Medicines & Healthcare products Regulatory Agency

MHRA

Early Access to Medicines Scheme – Treatment protocol – Information for healthcare professionals

Introduction

The aim of the Early Access to Medicines Scheme (EAMS) is to provide earlier availability of promising new unlicensed and 'off label' medicines to UK patients that have a high unmet clinical need. The medicinal products included in the scheme are those that are intended to treat, diagnose or prevent seriously debilitating or life threatening conditions where there are no adequate treatment options. More information about the scheme can be found here: http://www.mhra.gov.uk/Howweregulate/Innovation/EarlyaccesstomedicinesschemeEAMS/index.htm

This information is intended for healthcare professionals and is provided by the pharmaceutical company that manufactures the medicine. This medicine does not yet have a licence (marketing authorisation) and the information is provided to assist the doctor in prescribing an unlicensed medicine. Guidance on prescribing unlicensed medicines can be found on the GMC webpage: https://www.gmc-uk.org/guidance/ethical_guidance/14327.asp

The scientific opinion is based on the information supplied to the MHRA on the benefits and risks of a promising new medicine. As such this is a scientific opinion and should not be regarded as a medicine licensed by the MHRA or a future commitment by the MHRA to license such a medicine.

The prescribing doctor should also refer to the summary information on the pharmacovigilance system which is provided in the document 'Early Access to Medicines Scheme – Treatment protocol – Information on the pharmacovigilance system'.

Scientific opinion period: The MHRA will withdraw the EAMS positive scientific opinion when a marketing authorisation (drug licence) is issued for the product covering the EAMS indication, or if following scientific assessment, the EAMS criteria are considered to be no longer met.

Contact information regarding queries on using this EAMS medicine can be found at the end of this document

Information for the healthcare professionals:

1. NAME OF THE MEDICINAL PRODUCT

Dupixent 300 mg solution for injection in pre-filled syringe
Dupixent 200 mg solution for injection in pre-filled syringe

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each single-use pre-filled syringe contains 300 mg of dupilumab in 2 ml (150 mg/ml).

Each single-use pre-filled syringe contains 200 mg of dupilumab in 1.14 ml solution (175 mg/ml).

Dupilumab is a fully human monoclonal antibody produced by recombinant DNA technology in Chinese Hamster Ovary (CHO) cells.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection (injection)

Clear to slightly opalescent, colourless to pale yellow solution, which is free from visible particulates.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

For the purpose of EAMS, Dupixent is being made available to adolescent patients ≥12 to <18 years of age with severe atopic dermatitis who have responded inadequately to at least one systemic therapy or where the available systemic therapies are not recommended or are not tolerated.

4.2 Posology and method of administration

Posology

Under the EAMS program, treatment must be prescribed by physicians experienced in the treatment of dermatological conditions.

The recommended dose of Dupixent for adolescent patients ≥12 to <18 years of age is specified in Table 1.

Table 1: Dose of Dupixent for subcutaneous administration in adolescent patients ≥12 to <18 years of age with atopic dermatitis

Body Weight of Patient	Initial Dose*	Subsequent Doses (every other week)
less than 60 kg	400 mg (two 200 mg injections)	200 mg
60 kg or more	600 mg (two 300 mg injections)	300 mg

* Initial dose to be administered by health care professional

Dupixent can be used with or without topical corticosteroids. Topical calcineurin inhibitors may be used, but should be reserved for delicate areas only, such as the face, neck, intertriginous and genital areas.

If a dose is missed, administer the dose as soon as possible. Thereafter, resume dosing at the regular scheduled time.

Consideration should be given to discontinuing treatment in patients who have shown no response after 16 weeks of treatment. Some patients with initial partial response may subsequently improve with continued treatment beyond 16 weeks.

Special populations

Renal impairment
No dosage adjustment is needed in patients with mild or moderate renal impairment. Very limited data are available in patients with severe renal impairment (see section 5.2).

Hepatic impairment
No data are available in patients with hepatic impairment (see section 5.2).

Body weight
For patients ≥12 to <18 years of age with atopic dermatitis, the recommended every other week dose is 200 mg (<60 kg) or 300 mg (≥60 kg).

Paediatric patients
The safety and efficacy of Dupixent in children below the age of 12 years have not been established (see section 5.2).

Method of administration

Subcutaneous use

Dupixent is administered by subcutaneous injection into the thigh or abdomen, except for the 5 cm around the navel. If somebody else administers the injection, the upper arm can also be used.
For the initial 600 mg dose, two 300 mg Dupixent injections should be administered consecutively in different injection sites.

For the initial 400 mg dose, two 200 mg Dupixent injections should be administered consecutively in different injection sites.

It is recommended to rotate the injection site with each injection. Dupixent should not be injected into skin that is tender, damaged or has bruises or scars.

A patient may self-inject Dupixent or the patient's caregiver may administer Dupixent if their healthcare professional determines that this is appropriate. Proper training should be provided to patients and/or caregivers on the preparation and administration of Dupixent prior to use according to the Instructions for Use (IFU) and the Treatment Protocol for Patients.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

Patients should be excluded from EAMS where the patient:

- Has active chronic or acute infection requiring systemic treatment with antibiotics, antivirals, antiparasitics, antiprotozoals, or antifungals within 1 weeks before the baseline visit.
- Has known or suspected immunodeficiency, including history of invasive opportunistic infections (e.g., tuberculosis, histoplasmosis, listeriosis, coccidioidomycosis, pneumocystosis, aspergillosis) despite infection resolution, or otherwise recurrent infections of abnormal frequency or prolonged duration suggesting an immune compromised status, as judged by the treating physician.
- Has used any investigational drugs (other than dupilumab) within 5 half-lives (if known) or 12 weeks before the first anticipated date for Dupixent administration (if half-life is not known or not applicable).

- Is a pregnant or breast-feeding woman.
- Has severe concomitant illness(es), new conditions, or insufficiency understood conditions that, in the treating physician's judgment, might result in unreasonable risk to the patient.

4.4 Special warnings and precautions for use

Topical corticosteroids can be used intermittently, and according to their product information, alongside Dupixent to manage periods of exacerbation.

Traceability

In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded.

Hypersensitivity

If a systemic hypersensitivity reaction (immediate or delayed) occurs, administration of Dupixent should be discontinued immediately and appropriate therapy initiated. Very rare cases of serum sickness/serum sickness-like reactions have been reported in clinical trials following the administration of Dupixent (section 4.8).

Immunosupressives
Concomitant use of Dupixent with other systemic immunosuppressives has not been investigated and should be avoided. A limited period of overlap between systemic immunosuppressives (e.g. during tapering downwards towards discontinuation) and introduction of Dupixent may be appropriate to avoid disease relapse in severe cases.

Live or attenuated vaccines
Dupilumab has not been studied with live or atenuated vaccines. Live or attenuated vaccines are not recommended to be given concurrently with dupilumab. The interval between live or attenuated vaccines and initiation of dupilumab should be in accordance with current vaccination guidelines regarding immunomodulatory medicinal products.

Helminth infection
Patients with known helminth infections were excluded from participation in clinical studies. Dupixent may influence the immune response against helminth infections by inhibiting IL-4/IL-13 signaling. Patients with pre-existing helminth infections should be treated before initiating Dupixent. If patients become infected while receiving treatment with Dupixent and do not respond to anti-helminth treatment, treatment with Dupixent should be discontinued until infection resolves.

Conjunctivitis related events
Patients treated with Dupixent who develop conjunctivitis that does not resolve following standard treatment should undergo ophthalmological examination.

Comorbid asthma
Safety and efficacy of Dupixent have not been established in the treatment of asthma. Patients with comorbid asthma should not adjust or stop their asthma treatments without consultation with their physicians. Patients with comorbid asthma should be monitored carefully following discontinuation of Dupixent.

Eosinophilia

An increase in eosinophils in blood was observed during treatment of some patients, however this was generally transient and not associated with clinically relevant adverse events. Eosinophil counts declined to near baseline levels by the end of the clinical studies.

Excipients
This medicinal product contains less than 1 mmol sodium (23 mg) per 300 mg or 200 mg dose, i.e. is essentially "sodium-free".

4.5 Interaction with other medicinal products and other forms of interaction

Dupilumab has not been studied with live or attenuated vaccines. Live or attenuated vaccines should not be given concurrently with dupilumab. Inactivated (killed) vaccines may be given concurrently with dupilumab.

Immune responses to vaccination were assessed in a study in which patients with atopic dermatitis were treated once weekly for 16 weeks with 300 mg of dupilumab. After 12 weeks of dupilumab administration, patients were vaccinated with a Tdap vaccine (T cell-dependent), and a meningococcal polysaccharide vaccine (T cell-independent) and immune responses were assessed 4 weeks later. Antibody responses to both tetanus vaccine and meningococcal polysaccharide vaccine were similar in dupilumab-treated and placebo-treated patients. No adverse interactions between either of the non-live vaccines and dupilumab were noted in the study.
In a clinical study of AD patients, the effects of dupilumab on the PK of CYP substrates were evaluated. The data gathered from this study did not indicate clinically relevant effects of dupilumab on CYP1A2, CYP3A, CYP2C19, CYP2D6, or CYP2C9 activity.

4.6 Fertility, pregnancy and lactation

For the purposes of the EAMS, Dupixent should not be used by pregnant or breastfeeding women. If a woman becomes pregnant while receiving treatment during EAMS, then treatment should be stopped.

Women of childbearing potential should be advised to use an effective method of contraception while receiving dupilumab via the EAMS.

Pregnancy
There are limited amount of data from the use of Dupixent in pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity (see section 5.3).

Breast-feeding

It is unknown whether Dupixent is excreted in human milk or absorbed systemically after ingestion. A decision must be made whether to discontinue breast-feeding or to discontinue Dupixent therapy taking into account the benefit of breast feeding for the child and the benefit of therapy for the woman.
Fertility

Animal studies showed no impairment of fertility (see section 5.3).

4.7 Effects on ability to drive and use machines

Dupixent has no or negligible influence on the ability to drive or operate machinery.

4.8 Undesirable effects

Summary of the safety profile

Adults with atopic dermatitis
In the overall exposure pool, a total of 2526 patients with atopic dermatitis were treated with dupilumab in controlled and uncontrolled clinical trials. Of these, 739 patients were exposed for at least 1 year.
The safety of dupilumab monotherapy was evaluated through week 16 based on data from three randomized, double-blind, placebo-controlled multicenter studies (SOLO 1, SOLO 2, and a phase 2, dose-ranging study) that included 1564 adult patients with moderate-to-severe atopic dermatitis (AD). The study population had a mean age of 38.2 years, 41.1 % was female, 67.9 % white, 21.9 % Asian, 7.1 % black, and reported co-morbid atopic conditions such as asthma (39.6 %), allergic rhinitis (49.0 %), food allergy (37.3 %), and allergic conjunctivitis (23.1 %).

The safety of dupilumab with concomitant topical corticosteroids (TCS) was evaluated based on data from one randomized, double-blind, placebo-controlled multicenter study (CHRONOS). A total of 740 patients were treated up to 52 weeks. The study population had a mean age of 37.1 years, 39.7 % was female, 66.2 % white, 27.2 % Asian, 4.6 % black, and reported co-morbid atopic conditions such as asthma (39.3 %), allergic rhinitis (42.8 %), food allergy (33.4 %), and allergic conjunctivitis (23.2%).
The most common adverse reactions were injection site reactions, conjunctivitis, blepharitis, and oral herpes.

In the monotherapy studies, the proportion of patients who discontinued treatment due to adverse events was 1.9 % of the placebo group, 1.9 % of the dupilumab 300 mg Q2W group, 1.5 % of the dupilumab 300 mg QW group. One patient on dupilumab discontinued treatment due to an adverse reaction: conjunctivitis allergic.

In the concomitant TCS study, the proportion of patients who discontinued treatment due to adverse events was 7.6 % of the placebo + TCS group, 1.8 % of the dupilumab 300 mg Q2W + TCS group, and 2.9 % of the dupilumab 300 mg QW + TCS group. Three patients on dupilumab discontinued treatment due to an adverse reaction: injection site reaction (2 patients) and eye pruritus (1 patient).

Tabulated list of adverse reactions

Listed in Table 2 are adverse reactions observed in clinical trials presented by system organ class and frequency, using the following categories: very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1,000 to < 1/100); rare (≥ 1/10,000 to < 1/1,000); very rare (< 1/10,000). Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Table 2 List of adverse reactions in clinical studies

System Organ Class	Frequency	Adverse Reaction
Infections and infestations	Common	Conjunctivitis Oral herpes
Blood and lymphatic system disorders	Common	Eosinophilia
Immune system disorders	Very rare	Serum sickness/serum sickness-like reactions
Nervous system disorders	Common	Headache
Eye disorders	Common	Conjunctivitis allergic Eye pruritus Blepharitis

General disorders and administration site conditions	Very common	Injection site reactions

Adolescents with atopic dermatitis
The safety of Dupixent was assessed in a study of 250 patients ≥12 to <18 years of age with moderate-to-severe atopic dermatitis (R668-AD-1526, NCT03054428). The total number of patients exposed to Dupixent was 165. The safety profile of Dupixent in these patients followed through Week 16 was similar to the safety profile from studies in adults with atopic dermatitis.

The long-term safety of Dupixent was assessed in an open-label extension study in patients ≥12 to <18 years of age with moderate-to-severe atopic dermatitis (R668-AD-1434, NCT02612454). The safety profile of Dupixent in patients followed through Week 52 was similar to the safety profile observed at Week 16 in AD-1526 study. The long-term safety profile of Dupixent observed in adolescents was consistent with that seen in adults with atopic dermatitis.

Description of selected adverse reactions

Adults with atopic dermatitis

Hypersensitivity
Very rare cases of serum sickness/serum sickness-like reactions have been reported following administration of Dupixent (see section 4.4).

Eczema herpeticum
Eczema herpeticum was reported in <1 % of the Dupixent groups and in <1 % of the placebo group in the 16-week monotherapy studies. In the 52-week Dupixent + TCS study, eczema herpeticum was reported in 0.2 % of the Dupixent + TCS group and 1.9 % of the placebo + TCS group.

Eosinophilia
Transient eosinophilia was reported in <2 % of patients treated with Dupixent.

Infections
In the 16-week monotherapy clinical studies, serious infections were reported in 1.0 % of patients treated with placebo and 0.5 % of patients treated with Dupixent. In the 52-week CHRONOS study, serious infections were reported in 0.6 % of patients treated with placebo and 0.2 % of patients treated with Dupixent.

Herpes zoster
Herpes zoster was reported in <0.1 % of the Dupixent groups and in <1 % of the placebo group in the 16-week monotherapy studies. In the 52-week Dupixent + TCS study, herpes zoster was reported in 1 % of the Dupixent + TCS group and 2 % of the placebo + TCS group.

Immunogenicity
As with all therapeutic proteins, there is a potential for immunogenicity with Dupixent.

ADA responses were not generally associated with impact on Dupixent exposure, safety, or efficacy.
In the 52-week study, approximately 3 % of patients in the placebo group and 2 % of patients in the Dupixent group had anti-drug antibody (ADA) responses lasting more than 12 weeks. Among these patients, 0.7 % on placebo and 0.2 % treated with Dupixent also had neutralizing antibody responses, which were not generally associated with loss of efficacy.

In the overall exposure pool, less than 0.1 % of patients exhibited high titer ADA responses associated with reduced exposure and efficacy. In addition, there was one patient with serum sickness and one with serum sickness-like reaction (<0.1 %) associated with high ADA titers (see section 4.4).

Adolescents with atopic dermatitis
The safety profile observed in the paediatric population in atopic dermatitis clinical trials was similar to that seen in adults. Any additional specific findings are presented below

Conjunctivitis
In the pivotal phase 3 study R668-AD-1526, a higher incidence of conjunctivitis in the 2 dupilumab groups (4.2%) compared to the placebo group (1.2%) was observed; however, none of these events were serious or led to treatment discontinuation.

In the open-label extension study R668-AD-1434, Allergic conjunctivitis occurred in 2.2% of patients, and Conjunctivitis (unspecified etiology) occurred in 1.8% of patients. One patient experienced Conjunctivitis allergic, which was severe in intensity and hence classified as an AESI; this event did not lead to study drug discontinuation.

Hypersensitivity
Adolescents (12-17 years of age) (as of DLP of 21-Apr-2018):
No case of anaphylaxis to dupilumab has been observed. In contrast to the adult program, no case of serum sickness has been observed in the adolescent program, which is possibly related to the smaller number of patients studied in this specific age group.

4.9 Overdose

There is no specific treatment for Dupixent overdose. In the event of overdosage, monitor the patient for any signs or symptoms of adverse reactions and institute appropriate symptomatic treatment immediately.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

ATC code: D11AH05

Mechanism of action

Dupilumab is a recombinant human IgG4 monoclonal antibody that inhibits interleukin-4 and interleukin-13 signaling by specifically binding to the IL-4R alpha sub-unit shared by IL-4 and IL-13 receptor complexes. Dupilumab inhibits IL-4 signaling via the Type I receptor (IL-4Rα/γc), and both IL-4 and IL-13 signaling through the Type II receptor (IL-4Rα/IL-13Rα). IL-4 and IL-13 are key type 2 (including Th2) cytokines involved in atopic dermatitis.

Pharmacodynamic effects

In clinical trials, treatment with dupilumab was associated with decreases from baseline in concentrations of type 2-associated biomarkers, such as thymus and activation-regulated chemokine (TARC/CCL17), total serum IgE and allergen-specific IgE in serum. A reduction of lactate dehydrogenase (LDH), a biomarker associated with AD disease activity and severity, was observed with dupilumab treatment.

Clinical efficacy and safety

Treatment under this EAMS programme is intended for adolescent patients ≥12 to <18 years of age with severe atopic dermatitis who have responded inadequately to at least one systemic therapy or where the available systemic therapies are not recommended or are not tolerated.

The efficacy and safety of Dupixent have been assessed in adult and adolescent clinical studies, which are summarised below.

The data below regarding adult patients are from the SOLO 1, SOLO 2 and CHRONOS trials.

The efficacy and safety of dupilumab as monotherapy and with concomitant topical corticosteroids were evaluated in three pivotal randomised, double-blind, placebo-controlled studies (SOLO 1, SOLO 2, and CHRONOS) in 2119 patients 18 years of age and older with moderate to severe atopic dermatitis (AD) defined by Investigator's Global Assessment (IGA) score ≥3, an Eczema Area and Severity Index (EASI) score ≥16, and a minimum body surface area (BSA) involvement of ≥10 %. Eligible patients enrolled into the three studies had previous inadequate response to topical medication.

In all three studies, patients received 1) an initial dose of 600 mg dupilumab (two 300 mg injections) on day 1, followed by 300 mg once every two weeks (Q2W); 2) an initial dose of 600 mg dupilumab on day 1, followed by 300 mg once weekly (QW); or 3) matching placebo. Dupilumab was administered by subcutaneous (SC) injection in all studies. If needed to control intolerable symptoms, patients were permitted to receive rescue treatment at the discretion of the investigator. Patients who received rescue treatment were considered non-responders.

SOLO 1 enrolled 671 patients (224 to placebo, 224 to dupilumab 300 mg Q2W, and 223 to dupilumab 300 mg QW) and had a treatment period of 16 weeks.

SOLO 2 enrolled 708 patients (236 to placebo, 233 to dupilumab 300 mg Q2W, and 239 to dupilumab 300 mg QW) and had a treatment period of 16 weeks.

CHRONOS enrolled 740 patients (315 to placebo + topical corticosteroid (TCS), 106 to dupilumab 300 mg Q2W + TCS, and 319 to dupilumab 300 mg QW + TCS) and had a treatment period of 52 weeks. Patients received dupilumab or placebo with concomitant use of TCS starting at baseline using a standardized regimen. Patients were also permitted to use topical calcineurin inhibitors (TCI).

Endpoints

In all three pivotal studies, the co-primary endpoints were the proportion of patients with IGA 0 or 1 ("clear" or "almost clear") with a reduction of > 2 points on a 0-4 IGA scale and the proportion of patients with improvement of at least 75 % in EASI (EASI-75) from baseline to week 16. Other evaluated outcomes included the proportion of patients with improvement of at least 50 % and 90 % in EASI (EASI-50 and EASI-90, respectively), reduction in itch as measured by the peak pruritus Numerical Rating Scale (NRS), and percent change in the SCORing Atopic Dermatitis (SCORAD) scale from baseline to week 16. Additional secondary endpoints included mean change from baseline to week 16 in the Patient Oriented Eczema Measure (POEM), Dermatology Life Quality Index (DLQI), and Hospital Anxiety and Depression Scale (HADS) scores. In CHRONOS, efficacy was also evaluated at week 52.

IGA reflects physician's overall assessment (whole body average) of AD skin lesions. EASI is a composite score (ranging from 0-72) based on the extent and severity of the AD lesions assessed systematically for erythema, induration/papulation/oedema, excoriation, and lichenification for each anatomical region. The pruritus NRS is a patient-reported measure which assesses maximum itch intensity in the previous 24-

hours using 0-10-point scale (0 = no itch; 10 = worst itch imaginable.) The SCORAD is used to assess extent and severity of AD signs and includes two visual analogue scales for symptoms (itch and sleep). The POEM evaluates frequency of AD symptoms (including itch) and the impact of AD on sleep (score ranging from 0-28). The DLQI evaluates the health-related quality of life in dermatological patients (score ranging from 0-30). The HADS measures anxiety and depression symptoms (total score ranging from 0-42).

Baseline Characteristics

In the monotherapy studies (SOLO 1 and SOLO 2), across all treatment groups, 51.6 % of patients had a baseline IGA score of 3 (moderate AD), 48.3 % of patients had a baseline IGA of 4 (severe AD) and 32.4 % of patients had received prior systemic immunosuppressants. The baseline mean EASI score was 33.0, the baseline weekly averaged pruritus NRS was 7.4, the baseline mean SCORAD score was 67.8, the baseline mean POEM score was 20.5, the baseline mean DLQI was 15.0, and the baseline mean HADS total score was 13.3.

In the concomitant TCS study (CHRONOS), across all treatment groups, the mean age was 37.1, the mean weight was 74.5 kg, 39.7 % were female, 66.2 % were white, 27.2 % were Asian, and 4.6 % were black. In this study, 53.1 % of patients had a baseline IGA score of 3 and 46.9 % of patients had a baseline IGA of 4 and 33.6 % of patients received prior systemic immunosuppressants. The baseline mean EASI score was 32.5, the baseline weekly pruritus NRS was 7.3, the baseline mean SCORAD score was 66.4, the baseline mean POEM score was 20.1, the baseline mean DLQI was 14.5, and the baseline mean HADS total score was 12.7.

Clinical Response

16-Week Monotherapy Studies (SOLO 1 and SOLO 2)

In SOLO 1 and SOLO 2, from baseline to week 16, a significantly greater proportion of patients randomized to dupilumab achieved an IGA 0 or 1 response, EASI-75, and/or an improvement of ≥4 points on the pruritus NRS compared to placebo (see Table 3).

A significantly greater proportion of patients randomized to dupilumab achieved a rapid improvement in the pruritus NRS compared to placebo (defined as ≥4-point improvement as early as week 2; $p < 0.01$) and the proportion of patients responding on the pruritus NRS continued to increase through the treatment period. The improvement in pruritus NRS occurred in conjunction with the improvement of objective signs of atopic dermatitis.

Figure 1 and Figure 2 show the mean percent change from baseline in EASI and the mean percent change from baseline in NRS, respectively up to week 16.

Table 3: Efficacy Results of Dupilumab Monotherapy at Week 16 (FAS)

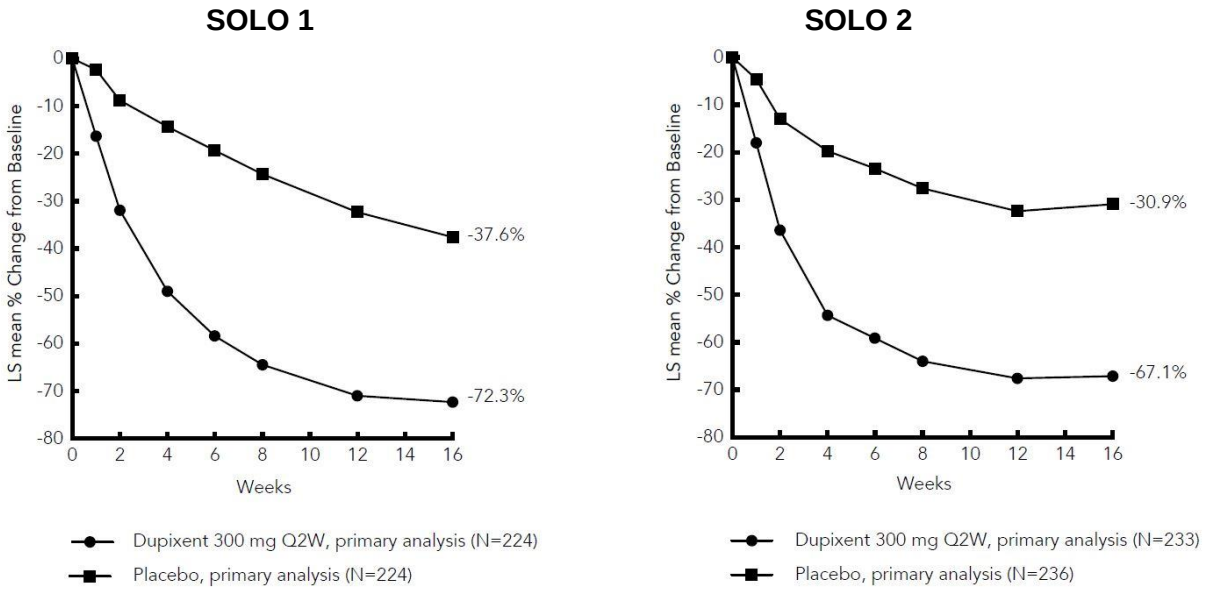
	SOLO 1 (FAS)[a]			SOLO 2 (FAS)[a]		
	Placebo	**Dupilumab 300 mg Q2W**	**Dupilumab 300 mg QW**	**Placebo**	**Dupilumab 300 mg Q2W**	**Dupilumab 300 mg QW**
Patients randomised	224	224	223	236	233	239
IGA 0 or 1[b], % responders[c]	10.3 %	37.9 %[e]	37.2 %[e]	8.5 %	36.1 %[e]	36.4 %[e]
EASI-50, % responders[c]	24.6 %	68.8 %[e]	61.0 %[e]	22.0 %	65.2 %[e]	61.1 %[e]
EASI-75, % responders[c]	14.7 %	51.3 %[e]	52.5 %[e]	11.9 %	44.2 %[e]	48.1 %[e]
EASI-90, % responders[c]	7.6 %	35.7 %[e]	33.2 %[e]	7.2 %	30.0 %[e]	30.5 %[e]
EASI, LS mean % change from baseline (+/- SE)	-37.6 % (3.28)	-72.3 %[e] (2.63)	-72.0 %[e] (2.56)	-30.9 % (2.97)	-67.1 %[e] (2.52)	-69.1 %[e] (2.49)
SCORAD, LS mean % change from baseline (+/- SE)	-29.0 % (3.21)	-57.7 %[e] (2.11)	-57.0 %[e] (2.11)	-19.7 % (2.52)	-51.1 %[e] (2.02)	53.5 %[e] (2.03)
Pruritus NRS, LS mean % change from baseline (+/- SE)	-26.1 % (3.02)	-51.0 %[e] (2.50)	-48.9 %[e] (2.60)	-15.4 % (2.98)	-44.3 %[e] (2.28)	-48.3 %[e] (2.35)
Number of patients with baseline pruritus NRS score ≥ 4	212	213	201	221	225	228
Pruritus NRS (≥4-point improvement), % responders[c, d]	12.3 %	40.8 %[e]	40.3 %[e]	9.5%	36.0 %[e]	39.0 %[e]

LS = least squares; SE= standard error

[a] Full analysis set (FAS) includes all patients randomized.

[b] Responder was defined as a patient with IGA 0 or 1 ("clear" or "almost clear") with a reduction of ≥ 2 points on a 0-4 IGA scale.
[c] Patients who received rescue treatment or with missing data were considered as non-responders.
[d] a significantly greater proportion of patients on dupilumab had improvement in pruritus NRS of ≥ 4 points compared to placebo at week 2 ($p < 0.01$).
[e] p-value <0.0001

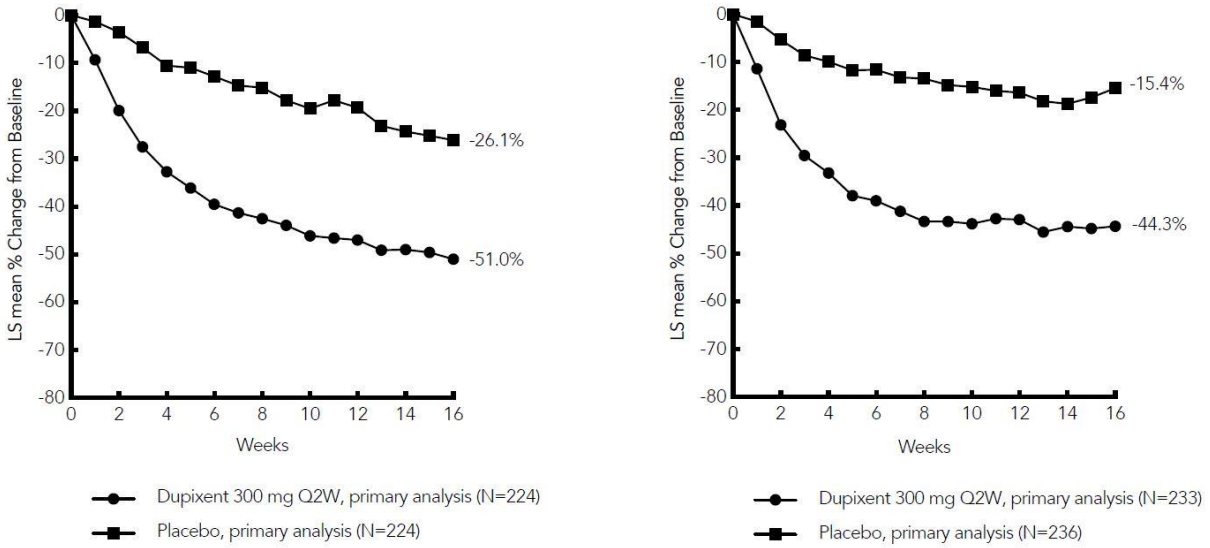
Figure 1: Mean percent change from baseline in EASI in SOLO 1[a] and SOLO 2[a] (FAS)[b]



LS = least squares
[a] In the primary analyses of the efficacy endpoints, patients who received rescue treatment or with missing data were considered non-responders.
[b] Full analysis set (FAS) includes all patients randomized.

Figure 2: Mean percent change from baseline in NRS in SOLO 1[a] and SOLO 2[a] (FAS)[b]

SOLO 1 **SOLO 2**



LS = least squares

[a] In the primary analyses of the efficacy endpoints, patients who received rescue treatment or with missing data were considered non-responders

[b] Full analysis set (FAS) includes all patients randomized.

Treatment effects in subgroups (weight, age, gender, race, and background treatment, including immunosuppressants) in SOLO 1 and SOLO 2 were consistent with the results in the overall study population.

52-Week Concomitant TCS Study (CHRONOS)

In CHRONOS, a significantly greater proportion of patients randomized to Dupixent 300 mg Q2W + TCS achieved an IGA 0 or 1 response, EASI-75, and/or an improvement of ≥4 points on the pruritus NRS from baseline to week 16 and week 52 compared to placebo + TCS (see Table 4).

A significantly greater proportion of patients randomized to Dupixent + TCS achieved a rapid improvement in the pruritus NRS compared to placebo + TCS (defined as ≥4-point improvement as early as week 2; p <0.05) and the proportion of patients responding on the pruritus NRS continued to increase through the treatment period. The improvement in pruritus NRS occurred in conjunction with the improvement of objective signs of atopic dermatitis.

Figure 3 and Figure 4 show the mean percent change from baseline in EASI and the mean percent change from baseline in NRS, respectively, up to Week 52 in CHRONOS.

Table 4: Efficacy results of Dupixent with concomitant TCS[a] at Week 16 and Week 52 in CHRONOS

	Week 16 (FAS)[b]			**Week 52 (FAS Week 52)[b]**		
	Placebo + TCS	**Dupixent 300 mg Q2W + TCS**	**Dupixent 300 mg QW + TCS**	**Placebo + TCS**	**Dupixent 300 mg Q2W + TCS**	**Dupixent 300 mg QW + TCS**
Patients randomized	315	106	319	264	89	270
IGA 0 or 1[c], % responders[d]	12.4 %	38.7 %[f]	39.2 %[f]	12.5 %	36.0 %[f]	40.0 %[f]
EASI-50, % responders[d]	37.5 %	80.2 %[f]	78.1 %[f]	29.9 %	78.7 %[f]	70.0 %[f]

EASI-75, % responders[d]	23.2 %	68.9 %[f]	63.9 %[f]	21.6 %	65.2 %[f]	64.1 %[f]
EASI-90, % responders[d]	11.1 %	39.6 %[f]	43.3 %[f]	15.5 %	50.6 %[f]	50.7 %[f]
EASI, LS mean % change from baseline (+/- SE)	-48.4 % (3.82)	-80.5 %[f] (6.34)	-81.5 %[f] (5.78)	-60.9 % (4.29)	-84.9 %[g] (6.73)	-87.8 %[h] (6.19)
SCORAD, LS mean % change from baseline (+/- SE)	-36.2 % (1.66)	-63.9 %[f] (2.52)	-65.9 %[f] (1.49)	-47.3 % (2.18)	-69.7 %[f] (3.06)	-70.4 %[f] (1.72)
Pruritus NRS, LS mean % change from baseline (+/- SE)	-30.3 % (2.36)	-56.6 %[f] (3.95)	-57.1 %[f] (2.11)	-31.7 % (3.95)	-57.0 %[i] (6.17)	-56.5 %[f] (3.26)
Number of patients with baseline pruritus NRS score ≥4	299	102	295	249	86	249
Pruritus NRS (≥4-point improvement), % responders[d, e]	19.7 %	58.8 %[f]	50.8 %[f]	12.9 %	51.2 %[f]	39.0 %[f]

LS = least squares; SE = standard error

[a] All patients were on background topical corticosteroids therapy and patients were permitted to use topical calcineurin inhibitors.

[b] Full analysis set (FAS) includes all patients randomized. FAS Week 52 includes all patients randomized at least one year before the cut-off date of the primary analysis.

[c] Responder was defined as a patient with IGA 0 or 1 ("clear" or "almost clear") with a reduction of ≥2 points on a 0-4 IGA scale.

[d] Patients who received rescue treatment or with missing data were considered as non-responders.

[e] a significantly greater proportion of patients on Dupixent had improvement in pruritus NRS of ≥4 points compared to placebo at week 2 ($p < 0.05$).

[f] p-value <0.0001

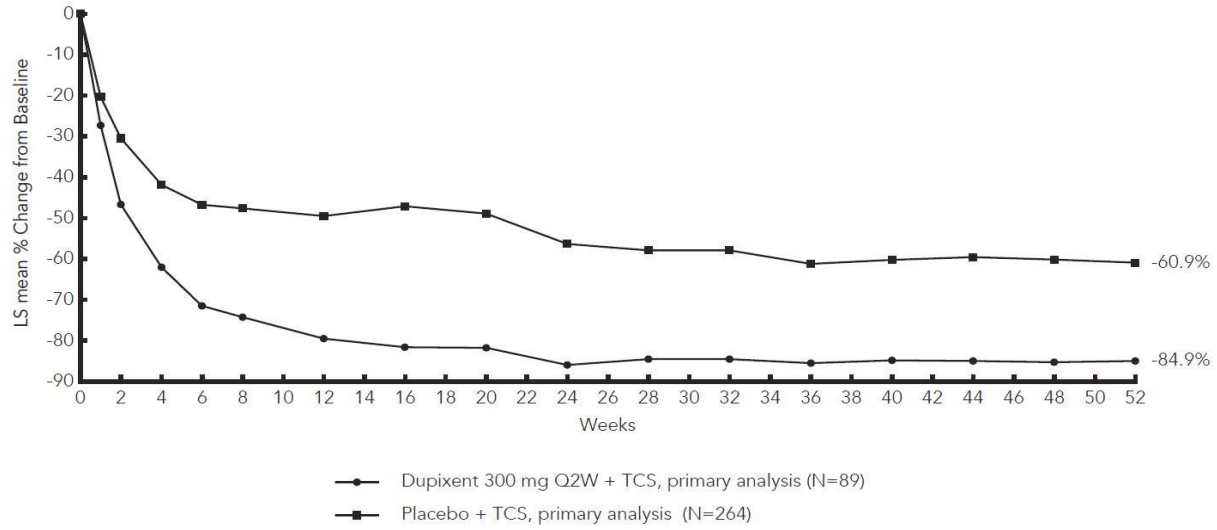
[g] p-value = 0.0015

[h] p-value = 0.0003

[i] p-value = 0.0005

Figure 3: Mean percent change from baseline in EASI in CHRONOS[a] (FAS Week 52)[b]

CHRONOS

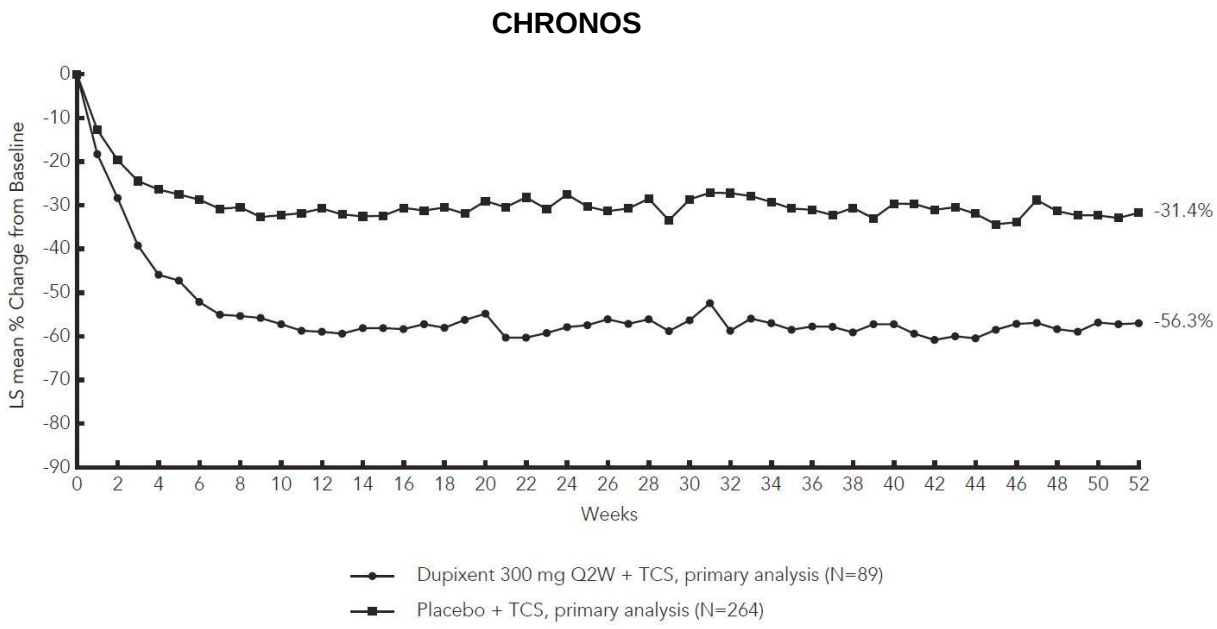


LS = least squares

[a] In the primary analyses of the efficacy endpoints, patients who received rescue treatment or with missing data were considered non-responders.

[b] FAS Week 52 includes all patients randomized at least one year before the cut-off date of the primary analysis.

Figure 4: Mean percent change from baseline in NRS in CHRONOS[a] (FAS Week 52)[b]



LS = least squares

[a]In the primary analyses of the efficacy endpoints, patients who received rescue treatment or with missing data were considered non-responders.

[b]FAS Week 52 includes all patients randomized at least one year before the cut-off date of the primary analysis.

Treatment effects in subgroups (weight, age, gender, race, and background treatment, including immunosuppressants) in CHRONOS were consistent with the results in the overall study population.

Clinical Response in Patients Not Adequately Controlled with, Intolerant to, or for whom Ciclosporin Treatment was Inadvisable (CAFE study)

CAFE study evaluated the efficacy of Dupixent compared to placebo during a 16-week treatment period, administered with concomitant TCS, in adult patients with AD who are not adequately controlled with, or

are intolerant to, oral ciclosporin, or when this treatment is currently contraindicated or not medically advisable.

A total of 325 patients were enrolled, with 210 patients who were previously exposed to ciclosporin and 115 patients who have never been exposed to ciclosporin because ciclosporin treatment was medically inadvisable. The mean age was 38.4 years, 38.8 % were female, the baseline mean EASI score was 33.1, the mean BSA was 55.7, the baseline weekly average pruritus NRS was 6.4, the baseline mean SCORAD score was 67.2, and the baseline mean DLQI was 13.8.

The primary endpoint was the proportion of patients with EASI-75 at week 16.
Primary and secondary endpoints for the 16 week CAFE study are summarized in table 5.

Table 5: Results of the primary and secondary endpoints in CAFE study

	Placebo + TCS	**Dupixent 300 mg Q2W + TCS**	**Dupixent 300 mg QW+TCS**
Patients randomised	108	107	110
EASI-75, % responders	29.6 %	62.6 %	59.1 %
EASI, LS mean % change from baseline (+/- SE)	-46.6 (2.76)	-79.8 (2.59)	-78.2 (2.55)
Pruritus NRS, LS mean % change from baseline (+/- SE)	-25.4 % (3.39)	-53.9 % (3.14)	-51.7 % (3.09)
SCORAD, LS mean % change from baseline (+/- SE)	-29.5 % (2.55)	-62.4 % (2.48)	-58.3 % (2.45)
DLQI, LS mean change from baseline (SE)	-4.5 (0.49)	-9.5 (0.46)	-8.8 (0.45)

In the subgroup of patients resembling the CAFE study population within the 52 week CHRONOS study, 69.6 % of Dupixent 300 mg Q2W-treated patients reached EASI-75 vs 18.0 % placebo-treated patients at week 16, and 52.4 % of Dupixent 300 mg Q2W-treated vs 18.6 % placebo-treated at week 52. In this subset, the percent change of pruritus NRS from baseline was -51.4 % vs -30.2 % at week 16 and -54.8 % vs -30.9 % at week 52, for the Dupixent 300 mg Q2W and placebo groups respectively.

Maintenance and Durability of Response (SOLO CONTINUE study)

To evaluate maintenance and durability of response, subjects treated with Dupixent for 16 weeks in SOLO 1 and SOLO 2 studies who achieved IGA 0 or 1 or EASI-75 were re-randomized in SOLO CONTINUE study to an additional 36-week treatment of Dupixent or placebo, for a cumulative 52-week study treatment. Endpoints were assessed at weeks 51 or 52.

The co-primary endpoints were the difference between baseline (week 0) and week 36 in percent change in EASI from SOLO 1 and SOLO 2 studies baseline and percentage of patients with EASI-75 at week 36 in patients with EASI-75 at baseline.

Patients who continued on the same dose regimen received in the SOLO 1 and SOLO 2 studies (300 mg Q2W or 300 mg QW) showed the optimal effect in maintaining clinical response while efficacy for other dose regimens diminished in a dose-dependent manner.

Primary and secondary endpoints for the 52 week SOLO CONTINUE study are summarized in table 6.

Table 6: Results of the primary and secondary endpoints in SOLO CONTINUE study

	Placebo	**Dupilumab 300 mg**		
	N=83	**Q8W N=84**	**Q4W N=86**	**Q2W/QW N=169**
Co-Primary Endpoints				

LS mean change (SE) between baseline and week 36 in percent change in EASI Score from Parent Study baseline	21.7 (3.13)	6.8*** (2.43)	3.8*** (2.28)	0.1*** (1.74)
Percent of patients with EASI-75 at week 36 for patients with EASI-75 at baseline, n (%)	24/79 (30.4%)	45/82* (54.9%)	49/84** (58.3%)	116/162*** (71.6%)
Key Secondary Endpoints				
Percent of patients whose IGA response at week 36 was maintained within 1 point of baseline in the subset of patients with IGA (0,1) at baseline, n (%)	18/63 (28.6)	32/64† (50.0)	41/66** (62.1)	89/126*** (70.6)
Percent of patients with IGA (0,1) at week 36 in the subset of patients with IGA (0,1) at baseline, n (%)	9/63 (14.3)	21/64† (32.8)	29/66** (43.9)	68/126*** (54.0)
Percent of patients whose peak pruritus NRS increased by ≥3 points from baseline to week 35 in the subset of patients with peak pruritus NRS ≤7 at baseline, n (%)	56/80 (70.0)	45/81 (55.6)	41/83† (49.4)	57/168*** (33.9)

†P<0.05, *P<0.01, **P<0.001, ***P≤0.0001

In SOLO CONTINUE, a trend for increased treatment-emergent ADA positivity with increased dosing intervals was observed. Treatment-emergent ADA: QW: 1.2%; Q2W: 4.3%; Q4W: 6.0%; Q8W: 11.7%. ADA responses lasting more than 12 weeks: QW: 0.0%; Q2W: 1.4%; Q4W: 0.0%; Q8W: 2.6%.

Quality of Life/Patient-Reported Outcomes

In both monotherapy studies (SOLO 1 and SOLO 2), both Dupixent 300 mg Q2W and 300 mg QW groups significantly improved patient-reported symptoms and the impact of AD on sleep and health-related quality of life as measured by POEM and DLQI total scores, respectively, at 16 weeks compared to placebo. A significantly larger proportion of patients administered Dupixent groups had clinically meaningful reductions in POEM and DLQI total score (each defined as ≥4 points improvement) from baseline to week 16 compared to placebo group. In addition, anxiety and depression symptoms as measured by the HADS total score were significantly reduced in the Dupixent groups compared to placebo at 16 weeks. In a subset of patients with HADS-anxiety or HADS-depression subscale scores ≥8 at baseline (the cut-off value for anxiety or depression), a larger proportion of patients in the Dupixent groups achieved HADS-anxiety and HADS-depression scores <8 at week 16 compared to placebo (See Table 7).

Table 7: Additional secondary endpoint results of Dupixent monotherapy at Week 16

	Monotherapy					
	SOLO 1 at Week 16			**SOLO 2 at Week 16**		
	Placebo	**Dupixent 300 mg Q2W**	**Dupixent 300 mg QW**	**Placebo**	**Dupixent 300 mg Q2W**	**Dupixent 300 mg QW**
Patients randomized	224	224	223	236	233	239
DLQI, LS mean change from baseline (SE)	-5.3 (0.50)	-9.3[a] (0.40)	-9.0[a] (0.40)	-3.6 (0.50)	-9.3[a] (0.38)	-9.5[a] (0.39)
POEM, LS mean change from baseline (SE)	-5.1 (0.67)	-11.6[a] (0.49)	-11.0[a] (0.50)	-3.3 (0.55)	-10.2[a] (0.49)	-11.3[a] (0.52)

HADS, LS mean change from baseline (SE)	-3.0 (0.65)	-5.2[b] (0.54)	-5.2[b] (0.51)	-0.8 (0.44)	-5.1[a] (0.39)	-5.8[a] (0.38)
Number of patients with DLQI ≥4 at baseline	213	209	209	225	223	234
DLQI (≥4-point improvement), % responders	30.5 %	64.1 %[a]	58.4 %[a]	27.6 %	73.1 %[a]	62.0 %[a]
Number of patients with POEM ≥4 at baseline	223	222	222	234	233	239
POEM (≥4-point improvement), % responders	26.9 %	67.6 %[a]	63.1 %[a]	24.4 %	71.7 %[a]	64.0 %[a]
Number of patients with HADS-anxiety ≥8 or HADS-depression ≥8 at baseline	97	100	102	115	129	136
Patients achieving HADS-anxiety and HADS-depression score <8, %	12.4 %	41.0 %[a]	36.3 %[b]	6.1 %	39.5 %[a]	41.2 %[a]

LS = least squares; SE = standard error

[a] p-value <0.0001

[b] p-value <0.001

In the concomitant TCS study (CHRONOS), Dupixent 300 mg Q2W + TCS and Dupixent 300 mg QW + TCS improved patient-reported symptoms and the impact of AD on sleep and health-related quality of life as measured by POEM and DLQI total scores, respectively, at 52 weeks compared to placebo + TCS. A larger proportion of patients administered Dupixent 300 mg Q2W + TCS and 300 mg QW + TCS had clinically meaningful reductions in POEM and DLQI total score (each defined as ≥4-point improvement) from baseline to week 52 compared to the placebo + TCS. In addition, Dupixent 300 mg Q2W + TCS and 300 mg QW + TCS reduced anxiety and depression as measured by the HADS total score at 52 weeks compared to placebo + TCS. In a post-hoc analysis in a subset of patients with HADS-anxiety or HADS-depression subscale scores ≥8 at baseline (the cut-off value for anxiety or depression), a larger proportion of patients in the Dupixent 300 mg Q2W + TCS and 300 mg QW + TCS groups achieved HADS-anxiety and HADS-depression scores <8 at week 52 compared to placebo + TCS (See Table 8).

Table 8: Other secondary endpoint results of Dupixent with concomitant TCS at Week 16 and Week 52 in CHRONOS

	Concomitant Use of TCS					
	CHRONOS at Week 16			**CHRONOS at Week 52**		
	Placebo	**Dupixent 300 mg Q2W + TCS**	**Dupixent 300 mg QW + TCS**	**Placebo +TCS**	**Dupixent 300 mg Q2W + TCS**	**Dupixent 300 mg QW + TCS**
Patients randomized	315	106	319	264	89	270
DLQI, LS mean change from baseline (SE)	-5.8 (0.34)	-10.0[a] (0.50)	-10.7[a] (0.31)	-7.2 (0.40)	-11.4[a] (0.57)	-11.1[a] (0.36)
POEM, LS mean change from baseline (SE)	-5.3 (0.41)	-12.7[a] (0.64)	-12.9[a] (0.37)	-7.0 (0.57)	-14.2[a] (0.78)	-13.2[a] (0.45)
HADS, LS mean change from baseline (SE)	-4.0 (0.37)	-4.9 (0.58)	-5.4[c] (0.35)	-3.8 (0.47)	-5.5[c] (0.71)	-5.9[b] (0.42)
Number of patients with DLQI ≥4 at baseline	300	100	311	254	85	264
DLQI (≥4-point improvement), % responders	43.0 %	81.0 %[a]	74.3 %[a]	30.3 %	80.0 %[a]	63.3 %[a]
Number of patients with POEM ≥4 at baseline	312	106	318	261	89	269
POEM (≥4-point improvement), % responders	36.9 %	77.4 %[a]	77.4 %[a]	26.1 %	76.4 %[a]	64.7 %[a]
Number of patients with HADS-anxiety ≥8 or HADS-depression ≥8 at baseline	148	59	154	133	53	138
Patients achieving HADS-anxiety and HADS-depression <8, %	26.4 %	47.5 %[c]	47.4 %[b]	18.0 %	43.4 %[b]	44.9 %[a]

LS = least squares; SE = standard error

[a] p-value <0.0001

[b] p-value <0.001

[c] p-value <0.05

Adolescents with atopic dermatitis

The efficacy and safety of Dupixent monotherapy in adolescent patients was evaluated in a multicentre, randomised, double-blind, placebo-controlled study (AD-1526) in 251 adolescent patients 12 to 17 years of age with moderate-to-severe atopic dermatitis (AD) defined by Investigator's Global Assessment (IGA) score ≥3 in the overall assessment of AD lesions on a severity scale of 0 to 4, an Eczema Area and Severity Index (EASI) score ≥16 on a scale of 0 to 72, and a minimum body surface area (BSA) involvement of ≥10%. Eligible patients enrolled into this study had previous inadequate response to topical medication.

Patients received 1) an initial dose of 400 mg Dupixent (two 200 mg injections) on day 1, followed by 200 mg once every other week (Q2W) for patients with baseline weight of <60 kg or an initial dose of 600 mg Dupixent (two 300 mg injections) on day 1, followed by 300 mg Q2W for patients with baseline weight of ≥ 60 kg; 2) an initial dose of 600 mg Dupixent (two 300 mg injections) on day 1, followed by 300 mg every 4 weeks (Q4W) regardless of baseline body weight; or 3) matching placebo. Dupixent was administered by subcutaneous (SC) injection. If needed to control intolerable symptoms, patients were permitted to receive rescue treatment at the discretion of the investigator. Patients who received rescue treatment were considered non-responders.

In this study, the mean age was 14.5 years, the median weight was 59.4 kg, 41.0 % were female, 62.5% were White, 15.1% were Asian, and 12.0% were Black. At baseline 46.2% of patients had a baseline IGA score of 3 (moderate AD), 53.8% of patients had a baseline IGA of 4 (severe AD), the mean BSA involvement was 56.5%, and 42.4 % of patients had received prior systemic immunosuppressants. Also at baseline the mean Eczema Area and Severity Index (EASI) score was 35.5, the baseline weekly averaged pruritus Numerical Rating Scale (NRS) was 7.6, the baseline mean SCORing Atopic Dermatitis (SCORAD) score was 70.3, the baseline mean Patient Oriented Eczema Measure (POEM) score was 21.0, and the baseline mean Children Dermatology Life Quality Index (CDLQI) was 13.6. Overall, 92.0% of patients had at least one co-morbid allergic condition; 65.6% had allergic rhinitis, 53.6% had asthma, and 60.8% had food allergies.
The co-primary endpoint was the proportion of patients with IGA 0 or 1 ("clear" or "almost clear") least a 2-point improvement and the proportion of patients with EASI-75 (improvement of at least 75% in EASI), from baseline to Week 16. Other evaluated outcomes included the proportion of subjects with EASI-50 or EASI-90 (improvement of at least 50% or 90% in EASI from baseline respectively), reduction in itch as measured by the peak pruritus NRS, and percent change in the SCORAD scale from baseline to Week 16. Additional secondary endpoints included mean change from baseline to week 16 in the POEM and CDLQI scores.

Clinical Response

The efficacy results at Week 16 for adolescent atopic dermatitis study are presented in Table 9.

Table 9: Efficacy results of Dupixent in the adolescent atopic dermatitis study at Week 16 (FAS)

	AD-1526(FAS)[a]	
	Placebo	**Dupixent 200 mg (<60 kg) and 300 mg (≥60 kg) Q2W**
Patients randomized	**85**[a]	**82**[a]
IGA 0 or 1[b], % responders[c]	2.4%	24.4%
EASI-50, % responders[c]	12.9%	61.0%

EASI-75, % responders[c]	8.2%	41.5%
EASI-90, % responders[c]	2.4%	23.2%
EASI, LS mean % change from baseline (+/-SE)	-23.6% (5.49)	-65.9% (3.99)
SCORAD, LS mean % change from baseline (+/-SE)	-17.6% (3.76)	-51.6% (3.23)
Pruritus NRS, LS mean % change from baseline (+/- SE)	-19.0% (4.09)	-47.9% (3.43)
Pruritus NRS (≥4-point improvement), % responders[c]	4.8%	36.6%
BSA LS mean % change from baseline (+/- SE)	-11.7% (2.72)	-30.1% (2.34)
CDLQI, LS mean change from baseline (+/-SE)	-5.1 (0.62)	-8.5 (0.50)
CDLQI, (≥6-point improvement), % responders	19.7%	60.6%
POEM, LS mean change from baseline (+/- SE)	-3.8 (0.96)	-10.1 (0.76)
POEM, (≥6-point improvement), % responders	9.5%	63.4%

[a] Full Analysis Set (FAS) includes all patients randomized.

[b] Responder was defined as a subject with IGA 0 or 1 ("clear" or "almost clear") with a reduction of ≥2 points on a 0-4 IGA scale.

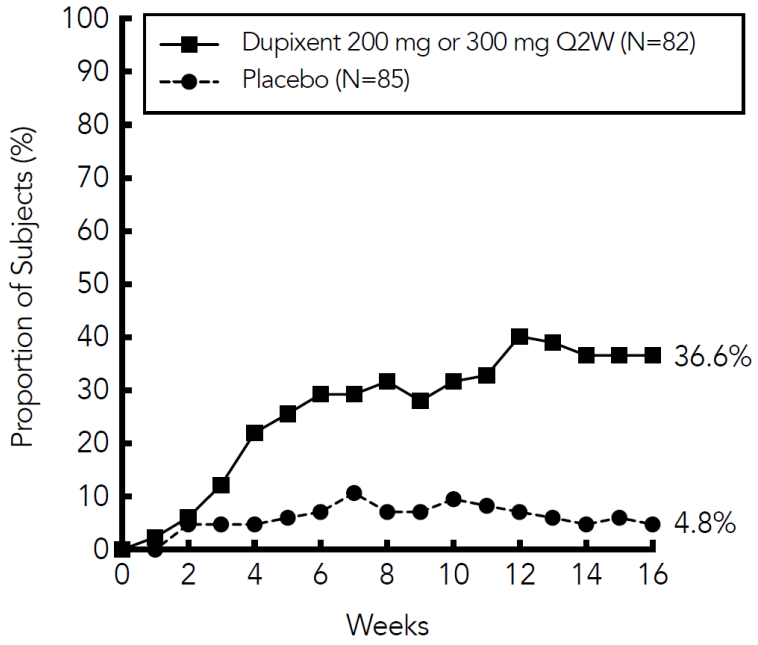
[c] Patients who received rescue treatment or with missing data were considered as non-responders (58.8% and 20.7% in the placebo and Dupixent arms, respectively).

All p –values <0.0001

A larger percentage of patients randomised to placebo needed rescue treatment (topical corticosteroids, systemic corticosteroids, or systemic non-steroidal immunosuppressants) as compared to the Dupixent group (58.8% and 20.7%, respectively).

A significantly greater proportion of patients randomised to Dupixent achieved a rapid improvement in the pruritus NRS compared to placebo (defined as ≥4-point improvement as early as week 4; nominal p<0.001) and the proportion of patients responding on the pruritus NRS continued to increase through the treatment period (see Figure 5). The improvement in pruritus NRS occurred in conjunction with the improvement of objective signs of atopic dermatitis.

Figure 5: Proportion of adolescent patients with ≥4-point improvement on the pruritus NRS in AD-1526 study[a] (FAS)[b]



[a] In the primary analyses of the efficacy endpoints, subjects who received rescue treatment or with missing data were considered non-responders.
[b] Full Analysis Set (FAS) includes all subjects randomised.

The Dupixent group significantly improved patient-reported symptoms, the impact of AD on sleep and health-related quality of life as measured by POEM, SCORAD, and CDLQI scores at 16 weeks compared to placebo.

The long-term efficacy of Dupixent in adolescent patients with moderate-to-severe AD who had participated in previous clinical trials of Dupixent was assessed in open-label extension study (AD-1434). Efficacy data from this study suggests that clinical benefit provided at week 16 was sustained through week 52.

5.2 Pharmacokinetic properties

Absorption
After a single subcutaneous (SC) dose of 75-600 mg dupilumab, median times to maximum concentration in serum (t_{max}) were 3-7 days. The absolute bioavailability of dupilumab following a SC dose is estimated to be 64 %, as determined by a population pharmacokinetics (PK) analysis.

Steady-state concentrations were achieved by Week 16 following the administration of 600 mg starting dose and 300 mg dose every other week. Across clinical trials, the mean ±SD steady-state trough concentrations ranged from 73.3±40.0 mcg/mL to 79.9±41.4 mcg/mL for 300 mg dose administered every other week.

Distribution
A volume of distribution for dupilumab of approximately 4.6 L was estimated by population PK analysis, indicating that dupilumab is distributed primarily in the vascular system.

Biotransformation
Specific metabolism studies were not conducted because dupilumab is a protein. Dupilumab is expected to degrade to small peptides and individual amino acids.

Elimination

Dupilumab elimination is mediated by parallel linear and nonlinear pathways. At higher concentrations, dupilumab elimination is primarily through a non-saturable proteolytic pathway, while at lower concentrations, the non-linear saturable IL-4R α target-mediated elimination predominates.
After the last steady state dose, the median time for dupilumab concentrations to decrease below the lower limit of detection, determined by population PK analysis, was 10 weeks for the 300 mg Q2W regimen and 13 weeks for the 300 mg QW regimen.

Linearity/non-linearity
Due to nonlinear clearance, dupilumab exposure, as measured by area under the concentration-time curve, increases with dose in a greater than proportional manner following single SC doses from 75-600 mg.

Special populations

Gender
Gender was not found to be associated with any clinically meaningful impact on the systemic exposure of dupilumab determined by population PK analysis.

Race
Race was not found to be associated with any clinically meaningful impact on the systemic exposure of dupilumab by population PK analysis.

Hepatic impairment
Dupilumab, as a monoclonal antibody, is not expected to undergo significant hepatic elimination. No clinical studies have been conducted to evaluate the effect of hepatic impairment on the pharmacokinetics of dupilumab.

Renal impairment
Dupilumab, as a monoclonal antibody, is not expected to undergo significant renal elimination. No clinical studies have been conducted to evaluate the effect of renal impairment on the pharmacokinetics of dupilumab. Population PK analysis did not identify mild or moderate renal impairment as having a clinically meaningful influence on the systemic exposure of dupilumab. Very limited data are available in patients with severe renal impairment.

Body Weight
Adolescent patients
For adolescents ≥12 to <18 years of age with atopic dermatitis receiving every other week dosing (Q2W) with either 200 mg (<60 kg) or 300 mg (≥60 kg), mean ±SD steady state trough concentration of dupilumab was 54.5±27.0 mcg/mL.

Since weight is the primary covariate affecting the PK of dupilumab, a weight-based tiered regimen was used to reduce the differences in exposure between patients across the adolescent

population. The similarity in the mean week 16 dupilumab concentrations and overlapping distribution (Figure 6) illustrates the utility of the 2-tiered weight-based 200/300 mg Q2W regimen for patients below and above 60 kg. In contrast, as would be expected when the same dose is administered across the entire range of body weights, lower Ctrough were observed at the higher weight category of ⩾ 60 kg compared to the <60 kg weight category for the 300 mg Q4W regimen.

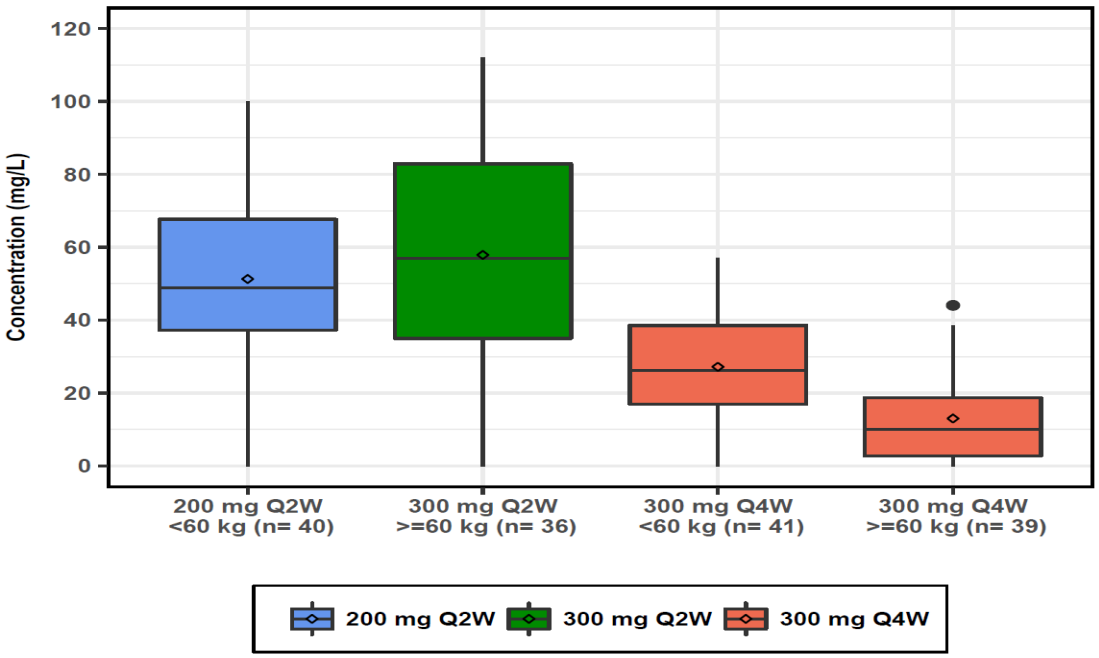


Figure 6: Concentrations of Functional Dupilumab in Serum (mg/L) at Week 16 vs. Body Weight (kg) by Dose Group in Adolescent Patients with Moderate-to- Severe AD (R668-AD-1526).

The pharmacokinetics of dupilumab in paediatric patients below 12 years of age has not been fully established.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of repeated dose toxicity (including safety pharmacology endpoints) and toxicity to reproduction and development.

The mutagenic potential of dupilumab has not been evaluated; however monoclonal antibodies are not expected to alter DNA or chromosomes.

Carcinogenicity studies have not been conducted with dupilumab. An evaluation of the available evidence related to IL-4Rα inhibition and animal toxicology data with surrogate antibodies does not suggest an increased carcinogenic potential for dupilumab.

During a reproductive toxicology study conducted in monkeys, using a surrogate antibody specific to the monkey IL-4Rα, no foetal abnormalities were observed at dosages that saturate the IL-4Rα.

An enhanced pre- and post-natal developmental study revealed no adverse effects in maternal animals or their offspring up to 6 months post-partum/post-birth.
Fertility studies conducted in male and female mice using a surrogate antibody against IL-4Rα showed no impairment of fertility (see section 4.6).

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sucrose
L-arginine hydrocholoride
L-histidine
Polysorbate 80
Sodium acetate
Water for injections
Acetic acid (for pH adjustment)

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

6.3 Shelf life

200 mg dose
3 years

300 mg dose
2 years

If necessary, pre-filled syringes may be kept at room temperature up to 25°C for a maximum of 14 days. Do not store above 25°C. If the carton needs to be removed permanently from refrigerator, the date of removal may be recorded on the outer carton. After removal from the refrigerator, Dupixent must be used within 14 days or discarded.

6.4 Special precautions for storage

Store in a refrigerator (2°C to 8°C).

Do not freeze.

Store in the original carton in order to protect from light.

6.5 Nature and contents of container

Pre-filled syringe 300 mg
2 ml solution in a siliconised type-1 clear glass pre-filled syringe with needle shield, with a fixed 27 gauge 12.7 mm (½ inch), thin wall stainless steel staked needle.

Pack size:
- 2 pre-filled syringes

Pre-filled syringe 200 mg
1.14 ml solution in a siliconised type-1 clear glass pre-filled syringe with needle shield, with a fixed 27 gauge 12.7 mm (½ inch), thin wall stainless steel staked needle.

Pack size:

- 1 pre-filled syringe

6.6 Special precautions for disposal and other handling

The instructions for the administration of Dupixent in a pre-filled syringe are given in the Patient Treatment Protocol.

The solution should be clear to slightly opalescent, colourless to pale yellow. If the solution is cloudy, discoloured or contains visible particulate matter, the solution should not be used.

After removing the 300 mg pre-filled syringe from the refrigerator, it should be allowed to reach room temperature by waiting for 45 min before injecting Dupixent.

After removing the 200 mg pre-filled syringe from the refrigerator, it should be allowed to reach room temperature by waiting for 30 min before injecting Dupixent

The pre-filled syringe should not be exposed to heat or direct sunlight and should not be shaken.

Store in the original carton in order to protect from light.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements. After use, place the pre-filled syringe into a puncture-resistant container and discard as required by local regulations. Do not recycle the container. Keep the container out of sight and reach of children.

7. SCIENTIFIC OPINION HOLDER

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8. EAMS NUMBER(S)

04425/0001

9. DATE OF SCIENTIFIC OPINION

23/01/2019

Additional information:

• Each prescribing dermatologist will be provided with a **physician pack** containing all the relevant documents needed to manage patients receiving Dupixent under EAMS.

The schedule of follow up visits is: 1 month from baseline (loading dose) and 3 monthly follow up in outpatient clinic.

In addition to pharmacovigilance data, additional data will be collected on clinical efficacy and quality of life whilst taking Dupixent. This will take place at baseline, after the first month, and thereafter during the 3 monthly visits.

• Prescribers will be provided with guidance on managing Adverse Events including immune-related adverse events and dose management.

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