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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/P46/015

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	29/04/2024	29/04/2024	☐
☐	CHMP Rapporteur Assessment Report	03/06/2024	03/06/2024	☐
☐	CHMP members comments	17/06/2024	n/a	☐
☐	Updated CHMP Rapporteur Assessment Report	20/06/2024	n/a	☐
☒	CHMP adoption of conclusions:	27/06/2024	27/06/2024	☐

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Abbreviations

%EASI:	percent change in EASI
AD:	atopic dermatitis
ADA:	anti-drug antibody
AE:	adverse event
AESI:	adverse event of special interest
ALT:	alanine aminotransferase
AST:	aspartate aminotransferase
BMI:	body mass index
BSA:	body surface area
CDLQI:	Children's Dermatology Life Quality Index
CFR:	Code of Federal Regulations
CMH:	Cochran-Mantel-Haenszel
COVID-19:	coronavirus disease 2019
CRF:	case report form
CRSwNP:	chronic rhinosinusitis with nasal polyposis
CSR:	clinical study report
EASI:	Eczema Area and Severity Index
EASI-50:	≥50% reduction in EASI
EASI-75:	≥75% reduction in EASI
EASI-90:	≥90% reduction in EASI
EC:	ethics committee
ECG:	electrocardiogram
eCRF:	electronic case report form
GCP:	Good Clinical Practice
GDPR:	General Data Protection Regulation
HCV:	hepatitis C virus
HIPAA:	Health Insurance Portability and Accountability Act
HIV:	human immunodeficiency virus
HLGT:	high-level group term
HLT:	high level term
IAF:	informed assent form
ICF:	informed consent form
ICH:	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IDQOL:	Infant’s Dermatitis Quality of Life Index
IGA:	Investigator's Global Assessment
IgG4:	immunoglobulin G4
IL:	interleukin
IMP:	investigational medicinal product
IRB:	institutional review board
IRT:	interactive response technology
ITT:	intent-to-treat
LDH:	lactate dehydrogenase
LLOQ:	lower limit of quantification
LOCF:	last observation carried forward
LS:	least squares
MedDRA:	Medical Dictionary for Regulatory Activities
NAb:	neutralizing antibody
nE/PY:	number of events per participant year
NIMP:	non-investigational medicinal product
NRS:	numerical rating scale
OLE:	open-label extension
PCSA:	potentially clinically significant abnormality

PK:	pharmacokinetics
POEM:	Patient Oriented Eczema Measure
PT:	preferred term
q2w:	every 2 weeks
q4w:	every 4 weeks
QOL:	quality of life
SAE:	serious adverse event
SAP:	statistical analysis plan
SD:	standard deviation
SMQ:	standardized MedDRA query
SOC:	system organ class
TARC:	thymus and activation-regulated chemokine
TB:	tuberculosis
TCI:	topical calcineurin inhibitor
TCS:	topical corticosteroids
TEAE:	treatment-emergent adverse event
ULN:	upper limit of normal
WOCF:	worst observation carried forward

1. Introduction

On 29 April 2024, the MAH submitted a completed paediatric study for study EFC16823, 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 EFC16823 is a stand-alone study and part of a clinical development program.

2.2. Information on the pharmaceutical formulation used in the study

- A 150 mg/mL dupilumab solution in a pre-filled syringe to deliver 300 mg in 2 mL
- A 175 mg/mL dupilumab solution in a pre-filled syringe to deliver 200 mg in 1.14 mL
- Matching placebo

2.3. Clinical aspects

2.3.1. Introduction

The MAH submitted a final clinical study report (CSR) for:

- Study EFC16823 entitled A randomized, double-blind, placebo-controlled, multi-center, parallel-group study to evaluate the efficacy, safety and pharmacokinetics of dupilumab compared to placebo in Japanese patients with atopic dermatitis (AD) aged 6 months to <18 years whose disease is not adequately controlled with existing therapies

2.3.2. Clinical study EFC16823 "A randomized, double-blind, placebo-controlled, multi-center, parallel-group study to evaluate the efficacy, safety and pharmacokinetics of dupilumab compared to placebo in Japanese patients with atopic dermatitis aged 6 months to <18 years whose disease is not adequately controlled with existing therapies"

Description

EFC16823 was a randomized, double-blind, placebo-controlled, Phase 3 study to assess the efficacy, safety, and PK of dupilumab with concomitant topical corticosteroid (TCS) use in Japanese participants aged ≥6 months to <18 years with moderate-to-severe AD whose disease was not adequately controlled with existing therapies. This study is a part of the Japan pediatric clinical development plan for dupilumab in AD.

The first step analysis CSR dated on 30 June 2022 presented the results of all analyses for the 24-week IMP intervention period (16-week randomized IMP intervention period and subsequent OLE period) of each participant with the data cut-off date of 09 February 2022 (date of first interim data cut-off). The first step analysis CSR reported the final analyses of primary efficacy of dupilumab compared with placebo during the 16-week double blind randomized IMP intervention period and safety up to Week 24 with dupilumab treatment. The results of primary and secondary efficacy endpoints during the 16-week randomized IMP intervention period and the tertiary/exploratory efficacy endpoints during the OLE period up to Week 24 have been summarized in the first step analysis CSR.

The second step analysis CSR dated on 27 January 2023 presented the results of all analyses for the 52-week IMP intervention period of each participant with the data cut-off date of 24 August 2022 (date of second interim data cut-off), along with the results of primary and secondary efficacy endpoints during the 16-week double blind randomized IMP intervention period from the first step analysis CSR.

In the second step analysis CSR, the results of the primary and secondary efficacy endpoints during the randomized IMP intervention period were reiterated from the first step analysis CSR, and the updated data on the tertiary/exploratory efficacy endpoints up to Week 32 (the last evaluation time point specified in the protocol) for peak pruritus NRS, worst itch NRS, worst scratch/itch NRS, CDLQI, and IDQOL, or Week 52 for EASI, IGA, and percent BSA affected by AD were provided.

This final analysis CSR reports the results of all analyses for the IMP intervention period (16-week randomized IMP intervention period and OLE period) and subsequent safety follow-up, along with the results of primary and secondary efficacy endpoints during the randomized IMP intervention period from the first step analysis CSR. The efficacy analyses were conducted for up to 116 weeks depending on the endpoint.

Methods

Study participants

The key inclusion and exclusion criteria for Study EFC16823 are presented below.

Key inclusion criteria:

• Participants were Japanese and ≥6 months to <18 years of age, at the time of signing the informed consent and/or assent.

• Participants who had diagnosis of AD according to the American Academy of Dermatology consensus criteria at screening visit.

• Chronic AD diagnosed at least 1 year prior to the screening visit (for participants between 6 months to <1 year of age, the requirement was to have had chronic AD for 3 months).

• IGA ≥3 and EASI ≥16 at screening and baseline visits.

• Baseline peak pruritus NRS average score for maximum itch intensity ≥4 for participants ≥12 to <18 years of age.

• Baseline worst itch NRS or worst scratch/itch NRS weekly average score for maximum itch or scratch/itch intensity ≥4 for participants ≥6 months to <12 years of age.

• Body surface area (BSA) of AD involvement >10% at screening and baseline visits.

• With documented recent history (within 6 months before the baseline visit) of inadequate response to topical AD medication(s).

• Capable of giving signed informed consent as described in 16-1-1-protocol [10.1] of the protocol which includes compliance with the requirements and restrictions listed in the informed consent form (ICF) and in this protocol. Participants ≥6 years of age (or above an age determined by the Institutional Review Board [IRB]) must provide written informed assent form (IAF), and their legally authorized representative must provide written informed consent.

Key exclusion criteria

• Active chronic or acute infection requiring treatment with systemic antibiotics, antivirals, antiprotozoals, or antifungals within 2 weeks before the baseline visit or during the

screening period.

• Known or suspected immunodeficiency, including history of invasive opportunistic infections (eg, tuberculosis [TB], histoplasmosis, listeriosis, coccidioidomycosis, pneumocystosis, and aspergillosis) despite infection resolution, or otherwise recurrent infections of abnormal frequency or prolonged duration suggesting an immune compromised status, as judged by the Investigator.

• Participants with active TB or non-tuberculous mycobacterial infection, or a history of incompletely treated TB were excluded from the study unless it was well documented by a specialist that the participant had been adequately treated and could start treatment with a biologic agent, in the medical judgement of the Investigator and/or infectious disease specialist. Tuberculosis testing was performed according to local guidelines of Japan, if required by regulatory authorities or ethics boards.

• Known history of human immunodeficiency virus (HIV)-1 and HIV-2 infection or HIV seropositivity at the screening.

• Participants with any of the following result at the screening:

- Positive (or indeterminate) Hepatitis B surface antigen (HBs Ag) or, - Positive hepatitis B core antibody (HBc Ab) confirmed by positive hepatitis B virus (HBV) DNA or,

- Positive hepatitis C antibody (HCV Ab) confirmed by positive hepatitis C virus (HCV) RNA.

Design

Study EFC16823 was comprised of the following 3 periods (see Fig. 1):

• Screening period: up to 5 weeks (including the TCS standardization period of 2 weeks)

• Investigational medicinal product intervention period:

  - The randomized IMP intervention period (expressed as the randomized treatment period in the analysis): 16 weeks

  - The OLE period (all participants switch to active treatment after 16 weeks): until approval of the indication in Japan or for 3 years, whichever was sooner

• Follow-up period (for participants who did not want to continue to the OLE period): 12 weeks

Participants enrolled into Study EFC16823 were randomly assigned (1:1) to the dupilumab group or the placebo group (matching placebo) in the 16-week randomized IMP intervention period.

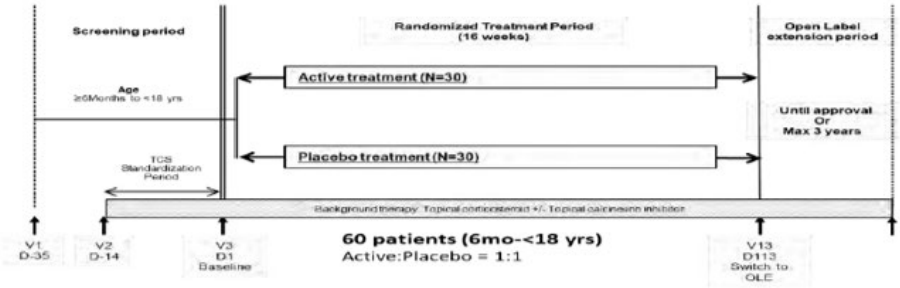
Dupilumab and placebo dose regimens were as follows:

- Dupilumab 300 mg q2w with 600 mg loading dose for ≥60 kg body weight at baseline
- dupilumab 200 mg q2w with 400 mg loading dose for ≥30 to <60 kg body weight at baseline
- dupilumab 300 mg q4w for ≥15 to <30 kg body weight at baseline
- dupilumab 200 mg q4w for ≥5 to <15 kg body weight at baseline
- Matching placebo

For the OLE period, all participants randomized to the dupilumab group in the randomized IMP intervention period continued the same treatment in the OLE period (the dupilumab/dupilumab group). Participants randomized to the placebo group in the randomized IMP intervention period started to receive the dupilumab treatment in the OLE period, with the dose determined by body weight (the placebo/dupilumab group). During screening, all participants underwent a 2-week TCS standardization

period using a standardized regimen, which could be continued, decreased, or stopped according to the severity of the disease throughout the study. TCS rescue medication was allowed. During the OLE period after Week 32, any class of TCS and topical calcineurin inhibitors could have been used according to the Investigator's discretion and in consultation with the Japanese AD guideline. For participants who declined to enter to the OLE period, the overall duration of the study was approximately 33 weeks (including screening [up to 5 weeks], treatment [16 weeks], and follow-up [12 weeks]). For participants who chose to enter the OLE, the duration of the interventional period was approximately 21 weeks (including screening and treatment) plus an additional 3 years OLE period or until approval of the indication in Japan, whichever was sooner. Approximately 60 participants were planned to be enrolled in the study and randomly assigned to study intervention (dupilumab or placebo in a 1:1 ratio).

Figure 1. Study design schema



Weight group	Dose/dose regimen Randomized treatment period*	Dose/dose regimen Open-label extension period *
≥60 kg	300 mg q2w SC with 600 mg LD Or placebo q2w SC with placebo LD	300 mg q2w SC with 600 mg or 300 mg LD#
≥30 to <60 kg	200 mg q2w SC with 400 mg LD Or placebo q2w SC with placebo LD	200 mg q2w SC with 400 mg or 200 mg LD§
≥15 to <30 kg	300 mg q4w SC Or placebo q4w SC	300 mg q4w SC
≥5 to <15 kg	200 mg q4w SC Or placebo q4w SC	200 mg q4w SC

*Dosing regimen was not changed during the randomized IMP intervention period. At the time of entering the open-label extension (OLE) period and after Week 32, if a participant's body weight exceeds the specific weight (15, 30, or 60 kg) at the previous in-clinic visit, the dosing regimen was adjusted. If a participant moved from a higher weight group to a lower weight group, the dose was to be adjusted if the participant fell in the lower weight group for 2 consecutive in-clinic visits.

#with 600 mg LD (for the participant who had placebo treatment on randomized treatment period) or 300 mg LD (300 mg + placebo, 2 injections for the participant who had active treatment during the randomized treatment period)

§with 400 mg LD (for the participant who had placebo treatment on randomized treatment period) or 200 mg LD (200 mg + placebo, 2 injections for the participant who had active treatment during the randomized treatment period)

D = Day; EOT = end of the treatment; IMP = investigational medicinal product; LD = loading dose; N = number of subjects; OLE = Open-label extension; q2w = every 2 weeks; q4w = every 4 weeks; SC = subcutaneous; TCS = topical corticosteroid; V = Visit

Treatments

The study interventions are outlined in Table 1, and the study arms with associated interventions are described in Table 2. The dupilumab treatment group in the study was a weight-tiered fixed-dose regimen described in Figure 1. Dosing regimen was not changed during the randomized IMP intervention period (until Week 16).

At the time of entering the OLE period (at Week 16) and every in-clinic visit after Week 32, if a participant's body weight exceeded the specific weight (15, 30, or 60 kg) at the previous in-clinic visit, the dosing regimen was to be adjusted to the higher weight regimen. If a participant moved from a higher weight group to a lower weight group for 2 consecutive in-clinic visits, the dose was to be adjusted to the lower weight dose regimen.

Table 1. Study interventions

Intervention label	Dupilumab 200 mg	Dupilumab 300 mg	Placebo	Placebo
Intervention name	Dupilumab 200 mg	Dupilumab 300 mg	Placebo matching dupilumab 200 mg	Placebo matching dupilumab 300 mg
Type	Biological	Biological	Other	Other
Dose formulation	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	Placebo matching dupilumab 200 mg will be supplied as an identical formulation to the active 200 mg formulation without dupilumab, in a pre-filled syringe to deliver placebo in 1.14 mL	Placebo matching dupilumab 300 mg will be supplied as an identical formulation to the active 300 mg formulation without dupilumab, in a pre-filled syringe to deliver placebo in 2 mL
Unit dose strength(s)	200 mg	300 mg	0 mg	0 mg
Dosage level(s)	200 mg every 14 ±3 days after an initial loading dose of 400 mg for body weight ≥30 to <60 kg 200 mg q4w for all participants weighing ≥5 to <15 kg	300 mg every 14 ±3 days after an initial loading dose of 600 mg for body weight ≥60 kg 300 mg q4w for all participants weighing ≥15 to <30 kg	For double-blind randomized treatment period + 0 mg loading dose at OLE entry for participants who were on dupilumab in the randomized portion. 0 mg every 14 ±3 days after an initial loading dose of 0 mg for body weight ≥30 to <60 kg 0 mg q4w for all participants weighing ≥5 to <15 kg	For double-blind randomized treatment period + 0 mg loading dose at OLE entry for participants who were on dupilumab in the randomized portion. 0 mg every 14 ±3 days after an initial loading dose of 0 mg for body weight ≥60 kg 0 mg q4w for all participants weighing ≥15 to <30 kg
Route of administration	Subcutaneous[a]	Subcutaneous[a]	Subcutaneous[a]	Subcutaneous[a]
Use	Experimental	Experimental	placebo-comparator	placebo-comparator
IMP or NIMP	IMP	IMP	IMP	IMP
Packaging and labeling	One glass pre-filled syringe packed in a kit box. Both the glass pre-filled syringe and the box were labeled as required per country requirement.	One glass pre-filled syringe packed in a patient kit box. Both the glass pre-filled syringe and the box were labeled as required per country requirement.	One glass pre-filled syringe packed in a patient kit box. Both the glass pre-filled syringe and the box were labeled as required per country requirement.	One glass pre-filled syringe packed in a patient kit box. Both the glass pre-filled syringe and the box were labeled as required per country requirement.
Current/Former name(s) or alias(es)	Dupixent®	Dupixent®	-	-

a Subcutaneous injection sites of the study drug should be alternated among the different quadrants of the abdomen (avoiding navel and waist areas), upper thighs, and upper arms so that the same site is not injected for 2 consecutive administrations. Injection in the upper arms can only be done by the study-site staff and/or by a trained person or health care professional but not the participant themselves.

Table 2. Study arms with associated interventions

Arm name	Dupilumab	Placebo	Dupilumab/Dupilumab	Placebo/Dupilumab
Associated interventions (intervention label[s])	Dupilumab 200 mg or 300 mg in the randomized treatment period	Placebo matching dupilumab 200 mg or 300 mg in the randomized treatment period	Dupilumab 200 mg or 300 mg in the randomized treatment period and the OLE period	Placebo matching dupilumab 200 mg or 300 mg in the randomized treatment period and Dupilumab 200 mg or 300 mg in the OLE period

Objective(s)

Table 3. Objectives and endpoints

Objectives	Endpoints
Primary	
• To evaluate the efficacy of dupilumab administered concomitantly with TCS	• Proportion of participants with EASI-75 at Week 16
Secondary	
• To evaluate the efficacy of dupilumab administered concomitantly with TCS	Key secondary endpoints • Percent change in EASI score from baseline to Week 16 • Percent change from baseline to Week 16 in weekly average of daily worst itch NRS for participants aged ≥6 years to <12 years old • Proportion of participants with an IGA score of 0 or 1 at Week 16 (5-point scale) Other secondary endpoints • Percent change from baseline to Week 16 in weekly average of daily worst pruritus, using the peak pruritus NRS for participants aged ≥12 years to <18 years old • Percent change from baseline to Week 16 in weekly average of daily worst scratch/itch NRS for participants aged ≥6 months to <6 years old • Percent change from baseline to Week 16 in weekly average of daily worst pruritus, using the peak pruritus NRS for participants aged ≥12 years to <18 years old, the worst itch NRS for participants aged ≥6 years to <12 years old, and the worst scratch/itch NRS (completed by caregiver) for participants aged ≥6 months to <6 years old • Proportion of participants with EASI-50 at Week 16 • Proportion of participants with EASI-90 at Week 16 • Change from baseline to Week 16 in percent BSA affected by AD • Change from baseline to Week 16 in CDLQI (≥4 years) • Change from baseline to Week 16 in IDQOL (<4 years) • Change from baseline to Week 16 in POEM

Objectives	Endpoints
	• Change from baseline to Week 16 in weekly average of daily worst pruritus, using the peak pruritus NRS for participants aged ≥12 years to <18 years old • Change from baseline to Week 16 in weekly average of daily worst itch NRS for participants aged ≥6 years to <12 years old • Change from baseline to Week 16 in weekly average of daily worst scratch/itch NRS for participants aged ≥6 months to <6 years old.
• To assess the safety of dupilumab over 16 weeks of treatment when administered concomitantly with TCS in participants	• Incidence of TEAEs, SAEs, and AESIs from baseline to 16 weeks of treatment (Visit 13) • Incidence of skin-infection TEAEs (excluding herpetic infections) from baseline to 16 weeks of treatment (Visit 13) • Incidence of serious TEAEs from baseline to 16 weeks of treatment (Visit 13) • Incidence of TEAEs, SAEs and AESIs from baseline of open-label extension (OLE, Visit 13) through the last study visit
• To assess immunogenicity as determined by the incidence, titer, and clinical impact of treatment-emergent ADA to dupilumab over time in pediatric patients with AD (aged ≥6 months to <18 years old)	• Incidence, titer, and clinical impact of treatment-emergent ADA to dupilumab over time in pediatric patients with AD (aged ≥6 months to <18 years old)
• To assess the concentration of dupilumab in serum following administration concomitantly with TCS	• Concentrations of functional dupilumab in serum over time and PK parameter (C_{trough})
Tertiary/exploratory	
• To evaluate the long term efficacy of dupilumab administered concomitantly with TCS	• During the OLE period, primary and secondary efficacy endpoints were summarized by each visit using descriptive statistics and frequency table, respectively.

AD: atopic dermatitis; ADA: antidrug antibody; AESI: adverse event of special interest; BSA: = body surface area; C_{trough}: lowest concentrations of functional dupilumab in serum over time; CDLQI Children's Dermatology Life Quality Index; EASI: Eczema Area and Severity Index; EASI-50: ≥50% improvement from baseline EASI; EASI-75: ≥75% improvement from baseline EASI; EASI-90: ≥90% improvement from baseline EASI; IDQOL: Infants' Dermatitis Quality of Life Index; IGA: Investigator's Global Assessment; NRS: numerical rating scale; OLE: open-label extension; PK: pharmacokinetic; POEM: Patient Oriented Eczema Measure; SAE: serious adverse event; TCS: topical corticosteroids; TEAE: treatment-emergent adverse event.

Outcomes/endpoints

See Table 3 above.

Recruitment

Study initiation date: 15 January 2021 (first participant first visit)

Primary completion date: 09 February 2022 (date of first interim data cut-off)

Study completion date: 28 October 2023 (last participant last visit)

Sample size

A total of 62 participants were randomized and exposed to the study intervention of either dupilumab or placebo in a 1:1 ratio during the 16-week randomized IMP intervention period (30 in the dupilumab group and 32 in the placebo group).

Based upon the data from R668-AD-1526 and R668-AD-1652, R668-AD-1539 part B data were not available at the time we planned our study) where the response rates for placebo and dupilumab arms were weighted averages from the global trials based on the assumed 12-18 year old and 6-11-year-old age groups representation in EFC16823, it assumes the response rate of the proportion of patients achieving EASI-75 after 16 weeks of treatment of 70% and 24% for dupilumab and placebo, respectively. The assumption considers that dupilumab q2w and q4w dosing regimens from R668-AD-1652 achieved similar effect sizes for EASI-75 and that the Japan local study is expected to enroll approximately 15% adolescent patients (aged ≥12 to <18 years). Fifty-six patients (60 randomized patients with a 7% drop out rate, which is a similar rate as the global pediatric studies) will ensure 90% power to detect the treatment group difference of 46% in EASI-75 by using Fisher exact test with two-sided alpha of 0.05 (Table 4).

Table 4. Number of patients and statistical power

6-11 vs 12-18 enrollment	Dupilumab 200 mg or 300 mg q2w	Placebo	Statistical Power	Number of completed patients	Drop-out rate	Number of randomized patients
85% vs 15%	70%	24%	0.908	56	7%	60

q2w = every 2 weeks.

The randomization will be stratified by three age categories (≥6 months to <6 years old, ≥6 years to <12 years old, and ≥12 years). For the age group of ≥6 years to <12 years old, the randomization will be further stratified by IGA of AD (3 vs 4) at baseline. In total, there will be 4 randomization strata.

Randomisation and blinding (masking)

The following populations for analyses are defined (Table 5):

Table 5. Populations for analyses

Population	Description
Screened	All participants who sign the informed consent form (ICF)
Randomized	The randomized population includes all participants with a treatment kit number allocated and recorded in the Interactive Response Technology (IRT) database, and regardless of whether the treatment kit was used or not. Participants treated without being randomized will not be considered randomized and will not be included in any efficacy population.
Intent-to-treat (ITT)	All randomized participants analyzed according to the treatment group allocated by randomization regardless if treatment kit is used or not.
Safety	All participants randomly assigned to study intervention and who take at least 1 dose of study intervention. Participants will be analyzed according to the intervention they actually received. Randomized participants for whom it is unclear whether they took the study medication will be included in the safety population as randomized. For participants who accidentally receive different treatment from the planned, the actual intervention allocation for as-treated analysis will be the dupilumab group.
Pharmacokinetic (PK)	The PK population includes all participants in the safety population with at least one non-missing result for functional dupilumab concentration in serum after first dose of the study treatment. Participants will be analyzed according to the intervention actually received.
Anti-drug antibody (ADA)	Anti-drug antibody population includes all participants in the safety population who have at least one non-missing result in the ADA assay after first dose of the study treatment. Participants will be analyzed according to the intervention actually received.
Population without trial impact (disruption) due to COVID-19	A Population without trial impact (disruption) due to COVID-19 is defined as any participant in randomized population: - without any critical or major deviation related to COVID-19 - and who didn't permanently discontinue treatment due to COVID-19 - and who didn't permanently discontinue study due to COVID-19.

Participants exposed to study intervention before or without being randomized will not be considered randomized and will not be included in any analysis population. The safety experience of these participants will be reported separately. Randomized participants for whom it is unclear whether they took the study intervention will be considered as exposed and will be included in the safety population as randomized. For any participant randomized more than once, only the data associated with the first randomization will be used in any analysis population. The safety experience associated with any later randomization will be reported separately. For participants who accidentally receive different treatment from the planned, the actual intervention allocation for as-treated analysis will be the dupilumab group. Regarding the COVID-19 pandemic, additional summaries by COVID-19 subgroups will be provided to assess the impact of the COVID-19 on treatment effect. Participants impacted by the COVID-19 pandemic are defined as randomized participants with any critical or major deviation related to COVID-19 or who permanently discontinued study intervention or study due to COVID-19.

No information on blinding procedure is included in the dossier.

Statistical Methods

Responder endpoints will be analyzed using the CMH test adjusted by randomization strata defined as "≥6 months to <6 years, ≥6 years to <12 years old and IGA=3, ≥6 years to <12 years old and IGA=4, and ≥12 years at baseline". Comparisons of the response rates between dupilumab and placebo will be derived from these analyses. For participants discontinuing the study treatment before Week 16, their off-study treatment values measured up to Week 16 (if no prohibited medications and/or rescue medications taken prior to the measurement) will be included in the analysis.

Participants taking the prohibited medications and/or rescue medications prior to Week 16 will be considered non-responders for Week 16 analyses. Additionally,

• If a participant discontinues from the study due to AE, lack of efficacy, withdrawal by subject or withdrawal by parent/guardian, this participant will be counted as a nonresponder for the time points after withdrawal.

• If the participant has the missing value at Week 16 due to any other reasons including COVID-19, the data will be imputed using multiple imputation (MI) based on all observed values as described below:

• The underlying continuous (e.g., EASI) or categorical variable (e.g., IGA) will be imputed 40 times to generate 40 complete data sets by using the SAS procedure MI using the following steps.

- Step 1: The monotone missing pattern is induced by Markov Chain Monte Carlo (MCMC) method in MI procedure using seed number 12345. The monotone missing pattern means that if a participant has missing value for a variable at a visit, then the values at all subsequent visits for the same variable are all missing for the participant.

- Step 2: The missing data at subsequent visits will be imputed using the regression method for the monotone pattern with seed number 54321 and adjustment for covariates including treatment groups, randomization strata (≥6 months to <6 years, ≥6 years to <12 years old and IGA=3, ≥6 years to <12 years old and IGA=4, and ≥12 years), and relevant baseline variables. For the categorical variable, such as IGA, a logistic regression under monotone option will be used.

Based on each imputed data, the response status (responder or non-responder) will be determined

for each subject. Once imputations are made, the Week 16 data (binary response) of each of the 40 complete datasets will be analyzed using CMH test. The SAS MIANALYZE procedure will be used to

generate valid statistical inferences by combining results from the 40 analyses using Rubin's formula. An appropriate transformation (such as Wilson-Hilferty transformation) of CMH test statistics can be used in Rubin's formula.

Sensitivity analysis

For the primary estimand for the primary endpoint, no sensitivity analysis will be performed.

However, two supplementary analyses will be performed as described in the section below.

Supplementary analyses

The following supplementary analyses will be performed:

<u>As-observed analysis</u> (including all data regardless of rescue medication or procedure use)

All observed data regardless of rescue medication or procedure use or data is collected after study withdrawal, will be included for the primary endpoint. Participants with missing values will be counted as non-responders.

<u>Last observation carried forward (LOCF) approach</u>

The post-baseline LOCF approach after censoring for rescue medication, procedural use, or study withdrawal to determine participant's status at Week 16 will be conducted to assess the robustness of the primary efficacy analysis with regards to handling of missing data. For participants with only baseline value, the baseline value will be carried forward to Week 16.

Results

Participant disposition

Of 75 participants screened for study eligibility, 13 participants were screen failures. The most frequent reason for screening failure was not meeting inclusion criterion (EASI ≥16 at screening and baseline visits [I05], 5 [6.7%] of all screened participants). A total of 62 participants were randomized and exposed to the study intervention of either dupilumab or placebo in a 1:1 ratio during the 16-week randomized IMP intervention period (30 in the dupilumab group and 32 in the placebo group). Overall, 60 (96.8%) participants completed the randomized IMP intervention period as planned (28 in the dupilumab group and 32 in the placebo group) and rolled over to the OLE period to receive continued or new treatment with dupilumab. Overall, 57 (91.9%) participants completed the study (27 [90.0%] in the dupilumab/dupilumab group, and 30 [93.8%] in the placebo/dupilumab group). One of the 27 participants in the dupilumab/dupilumab group had permanent study intervention discontination due to a pretreatment AE during the randomized IMP intervention period but continued the study until Week 16 (the end of the planned randomization IMP intervention period), and was considered to have completed the study (Table 6).

Table 6. Participant disposition

n (%)	Placebo (N=32)	Dupilumab (N=30)	ALL (N=62)
Exposed and not randomized	0	0	0
Randomized and not exposed	0	0	0
Randomized and exposed	32 (100)	30 (100)	62 (100)
Completed the randomized treatment period	32 (100)	28 (93.3)	60 (96.8)
Did not complete the randomized treatment period	0	2 (6.7)	2 (3.2)
Rolled over to the OLE period	32 (100)	28 (93.3)	60 (96.8)
Withdrew during the OLE period	2 (6.3)	2 (6.7)	4 (6.5)
Reason for permanent study intervention withdrawal during the randomized treatment period			
Adverse event	0	1 (3.3)	1 (1.6)
Related to COVID-19	0	0	0
Not related to COVID-19	0	1 (3.3)	1 (1.6)
Progressive disease	0	0	0
Lack of efficacy	0	0	0
Poor compliance to protocol	0	0	0
Withdrawal by subject	0	1 (3.3)	1 (1.6)
Withdrawal by parent/guardian	0	0	0
Other[a]	0	0	0
Related to COVID-19	0	0	0
Not related to COVID-19	0	0	0
Reason for study intervention withdrawal by subject during the randomized treatment period			
Adverse event	0	0	0
Related to COVID-19	0	0	0
Not related to COVID-19	0	0	0
Study procedure	0	1 (3.3)	1 (1.6)
Inconvenience of device use	0	0	0
Other[a]	0	0	0
Related to COVID-19	0	0	0

n (%)	Placebo (N=32)	Dupilumab (N=30)	ALL (N=62)
Not related to COVID-19	0	0	0
Reason for permanent study intervention withdrawal during the OLE period			
Adverse event	0	0	0
Related to COVID-19	0	0	0
Not related to COVID-19	0	0	0
Progressive disease	0	0	0
Lack of efficacy	0	0	0
Poor compliance to protocol	0	0	0
Withdrawal by subject	1 (3.1)	1 (3.3)	2 (3.2)
Withdrawal by parent/guardian	0	0	0
Other[a]	1 (3.1)	1 (3.3)	2 (3.2)
Related to COVID-19	0	0	0
Not related to COVID-19	1 (3.1)	1 (3.3)	2 (3.2)
Reason for study intervention withdrawal by subject during the OLE period			
Adverse event	0	0	0
Related to COVID-19	0	0	0
Not related to COVID-19	0	0	0
Study procedure	0	1 (3.3)	1 (1.6)
Inconvenience of device use	0	0	0
Other[a]	1 (3.1)	0	1 (1.6)
Related to COVID-19	0	0	0
Not related to COVID-19	1 (3.1)	0	1 (1.6)
Completed the study period	30 (93.8)	27 (90.0)	57 (91.9)
Did not complete the study period	2 (6.3)	3 (10.0)	5 (8.1)
Ongoing during the study period	0	0	0
Reason for study discontinuation			
Adverse event	0	0	0
Poor compliance to protocol	0	0	0
Withdrawal by subject	1 (3.1)	2 (6.7)	3 (4.8)
Site terminated by sponsor	0	0	0
Study terminated by sponsor	0	0	0
Withdrawal by parent/guardian	0	0	0
Other[a]	1 (3.1)	1 (3.3)	2 (3.2)
Related to COVID-19	0	0	0
Not related to COVID-19	1 (3.1)	1 (3.3)	2 (3.2)
Status at last contact	32 (100)	30 (100)	62 (100)
Alive	32 (100)	30 (100)	62 (100)
Dead	0	0	0

EOT: End of treatment

[a] Verbatim term for these discontinuations are provided in the listing of participants with permanent study intervention discontinuation

Note: Permanent study intervention discontinuation is defined as the discontinuation of IMP during the each treatment period (ie, randomized treatment period and OLE period).

Baseline data

Baseline demographic and disease characteristics are presented in Table 7 and Table 8.

Table 7. Demographics and participant characteristics at baseline

	Placebo (N=32)	Dupilumab (N=30)	ALL (N=62)
Age (years)			
Number	32	30	62
Mean (SD)	9.6 (4.2)	10.0 (4.1)	9.8 (4.1)
Median	10.0	10.0	10.0
Q1 ; Q3	6.5 ; 11.5	8.0 ; 14.0	7.0 ; 14.0
Min ; Max	2 ; 17	1 ; 17	1 ; 17
Age group [n(%)]			
Number	32	30	62
≥6 months-<2 years	0	1 (3.3)	1 (1.6)
≥2 years-<6 years	6 (18.8)	3 (10.0)	9 (14.5)
≥6 years-<12 years	18 (56.3)	17 (56.7)	35 (56.5)
≥12 years-<18 years	8 (25.0)	9 (30.0)	17 (27.4)
Sex [n(%)]			
Number	32	30	62
Male	21 (65.6)	18 (60.0)	39 (62.9)
Female	11 (34.4)	12 (40.0)	23 (37.1)
Race [n(%)]			
Number	32	30	62
Asian	32 (100)	30 (100)	62 (100)
Japanese	32 (100)	30 (100)	62 (100)
Baseline Weight (kg)			
Number	32	30	62
Mean (SD)	35.6 (17.8)	36.8 (17.2)	36.2 (17.4)
Median	32.8	35.0	34.7
Q1 ; Q3	21.6 ; 49.0	21.9 ; 51.6	21.6 ; 50.9
Min ; Max	10 ; 77	13 ; 66	10 ; 77
Baseline Weight group (kg) [n (%)]			
Number	32	30	62
≥5-<15 kg	2 (6.3)	3 (10.0)	5 (8.1)
≥15-<30 kg	12 (37.5)	10 (33.3)	22 (35.5)
≥30-<60 kg	15 (46.9)	14 (46.7)	29 (46.8)
≥60 kg	3 (9.4)	3 (10.0)	6 (9.7)
Baseline BMI (kg/m^2)			
Number	32	30	62
Mean (SD)	18.2 (3.6)	18.3 (3.4)	18.3 (3.5)
Median	16.7	17.4	17.0
Q1 ; Q3	16.0 ; 19.6	15.8 ; 20.7	15.9 ; 20.5
Min ; Max	14 ; 29	13 ; 27	13 ; 29
Baseline BMI group (kg/m^2) [n (%)]			
Number	32	30	62
<20	25 (78.1)	20 (66.7)	45 (72.6)
≥20	7 (21.9)	10 (33.3)	17 (27.4)

BMI: Body mass index

Note: Age (years) for participants less than 2 years old was derived as integer part of (Age in months) / 12

PGM=PRODOPS/SAR231893/EFC16823/CSR_04/REPORT/PGM/dem_demo_r_t_i.sas OUT=REPORT/OUTPUT/dem_demo_r_t_i.rtf (05DEC2023 10:45)

Table 8. Disease characteristics at baseline

	Placebo (N=32)	Dupilumab (N=30)	ALL (N=62)
Age at onset of atopic dermatitis[a] (years)			
Number	32	30	62
Mean (SD)	2.9 (3.2)	2.1 (2.4)	2.5 (2.9)
Median	2.0	1.0	1.0
Q1 ; Q3	0.0 ; 5.5	0.0 ; 4.0	0.0 ; 4.0
Min ; Max	0 ; 12	0 ; 9	0 ; 12
Age group at onset of atopic dermatitis (years) [n(%)]			
Number	32	30	62
<5 years	23 (71.9)	25 (83.3)	48 (77.4)
≥5 years	9 (28.1)	5 (16.7)	14 (22.6)
Time since first diagnosis of atopic dermatitis[b] (years)			
Number	32	30	62
Mean (SD)	6.7 (5.0)	8.2 (4.6)	7.4 (4.8)
Median	4.5	8.0	6.5
Q1 ; Q3	3.0 ; 10.0	5.0 ; 13.0	3.0 ; 11.0
Min ; Max	1 ; 17	1 ; 16	1 ; 17
Time since first diagnosis of atopic dermatitis (years) [n(%)]			
Number	32	30	62
<5 years	16 (50.0)	7 (23.3)	23 (37.1)
≥5 years	16 (50.0)	23 (76.7)	39 (62.9)
Baseline EASI score			
Number	32	30	62
Mean (SD)	26.5 (7.5)	23.9 (5.7)	25.2 (6.8)

	Placebo (N=32)	Dupilumab (N=30)	ALL (N=62)
Median	25.5	23.7	24.6
Q1 ; Q3	20.4 ; 31.1	19.1 ; 27.2	19.8 ; 29.2
Min ; Max	17 ; 47	16 ; 41	16 ; 47
Baseline EASI score group [n(%)]			
Number	32	30	62
<20	7 (21.9)	10 (33.3)	17 (27.4)
20 to <25	8 (25.0)	9 (30.0)	17 (27.4)
≥25	17 (53.1)	11 (36.7)	28 (45.2)
Baseline IGA score [n(%)]			
Number	32	30	62
3	24 (75.0)	22 (73.3)	46 (74.2)
4	8 (25.0)	8 (26.7)	16 (25.8)
Baseline weekly average of daily worst scratch/itch NRS (aged ≥6 months to <6 years old)			
Number	6	4	10
Mean (SD)	7.567 (1.464)	8.607 (1.307)	7.983 (1.431)
Median	8.131	8.548	8.131
Q1 ; Q3	6.286 ; 8.571	7.500 ; 9.714	7.333 ; 9.000
Min ; Max	5.29 ; 9.00	7.33 ; 10.00	5.29 ; 10.00
Baseline weekly average of daily worst itch NRS (aged ≥6 years to <12 years old)			
Number	18	17	35
Mean (SD)	7.369 (1.553)	7.571 (1.205)	7.467 (1.378)
Median	7.429	7.571	7.571
Q1 ; Q3	6.500 ; 8.571	7.143 ; 8.000	6.500 ; 8.571
Min ; Max	4.43 ; 9.43	5.43 ; 10.00	4.43 ; 10.00
Baseline weekly average of daily worst pruritus using peak pruritus NRS (aged ≥12 years to <18 years old)			
Number	8	9	17
Mean (SD)	7.134 (1.522)	6.511 (1.067)	6.804 (1.298)
Median	7.429	6.500	7.000
Q1 ; Q3	6.214 ; 8.369	5.500 ; 7.200	5.714 ; 7.857
Min ; Max	4.33 ; 8.71	5.29 ; 8.17	4.33 ; 8.71
BSA affected by atopic dermatitis (%)			
Number	32	30	62
Mean (SD)	54.492 (15.583)	44.858 (16.636)	49.831 (16.689)
Median	52.375	40.750	46.750
Q1 ; Q3	43.250 ; 60.625	33.500 ; 56.000	37.000 ; 59.000
Min ; Max	28.50 ; 87.75	17.25 ; 77.00	17.25 ; 87.75
BSA group affected by atopic dermatitis (%) [n(%)]			
Number	32	30	62

	Placebo (N=32)	Dupilumab (N=30)	ALL (N=62)
10 to <30	2 (6.3)	5 (16.7)	7 (11.3)
30 to <50	13 (40.6)	15 (50.0)	28 (45.2)
≥50	17 (53.1)	10 (33.3)	27 (43.5)
Participant Oriented Eczema Measure (POEM)			
Number	32	30	62
Mean (SD)	15.3 (7.2)	17.5 (7.1)	16.3 (7.2)
Median	14.0	18.0	16.0
Q1 ; Q3	12.0 ; 20.0	13.0 ; 23.0	12.0 ; 22.0
Min ; Max	0 ; 28	3 ; 28	0 ; 28
Children's Dermatology Life Quality Index (CDLQI) Total Score			
Number	26	26	52
Mean (SD)	5.8 (3.1)	6.7 (4.1)	6.3 (3.6)
Median	5.5	6.5	6.0
Q1 ; Q3	4.0 ; 7.0	3.0 ; 9.0	3.5 ; 8.5
Min ; Max	1 ; 13	1 ; 14	1 ; 14
Infants' Dermatology Quality of Life Index (IDQOL) Total Score			
Number	2	2	4
Mean (SD)	13.5 (9.2)	21.0 (0.0)	17.3 (6.8)
Median	13.5	21.0	20.5
Q1 ; Q3	7.0 ; 20.0	21.0 ; 21.0	13.5 ; 21.0
Min ; Max	7 ; 20	21 ; 21	7 ; 21
Baseline eosinophil count (Giga/L)			
Number	32	30	62
Mean (SD)	0.5 (0.3)	0.6 (0.3)	0.5 (0.3)
Median	0.5	0.6	0.5
Q1 ; Q3	0.3 ; 0.7	0.3 ; 0.7	0.3 ; 0.7
Min ; Max	0 ; 1	0 ; 1	0 ; 1
Baseline eosinophil count (Giga/L) category [n(%)]			
Number	32	30	62
<0.15	1 (3.1)	3 (10.0)	4 (6.5)
0.15 to <0.3	7 (21.9)	4 (13.3)	11 (17.7)
≥0.3	24 (75.0)	23 (76.7)	47 (75.8)
Baseline serum total IgE (IU/mL)			
Number	31	30	61
Mean (SD)	6519.6 (9753.5)	4532.2 (5350.3)	5542.2 (7899.7)
Median	2878.0	2059.0	2328.0
Q1 ; Q3	1047.0 ; 6311.0	720.0 ; 8631.0	959.0 ; 6311.0
Min ; Max	38 ; 39846	26 ; 20944	26 ; 39846
Baseline serum TARC (pg/mL)			

	Placebo (N=32)	Dupilumab (N=30)	ALL (N=62)
Number	31	30	61
Mean (SD)	1695.2 (1545.1)	1847.4 (3116.7)	1770.0 (2427.9)
Median	1140.0	752.0	992.0
Q1 ; Q3	816.0 ; 1890.0	445.0 ; 1640.0	530.0 ; 1640.0
Min ; Max	333 ; 6440	180 ; 15400	180 ; 15400

[a] derived as integer of (Year of first diagnosis of Atopic dermatitis - Year of birth) + (Month of first diagnosis of Atopic dermatitis - Month of birth)/12

[b] derived as (Year of randomization - Year of first diagnosis of Atopic dermatitis) + (Month of randomization - Month of first diagnosis of Atopic dermatitis)/12

EASI: Eczema Area and Severity Index, IGA: Investigator's Global Assessment, IgE: immunoglobulin E, NRS: numerical rating scale, TARC: thymus and activation-regulated chemokine

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Number analysed

The number of participants included in each analysis population (as defined in the SAP) is provided in Table 9. No participant was excluded from the efficacy population (ITT population) or safety population (both randomized treatment period and dupilumab exposure period). The PK population and the ADA population included 62 participants (30 out of 30 in the dupilumab group and 32 out of 32 in the placebo group). Overall, the population without trial impact (disruption) due to COVID-19 consisted of 61 (98.4%) participants.

Table 9. Analysis populations

n (%)	Placebo	Dupilumab	ALL
Randomized population	32 (100)	30 (100)	62 (100)
Efficacy population			
Intent-to-treat (ITT)	32 (100)	30 (100)	62 (100)
Anti-drug antibody (ADA) population	32 (100)	30 (100)	62 (100)
Pharmacokinetic (PK) population	32 (100)	30 (100)	62 (100)
Population without trial impact (disruption) due to COVID-19	31 (96.9)	30 (100)	61 (98.4)
Safety population			
Randomized treatment period[a]	32	30	62
Dupilumab exposure period[b]	32	30	62

Note: For the safety, PK and ADA populations, participants are tabulated according to study intervention actually received (as treated)

For the other populations, participants are tabulated according to the study intervention allocated by randomization

[a] All participants randomly assigned to study intervention and who take at least 1 dose of study intervention.

[b] All participants randomly assigned to study intervention and who take at least 1 dose of Dupilumab.

PGM=PRODOPS/SAR231893/EFC16823/CSR_04/REPORT/PGM/dis_ana_pop_a_t_i.sas OUT=REPORT/OUTPUT/dis_ana_pop_a_t_i.rtf (19DEC2023 2:15)

Pharmacology results

The PK, PD, and immunogenicity analyses results in Study EFC16823 are consistent with the known PK, PD, and immunogenicity of dupilumab.

Pharmacokinetics

In the dupilumab/dupilumab group, following administration of dupilumab 300 mg q2w after an initial loading dose of 600 mg (in participants with body weight ≥60 kg), 200 mg q2w after an initial loading dose of 400 mg (in participants with body weight ≥30 to <60 kg), 300 mg q4w (in participants with body weight ≥15 to <30 kg), or 200 mg q4w (in participants with body weight ≥5 to <15 kg), the trough concentration of functional dupilumab in serum increased over time, reached steady-state between Week 16 and Week 24 and maintained steady throughout Week 116.

Pharmacodynamics

Consistent with the mechanism of action of dupilumab, a continuous and marked decrease in total IgE concentrations was observed in the dupilumab group throughout the 16-week randomized IMP intervention period, while no notable effects were observed in participants receiving placebo. Further decrease in total IgE concentration in the dupilumab/dupilumab group was observed over time until the end of the study (up to Week 116). A marked decrease of total IgE in serum was also observed after switching IMP at Week 16 from placebo to dupilumab in the placebo/dupilumab group. Additionally, a marked decrease in TARC/CCL17 (a type 2 chemokine whose receptor CCR4 is predominantly expressed on Th2 lymphocytes and basophils) in serum was observed in the dupilumab group as compared with placebo at Week 4 (the first measurement after the start of IMP administration) and thereafter the concentration was sustained at low levels in the dupilumab group up to Week 16 (the last measurement time point specified in the protocol).

Immunogenicity

During the randomized IMP intervention period, treatment-emergent positive ADA responses were observed in 2 (6.7%) participants in the dupilumab group and 2 (6.3%) participants in the placebo group. Among the participants with treatment-emergent positive ADA responses, all had low titer indeterminate response (for the dupilumab group) or low titer transient response (for the placebo group). Positive neutralizing antibody responses were observed in 1 (3.3%) participant in the dupilumab group as compared with 0 in the placebo group. From Week 16 to Week 116, 1 (3.1%) treatment-emergent positive ADA response was observed in the placebo/dupilumab group, while no treatment-emergent positive ADA responses were observed in the dupilumab/dupilumab group.

Overall, the number of participants with treatment-emergent ADA response was small and no meaningful conclusions on the potential impact of ADA could be drawn.

Efficacy results

The primary endpoint was the proportion of participants with EASI-75 (≥75% improvement from

baseline) at Week 16 in the ITT population. The proportion of participants achieving EASI75 at Week 16 was higher in the dupilumab group than in the placebo group (43.3% [13/30] versus 18.8% [6/32]). The difference was statistically significant (response rate difference versus placebo: 25.1% [95% confidence interval (CI): 3.26, 46.90]; p=0.0304), see Table 10. Superiority of dupilumab over placebo was therefore demonstrated for the primary endpoint, proportion of participants with EASI-75 at Week 16, in Japanese participants with AD aged 6 months to <18 years whose disease was not adequately controlled with existing therapies.

Table 10. Primary endpoint analysis: Proportion of participants with EASI-75 at Week 16 by treatment group – ITT population

	Placebo (N=32)	Dupilumab (N=30)
Proportion of patients with EASI-75 at Week 16		
Responders	6 (18.8)	13 (43.3)
Non-responders	26 (81.3)	17 (56.7)
Imputed non-responder	8 (25.0)	4 (13.3)
OR, 95% CI vs. placebo[a]		3.6 (1.12, 11.89)
P-value vs. placebo[b]		0.0304
RRD (%), 95% CI vs. placebo[a]		25.1 (3.26, 46.90)

EASI: Eczema Area and Severity Index, EASI-75: ≥75% improvement from baseline EASI

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

[b] CMH test was performed on the association between the responder status and intervention group, adjusted by randomization strata (≥6 months to <6 years, ≥6 years to <12 years old and IGA=3, ≥6 years to <12 years old and IGA=4, and ≥12 years at baseline).

For participants discontinuing the study treatment before Week 16, their off-study treatment values measured up to Week 16 are included

Participants taking the prohibited medications and/or rescue medications prior to Week 16 or who discontinued from the study due to adverse event, withdrawal by subject or withdrawal by parent/guardian prior to Week 16 are considered non-responders

Note: Participants with missing value due to other reasons including COVID-19 at Week 16 were imputed by multiple imputation (MI), and the response status is then derived. All non-missing data were used for MI.

Current data cutoff: 09FEB2022

PGM=PRODOPS/SAR231893/EFC16823/CSR_01/REPORT/PGM/eff_resp_i_t_i.sas
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For comparison, the results of EASI-75 at Week 16, including adolescent participants in study R668-AD-1526 and pediatric patients aged ≥6 to <12 years with ≥30 kg in q2w and <30 kg in q4w in study R668-AD-1652, are shown below in Table 11.

Table 11. Results of EASI-75 from R668-AD-1526 and R668-AD-1652

Study	Dupilumab	Placebo	LS Mean Difference (95% CI)
	Dupilumab 200 mg or 300 mg q2w		
R668-AD-1526 study Age≥12 & Age<18	34/82 (41.5%)	7/85 (8.2%)	33.2 (21.07, 45.39)
	Dupilumab 200 mg q2w		
R668-AD-1652 study Age≥6 & Age<12 (Body weight: ≥30 kg)	44/59 (74.6%)	16/62 (25.8%)	48.8 (33.21, 64.33)
	Dupilumab 300 q4w		
R668-AD-1652 study Age≥6 & Age<12 (Body weight:<30 kg)	46/61 (75.4%)	17/61 (27.9%)	47.5 (21.94, 63.14)

The following 3 key secondary endpoints were evaluated as supportive analyses to the primary analysis:

• Percent change in EASI (%EASI) score change from baseline to Week 16

• Percent change from baseline to Week 16 in weekly average of daily worst itch NRS for participants aged ≥6 years to <12 years old

• Proportion of participants with an IGA score of 0 or 1 at Week 16 (5-point scale)

Dupilumab treatment resulted in a reduction from baseline to Week 16 compared with placebo in %EASI (least squares [LS] mean difference in percent change from baseline versus placebo: -39.38% [95% CI: -60.57, -18.19]; p=0.0003) (Table 12) and in weekly average of daily worst itch NRS for participants aged ≥6 years to <12 years old (LS mean difference in percent change from baseline versus placebo: -33.28% [95% CI: -59.15, -7.42]; p=0.0117) (Table 13). There were no between-group differences in the proportion of participants with an IGA score of 0 or 1 at Week 16, as the study did not have enough statistical power to demonstrate the difference between groups in this endpoint (Table 14).

In conclusion, dupilumab treatment provided substantial clinical benefit to Japanese participants aged 6 months to <18 years with moderate-to-severe AD on different domains of disease such as intensity and extent of objective AD signs (as measured by EASI, and percent BSA affected by AD), intensity of subjective symptoms (as measured by pruritus NRS and POEM), and quality of life (measured by CDLQI) during the randomized IMP intervention period and OLE period.

Table 12. Key secondary endpoint analysis: Percent change in EASI (%EASI) score change from baseline to Week 16 by treatment group – ITT population)

	Placebo (N=32)	Dupilumab (N=30)
Baseline		
Number	32	30
Mean (SD)	26.50 (7.47)	23.85 (5.74)
Median	25.45	23.70
Q1 ; Q3	20.40 ; 31.10	19.10 ; 27.20
Min ; Max	17.0 ; 46.5	16.3 ; 40.9
Week 16		
Number	32	29
Mean (SD)	19.84 (14.38)	8.87 (7.04)
Median	19.15	7.80
Q1 ; Q3	9.05 ; 31.95	3.60 ; 11.90
Min ; Max	0.4 ; 53.8	1.8 ; 28.2
Percent change from baseline		
Number (observed/imputed)	32 (24/8)	29 (26/3)
Mean (SD)	-24.78 (47.90)	-62.40 (29.87)
Median	-22.29	-72.18
Q1 ; Q3	-66.56 ; 17.55	-84.84 ; -57.50

Min ; Max	-98.5 ; 58.5	-93.6 ; 0.0
LS Mean (SE) [a]	-23.27 (7.81)	-62.65 (7.87)
LS Mean Diff vs. placebo (95% CI) [a]		-39.38 (-60.57, -18.19)
P-value vs. placebo [a]		0.0003

%EASI: percent change in Eczema Area and Severity Index, LS: least squares; WOCF: worst observation carried forward; MI: multiple imputation.

[a] Each of the imputed complete data were analyzed by fitting an analysis of covariance model with treatment group (placebo vs pooled dupilumab), randomization strata defined as (≥6 months to <6 years old, ≥6 years to <12 years old and IGA=3, ≥6 years to <12 years old and IGA=4, and ≥12 years old), and baseline EASI score as covariates.

Note: Data collected after study intervention discontinuation were included. Data post the select prohibited medications/procedures and/or rescue medications that impacted efficacy were set to missing and imputed by WOCF. Missing data after study intervention discontinuation for lack of efficacy were imputed by WOCF, and other missing data were imputed by MI.

Descriptive statistics at Week 16 include participants after WOCF at Week 16, and participants whose values were imputed by MI at Week 16 were excluded from the descriptive analysis.

Current data cutoff: 09FEB2022

PGM=PRODOPS/SAR231893/EFC16823/CSR_01/REPORT/PGM/eff_ancova_i_t_i.sas
OUT=REPORT/OUTPUT/eff_ancova_easi_p_wk16_i_t_i.rtf (28MAR2022 13:14)

Table 13. Key secondary endpoint analysis: Percent change from baseline to Week 16 in weekly average of daily worst itch NRS for participants aged ≥6 years to ≤12 years old by treatment group – ITT population

	Placebo (N=18)	Dupilumab (N=17)
Baseline		
Number	18	17
Mean (SD)	7.37 (1.55)	7.57 (1.20)
Median	7.43	7.57
Q1 ; Q3	6.50 ; 8.57	7.14 ; 8.00
Min ; Max	4.4 ; 9.4	5.4 ; 10.0
Week 16		
Number	18	14
Mean (SD)	6.22 (2.62)	3.55 (2.19)
Median	6.79	2.95
Q1 ; Q3	4.00 ; 8.33	2.14 ; 3.70
Min ; Max	0.6 ; 9.2	1.2 ; 9.3
Percent change from baseline		
Number (observed/imputed)	18 (14/4)	14 (13/1)
Mean (SD)	-12.78 (42.87)	-52.75 (26.95)
Median	-13.26	-61.73
Q1 ; Q3	-26.32 ; 6.90	-66.67 ; -48.72
Min ; Max	-90.2 ; 103.2	-85.4 ; 12.2
LS Mean (SE) [a]	-6.16 (9.65)	-39.45 (10.14)
LS Mean Diff vs. placebo (95% CI) [a]		-33.28 (-59.15, -7.42)
P-value vs. placebo [a]		0.0117

NRS: numerical rating scale, LS: least squares; WOCF: worst observation carried forward; MI: multiple imputation.

[a] Each of the imputed complete data were analyzed by fitting an analysis of covariance model with treatment group (placebo vs pooled dupilumab), randomization strata defined as (IGA=3 vs 4), and baseline NRS score as covariates.

Note: Data collected after study intervention discontinuation were included. Data post the select prohibited medications/procedures and/or rescue medications that impacted efficacy were set to missing and imputed by WOCF. Missing data after study intervention discontinuation for lack of efficacy were imputed by WOCF, and other missing data were imputed by MI.

Descriptive statistics at Week 16 include participants after WOCF at Week 16, and participants whose values were imputed by MI at Week 16 were excluded from the descriptive analysis.

Current data cutoff: 09FEB2022

PGM=PRODOPS/SAR231893/EFC16823/CSR_01/REPORT/PGM/eff_ancova_i_t_i.sas
OUT=REPORT/OUTPUT/eff_ancova_inrs_p_wk16_i_t_i.rtf (28MAR2022 13:15)

Table 14. Key secondary endpoint analysis: Proportion of participants with IGA 0 or 1 at Week 16 by treatment group – ITT population

	Placebo (N=32)	Dupilumab (N=30)
Proportion of patients with IGA 0 or 1 at Week 16		
Responders	3 (9.4)	3 (10.0)
Non-responders	29 (90.6)	27 (90.0)
Imputed non-responder	8 (25.0)	4 (13.3)
OR, 95% CI vs. placebo[a]		1.2 (0.23, 6.10)
P-value vs. placebo[b]		0.8476
RRD (%), 95% CI vs. placebo[a]		1.5 (-13.73, 16.66)

IGA: Investigator's Global Assessment

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

[b] CMH test was performed on the association between the responder status and intervention group, adjusted by randomization strata (≥6 months to <6 years, ≥6 years to <12 years old and IGA=3, ≥6 years to <12 years old and IGA=4, and ≥12 years at baseline).

For participants discontinuing the study treatment before Week 16, their off-study treatment values measured up to Week 16 are included

Participants taking the prohibited medications and/or rescue medications prior to Week 16 or who discontinued from the study due to adverse event, withdrawal by subject or withdrawal by parent/guardian prior to Week 16 are considered non-responders

Note: Participants with missing value due to other reasons including COVID-19 at Week 16 were imputed by multiple imputation (MI), and the response status is then derived. All non-missing data were used for MI.

Current data cutoff: 09FEB2022

PGM=PRODOPS/SAR231893/EFC16823/CSR_01/REPORT/PGM/eff_resp_i_t_i.sas
OUT=REPORT/OUTPUT/eff_resp_iga_wk16_i_t_i.rtf (28MAR2022 13:14)

Safety results

Extent of exposure

The mean (SD) duration of IMP exposure during the randomized IMP intervention period in the safety population was similar between intervention groups (107.4 [21.3] days in the dupilumab group and 112.1 [5.0] days in the placebo group). Most (≥86.7%) participants were exposed for ≥16 weeks of treatment with IMP in both intervention groups.

The mean (SD) duration of dupilumab exposure during the dupilumab exposure period (including both the randomized IMP treatment period and the OLE period) in the safety population was 777.9 (181.9) days overall (794.6 [252.0] days in the dupilumab/dupilumab group and 762.3 [72.2] days in the placebo/dupilumab group), with a maximum duration of 954 days. Overall, 47 (75.8%) participants were exposed for ≥104 weeks of treatment with dupilumab (27 [90.0%] in the dupilumab/dupilumab group and 20 [62.5%] in the placebo/dupilumab group) and 33 (53.2%) participants were exposed for ≥116 weeks (20 [66.7%] in the dupilumab/dupilumab group and 13 [40.6%] in the placebo/dupilumab group).

ADVERSE EVENTS

An overview of the AE profile during the randomized IMP intervention period is provided in Table 15.

Table 15. Overview of adverse event profile

n (%)	Placebo (N=32)	Dupilumab (N=30)
Participants with any TEAE	19 (59.4)	19 (63.3)
Participants with any severe TEAE	0	0
Participants with any serious AE (regardless of treatment-emergent status)[a]	1 (3.1)	1 (3.3)
Participants with any treatment emergent SAE	1 (3.1)	1 (3.3)
Participants with any AE leading to death (regardless of treatment-emergent status)[a]	0	0
Participants with any TEAE leading to death	0	0
Participants with any TEAE leading to permanent study intervention discontinuation	0	0
Participants with any TEAE related to IMP	3 (9.4)	5 (16.7)
Participants with any treatment emergent AESI	0	0
Participants with any treatment emergent other selected AE grouping event	3 (9.4)	8 (26.7)

TEAE: Treatment emergent adverse event, SAE: Serious adverse event, AESI: Adverse event of special interest, IMP: Investigational medicinal product

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

[a] All adverse events occurred before Dupilumab administration of the open-label extension period were included.

PGM=PRODOPS/SAR231893/EFC16823/CSR_04/REPORT/PGM/ae_overview_s_t_i.sas
OUT=REPORT/OUTPUT/ae_overview_wk16_s_t_i.rtf (05DEC2023 10:47)

TEAEs during the randomized IMP intervention period

The proportion of participants with TEAEs was similar between the dupilumab and placebo groups (63.3% [19/30] and 59.4% [19/32], respectively) (Table 15 above). During the randomized IMP intervention period, the most frequently reported TEAEs (in ≥5% of participants in either intervention group) by PT were:

- conjunctivitis allergic (4 [13.3%] in the dupilumab group and 0 [0%] in the placebo group);
- nasopharyngitis (3 [10.0%] and 7 [21.9%], respectively);
- pyrexia (3 [10.0%] and 0 [0%], respectively);
- oral herpes (2 [6.7%] and 0 [0%], respectively);
- syncope (2 [6.7%] and 0 [0%], respectively);
- constipation (2 [6.7%] and 0 [0%], respectively);
- dental caries (1 [3.3%] and 2 [6.3%], respectively);
- dermatitis atopic (0 [0%] and 2 [6.3%], respectively); and
- arthropod bite (0 [0%] and 2 [6.3%], respectively).

Out of the 62 randomized participants, 1 participant in the placebo group experienced a TEAE related to COVID-19 during the randomized treatment period. This event was mild in intensity but reported as serious due to hospitalization and did not lead to permanent study intervention discontinuation.

TEAEs during the dupilumab exposure period

The number (%) of participants with TEAEs during the dupilumab exposure period was 58 (93.5%) in the overall population (N=62). During the dupilumab exposure period, the most frequently reported TEAEs by PT (≥5% of participants) in the overall population were:

- nasopharyngitis (31 [50.0%]);

• COVID-19 (29 [46.8%]);

• pyrexia (18 [29.0%]);

• conjunctivitis allergic (14 [22.6%]);

• dental caries, acne (7 [11.3%] each);

• gastroenteritis (6 [9.7%]);

• influenza, urticaria (5 [8.1%] each); and

• hordeolum, headache, dermatitis contact, foot fracture, hand fracture, and ligament sprain (4 [6.5%] each).

TEAEs considered related to IMP

In the randomized IMP intervention period, the proportion of participants with TEAEs considered related to IMP (per Investigator) was higher in the dupilumab group compared with the placebo group (5 [16.7%] and 3 [9.4%], respectively). The most frequently reported TEAE considered related to IMP by PT with an incidence of ≥5% in either intervention group was conjunctivitis allergic (2 [6.7%] in the dupilumab group and none in the placebo group). In the dupilumab exposure period (when the IMP was dupilumab), the number (%) of participants with TEAEs considered related to IMP (dupilumab) was 17 (27.4%) participants in the overall population. The most frequently reported TEAE considered related to IMP by PT with an incidence of ≥5% overall was conjunctivitis allergic (7 [11.3%] overall; 4 [13.3%] in the dupilumab/dupilumab group and 3 [9.4%] in the placebo/dupilumab group). The TEAE of neutropenia considered related to IMP was reported in 2 (3.2%) participants during the dupilumab exposure period, both of whom were aged ≥6 years to <12 years old at baseline. These TEAEs were mild in intensity, did not required corrective treatment/therapy and resolved without permanent discontinuation of IMP.

TEAEs by intensity

During the randomized IMP intervention period, a total of 18 (60.0%) participants in the dupilumab group and 19 (59.4%) participants in the placebo group reported TEAEs of mild intensity. A total of 2 (6.7%) participants in the dupilumab group and 2 (6.3%) participants in the placebo group reported TEAEs of moderate intensity. No participants in either the dupilumab group or the placebo group reported a TEAE of severe intensity.

During the dupilumab exposure period, a total of 55 (88.7%) and 18 (29.0%) participants in the overall population reported TEAEs of mild and moderate intensity, respectively. Two (3.2%) participants reported TEAEs of severe intensity during the dupilumab exposure period. All TEAEs of severe intensity were considered not related to IMP and resolved during the study; the corrective treatment/therapy was required for the events of viral infection, febrile convulsion, and seizure, and not required for 2 episodes of attention deficit hyperactivity disorder.

Serious adverse events

During the randomized IMP intervention period, treatment-emergent SAEs were reported in 1 (3.3%) participant in the dupilumab group and 1 (3.1%) participant in the placebo group. None of these events were considered related to IMP by the Investigator. During the dupilumab exposure period, overall, 4 (6.5%) participants reported treatment-emergent SAEs. In the dupilumab/dupilumab group, 1 (3.3%) participant reported an event of terminal ileitis (during the IMP intervention period), 1 (3.3%) participant reported 2 events of febrile convulsion and seizure (during the OLE period), and 1 (3.3%) participant reported an event of skin laceration (during the OLE period); in the placebo/dupilumab group, 1 (3.1%) participant reported 2 episodes of attention deficit hyperactivity

disorder (during the OLE period). None of these events were considered related to IMP by the Investigator. During the randomized IMP intervention period and during the dupilumab exposure period, no participants died during this study.

Discontinuation and adverse events of special interest

In both the randomized IMP intervention period and the dupilumab exposure period, no participants permanently discontinued the study intervention due to a TEAE. One participant in the dupilumab group permanently discontinued the study intervention due to a pretreatment AE during the randomized IMP intervention period. No participants had any treatment-emergent AESI in the randomized IMP intervention period. The proportion of participants with any treatment-emergent other selected AE grouping event was higher in the dupilumab group compared with the placebo group (26.7% [8/30] and 9.4% [3/32], respectively), and this difference was primarily driven by TEAEs of conjunctivitis. During the dupilumab exposure period, there was 1 participant (1.6%) with at least 1 treatment-emergent AESI in the overall population (1 [3.3%] in the dupilumab/dupilumab group). This AESI was a non-serious event of anaphylactoid reaction.

2.3.3. Discussion on clinical aspects

The MAH submitted the results of the clinical study EFC16823 that was part of the Japan paediatric clinical development programme, however, it was not part of the completed European Paediatric Investigation Plan (PIP) for dupilumab for the treatment of atopic dermatitis. These results are assessed in terms of their possible impact on the benefit-risk balance and the product information, respectively.

Study EFC16823 was a randomized, double-blind, placebo-controlled, Phase 3 study to assess the efficacy, safety, and PK of dupilumab with concomitant TCS use in Japanese participants aged 6 months to <18 years with moderate-to-severe AD whose disease was not adequately controlled with existing therapies. The primary objective was to evaluate the efficacy of dupilumab administered concomitantly with TCS as measured by the proportion of participants with EASI-75 at Week 16. Key secondary endpoints were the percent change in EASI score from baseline to Week 16, percent change from baseline to Week 16 in weekly average of daily worst itch NRS for participants aged ≥6 years to <12 years old, and the proportion of participants with an IGA score of 0 or 1 at Week 16. All objectives and endpoints are established for clinical studies in AD and with Dupixent. The study intervention period was 16 weeks with a subsequent open-label period with active treatment for all study participants lasting three years or until approval. The dosing regimens were in line with the authorised weight-based dose regimens included in the product information. All patients received topical corticosteroids with an initial standardisation period, and the TCS regimen could be adapted during the study according to the individual needs of the participants. In the OLE period, topical calcineurin inhibitors were allowed in addition to TCS.

The different analysis populations included all enrolled participants. Overall 62 participants with a diagnosis of AD according to the American Academy of Dermatology consensus criteria were enrolled. Most patients were between 6 and 12 years of age with a body weight between 30 and 60 kg, no participants were included in the youngest age group (≥6 months-<2 years). Two thirds were male and all were of Japanese origin. The vast majority completed the intervention period as well as the study.

Reasons for early and permanent study intervention discontinuation in the dupilumab group were an adverse event and a withdrawal by subject. No participant in the placebo group withdrew permanently from study intervention. Disease characteristics at baseline indicate that the study population had moderate-to-severe disease activity with a mean time since first diagnosis of AD of 7.4 years. Baseline

serum total IgE was significantly increased in all participants suggesting an extrinsic phenotype which is the predominant AD phenotype in all children with AD, especially in male patients.

The clinical pharmacology results (PK, PD, and immunogenicity analyses) are in line with the known PK, PD, and immunogenicity of the dupilumab clinical programme. A significant decrease total IgE and in TARC/CCL17 concentrations as compared with placebo at Week 4 was observed during the 16-week intervention period. Immunogenicity appears to be low, however, overall participant numbers were rather limited for the verification of an ADA response to treatment. As to efficacy results, superiority of dupilumab over placebo was demonstrated for the primary endpoint, and the results were comparable to those observed in studies R668-AD-1526 and R668-AD-1652. Superiority of dupilumab over placebo was also demonstrated for two out of three key secondary endpoints, i.e. percent change in EASI (%EASI) score change from baseline to Week 16 and percent change from baseline to Week 16 in weekly average of daily worst itch NRS for participants aged ≥6 years to <12 years old. No differences between the dupilumab and the placebo group were observed regarding the proportion of participants achieving an IGA score of 0 or 1 at Week 16. This result appears unusual as treatment effects as measured by IGA scale were apparent around week 2 in AD studies with dupilumab, e.g. in study R668-AD-1652. The MAH justifies this result by an insufficient statistical power to demonstrate the difference between groups in this endpoint.

The IMP exposure was balanced between both treatment groups and the majority of participants was exposed for ≥16 weeks of treatment with IMP in both intervention groups. Most participants were exposed for ≥104 weeks of treatment. Participants with any treatment-emergent adverse event (TEAE) were numerically balanced between both treatment groups. During IMP intervention period most frequently reported TEAEs by preferred term were allergic conjunctivitis, nasopharyngitis, and pyrexia. No severe TEAEs or TEAEs leading to death were observed. One serious adverse events (SAE) occurred in each intervention group that were considered unrelated to study treatment. During the whole dupilumab exposure period including the open-label extension phase, four participants experienced unrelated SAEs, i.e. three in the dupilumab/dupilumab group (terminal ileitis, febrile convulsion and seizure and skin laceration) and one in the placebo group (attention deficit hyperactivity disorder).

Treatment-related TEAEs were rare; most frequently reported in the dupilumab group during the intervention and exposure periods was allergic conjunctivitis, a known adverse drug reaction that occurred predominantly in atopic dermatitis studies.

In conclusion, dupilumab was well tolerated and no safety concerns were identified. The treatment effect as measured by IGA scale was unconvincing, however, the results regarding the primary and other key secondary endpoints were acceptable suggesting a meaningful clinical treatment benefit in the Japanese study participants. It is concurred that the obtained results do not impact the information included in the product information.

3. Rapporteur's overall conclusion and recommendation

☒ Fulfilled:

No regulatory action required.