.41)
Median (Q1, Q3)	113.0 (112.0, 115.0)
Min, Max	109, 120
Treatment compliance (%)	
N (Missing)	7 (0)
Mean (SD)	100.00 (0.000)
Median (Q1, Q3)	100.00 (100.00, 100.00)
Min, Max	100.0, 100.0
Compliance <80%	0 (0.0)
Above-planned dosing percentages (%)	0 (0.0)
Under-planned dosing percentages (%)	0 (0.0)
Percentage of under-planned dosing administrations patients	
0	7 (100.0)
0-20%	0 (0.0)
>20%	0 (0.0)
Percentage of above-planned dosing administrations patients	
0	7 (100.0)
0-20%	0 (0.0)
>20%	0 (0.0)
Have at least 1 above-planned dosing administration	0 (0.0)

Duration of IMP exposure (days) = last dose date - first dose date + 14 days (Injection: 600/400 mg loading dose + 300/200 mg q2w), regardless of unplanned intermittent discontinuations (If the patient's date of last dose is unknown, his/her last IMP dispensing date will be used in its place.)

Treatment compliance = the number of administrations compliant / the total number of administrations planned to take *100% (on or before the last IMP administration date), a given administration will be considered noncompliant if the patient did not take the planned dose of treatment as required by the protocol.

Percentage of under-planned dosing administrations patients = (the total dose of administrations planned to take - the total dose of administrations compliant) / the total dose of administrations planned to take *100%)

Percentage of above-planed dosing administrations patients = (the number total dose of administrations compliant - the total number dose of administrations planned to take) / the total number dose of administrations planned to take *100%

Generated datetime: 2024-03-18 10:04

ADVERSE EVENTS

Overview of the safety population

A total of 20 treatment-emergent adverse events (TEAEs) were reported in 11 participants (45.8%) in the dupilumab cohort of the safety population. No drug withdrawal happened due to TEAEs. In the dupilumab cohort, the most common TEAEs by PTs (≥ 10.0%) reported were upper respiratory tract infection and conjunctivitis (3 participants [12.5%] for both). A total of 9 AEs were reported for 6 participants (30.0%) in the healthy volunteer cohort, among which the most common AEs was upper respiratory tract infection (4 participants, [20.0%]). 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 not 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 pressures, body temperature and respiratory rate) and the mean changes from baseline were minimal and similar between the two cohorts. There were no participants with PCSA in the safety population.

TEAEs in the adolescent population

Four out of the 7 adolescents (57.14%) in the dupilumab cohort presented with TEAEs. TEAE reported in the 4 adolescents in the dupilumab cohort by PT were as follows:

• Upper respiratory tract infection: 2 participants (3 events),

• Conjuctivitis: 1 participant,

• Gastritis: 1 participant,

• Abdominal pain: 1 participant.

One out of 4 adolescents in the healthy volunteer cohort presented with AEs of pyrexia and upper respiratory tract infection.

2.3.2. Discussion on clinical aspects

The applicant submitted efficacy and safety results from study LPS17250, a phase 4, open-label, exploratory study to evaluate the effect of dupilumab on skin barrier function in Chinese adult and pediatric patients aged between 12 and 65 years 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), 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 intent-to-treat (ITT), modified intent-totreat (mITT) and safety populations included 44 participants). Of these, 33 participants were enrolled. Overall 11 adolescents were included in the study; 7 patients were assigned to the dupilumab group, and 4 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 mean age was 23.3±8.98 years in the AD group with a median disease

duration of 52.1 months (range, 30.7 to 84.3 months). Accordingly, the majority of AD patients had concomitant medications and prior medications such as antipruritics and corticosteroids, emollients and protectives. 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.

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 total study duration per participant including screening and follow-up was 24 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.

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 Percent change from baseline in TEWL after 5 STS assessed on lesional skin at Week 16 in AD patients. After 5 STS on lesional skin in AD participants the TEWL was reduced by 36.85% at week 16. There was no significant difference of mean TEWL value among AD participants before 15 STS on non-lesional skin at week 16 compared with baseline, however, the mean TEWL after 20 STS at week 16 was significantly decreased from baseline. In HV, the mean TEWL values after 5 and 20 STS at week 16 were significantly increased from baseline. As to subgroup analyses, similar results were noticed in adults and adolescents.

As demonstrated before, dupilumab had a positive effect on further clinical and patient-reported outcomes EASI, ISS, POEM, SCORAD, and skin pruritus NRS. Major protocol deviations are deemed not to have impacted efficacy analyses.

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 significantly 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. 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.