



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 medicines and medicines used outside their licence, 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 physicians and is provided by the pharmaceutical company that manufactures the EAMS medicine. This medicine does not yet have a licence (marketing authorisation) in this indication and the information is provided to assist the physician in prescribing this medicine outside the licence. 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 assessment of the information supplied to the MHRA on the benefits and risks of the medicine in this new promising indication. As such, this is a scientific opinion and should not be regarded as an indication licensed by the MHRA or a future commitment by the MHRA to license such an indication, nor should it be regarded as an authorisation to sell or supply a medicine for such an indication. A positive scientific opinion is not a recommendation for use of the medicine and should not be interpreted as such. Under EAMS the risk and legal responsibility for prescribing a 'special' remains with the physician, and the opinion and EAMS documentation published by the MHRA are intended only to inform physicians' decision making and not to recommend use. An EAMS scientific opinion does not affect the civil liability of the manufacturer or any physician in relation to the product.

Healthcare professionals 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 EAMS product covering the EAMS indication, or if following scientific assessment, the EAMS criteria are considered to be no longer met.

Treatment protocol update(s): In case of substantial new efficacy or safety data, the treatment protocol may need to be updated. However, for other updates of the safety information, please refer to the product information of Dupixent (dupilumab) on the electronic Medicines Compendium (eMC) website: <https://www.medicines.org.uk/emc/product/8553>

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

Dupilumab 300 mg solution for injection in pre-filled syringe

Dupilumab 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 solution (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 against interleukin (IL)-4 receptor alpha that inhibits IL-4/IL-13 signalling, produced in Chinese Hamster Ovary (CHO) cells by recombinant DNA technology. 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 sterile solution, which is free from visible particulates, with a pH of approximately 5.9.

4. CLINICAL PARTICULARS

4.1 EAMS therapeutic indication

For the purpose of EAMS, dupilumab is being made available to children 6 to 11 years of age with severe atopic dermatitis who are candidates for systemic therapy and where existing systemic therapies are not advisable.

4.2 Posology and method of administration

Posology

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

The recommended dose of dupilumab for paediatric patients ≥ 6 to < 12 years of age is specified in Table 1.

Table 1: Dose of dupilumab for subcutaneous administration in paediatric patients ≥ 6 to < 12 years of age with severe atopic dermatitis

Body Weight	Initial Dose(s)*	Subsequent Doses
15 to less than 30 kg	300 mg (one 300 mg injection), then 300 mg 2 weeks later	300 mg every four weeks (Q4W)
30 to less than 60 kg	400 mg (two 200 mg injections)	200 mg every other week (Q2W)

* Initial dose to be administered by health care professional

Dupilumab 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.

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. If dupilumab treatment interruption becomes necessary, patients can still be successfully re-treated.

Missed dose

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

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 ≥ 6 to < 12 years of age with atopic dermatitis, the recommended doses are:

- 15 to less than 30 kg: 300 mg every 4 weeks (Q4W)
- 30 to less than 60 kg: 200 mg every other week (Q2W)

Paediatric patients

The safety and efficacy of dupilumab in children below the age of 6 years have not been established (see section 5.2).

Method of administration

Subcutaneous use

Dupilumab 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.

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

A patient's parent/guardian may administer dupilumab if their healthcare professional determines that this is appropriate. Proper training should be provided to caregivers on the preparation and administration of dupilumab prior to use according to the Instructions for Use (IFU) section in the EAMS package leaflet.

4.3 Contraindications

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

4.4 Special warnings and precautions for use

Systemic, topical, or inhaled corticosteroids should not be discontinued abruptly upon initiation of therapy with dupilumab. Reductions in corticosteroid dose, if appropriate, should be gradual and performed under the direct supervision of a physician. Reduction in corticosteroid dose may be associated with systemic withdrawal symptoms and/or unmask conditions previously suppressed by systemic corticosteroid therapy.

Biomarkers of type 2 inflammation may be suppressed by systemic corticosteroid use. This should be taken into consideration to determine type 2 status in patients taking oral corticosteroids (see section 5.1).

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 dupilumab should be discontinued immediately and appropriate therapy initiated. Cases of anaphylactic reaction, angioedema, and serum sickness/serum sickness-like reaction have been reported. Anaphylactic reactions and angioedema have occurred from minutes to up to seven days after the dupilumab injection (section 4.8).

Helminth infection

Patients with known helminth infections were excluded from participation in clinical studies. Dupilumab 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 dupilumab. If patients become infected while receiving treatment with dupilumab and do not respond to anti-helminth treatment, treatment with dupilumab should be discontinued until infection resolves.

There is a risk of worsening of *Strongyloides* infestation in patients who have travelled to the UK from regions of the world where *Strongyloides* is endemic. Patients who have travelled to the UK from such regions and who are suspected to have *Strongyloides* infestation should be screened by stool and serology tests, and if necessary receive appropriate anti-helminth treatment, prior to commencement of the treatment with dupilumab.

Dry eye

If dry eye is suspected (irritated, gritty eyes, foreign body sensation), prompt use of lubricant eye drops and/or ointments may be considered, and continued on a regular basis, as this may help to prevent inflammatory damage to the ocular surface epithelium. If eye symptoms do not improve, or worsen, patients should undergo ophthalmological examination as appropriate.

Conjunctivitis and keratitis related events

Conjunctivitis and keratitis related events have been reported with dupilumab, predominantly in atopic dermatitis patients (see section 4.8). Some patients reported visual disturbances (e.g. blurred vision) associated with conjunctivitis or keratitis (section 4.8).

Patients should be advised to report new onset or worsening eye symptoms to their healthcare provider. Patients treated with dupilumab who develop conjunctivitis that does not resolve following standard treatment or signs and symptoms suggestive of keratitis should undergo ophthalmological examination as appropriate (section 4.8).

Atopic dermatitis patients with comorbid asthma

Patients on dupilumab for moderate-to-severe atopic dermatitis who also have 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 dupilumab.

Vaccinations

Live and live attenuated vaccines (such as the nasal flu vaccination administered in this age group) should not be given concurrently with dupilumab or for a period of 12 weeks after treatment has stopped as clinical safety and efficacy has not been established. Immune responses to Tdap vaccine and meningococcal polysaccharide vaccine were assessed, see section 4.5. It is recommended that patients should be brought up to date with live and live attenuated immunisations in agreement with current immunisation guidelines prior to treatment with dupilumab.

Sodium content

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

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.

Therefore, patients receiving dupilumab may receive concurrent inactivated or non-live vaccinations. For information on live vaccines see section 4.4.

In a clinical study of AD patients, the effects of dupilumab on the pharmacokinetics (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.

An effect of dupilumab on the PK of co-administered medications is not expected. Based on the population analysis, commonly co-administered medications had no effect on dupilumab pharmacokinetics on patients with moderate to severe asthma.

4.6 Fertility, pregnancy and lactation

Pregnancy

There are limited amounts of data from the use of dupilumab in pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity (see section 5.3). Dupilumab should be used during pregnancy only if the potential benefit justifies the potential risk to the foetus.

Breast-feeding

It is unknown whether dupilumab is excreted in human milk or absorbed systemically after ingestion. A decision must be made whether to discontinue breast-feeding or to discontinue dupilumab 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

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

4.8 Undesirable effects

Adults with atopic dermatitis

Summary of the safety profile

The most common adverse reactions were injection site reactions, conjunctivitis, blepharitis, and oral herpes. Very rare cases of serum sickness/serum sickness-like reaction have been reported in the atopic dermatitis development programme (see section 4.4).

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. 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.

Tabulated list of adverse reactions

The safety of dupilumab was evaluated in four randomized, double-blind, placebo-controlled studies and one dose-ranging study in patients with moderate-to-severe atopic dermatitis. In these 5 trials, 1,689 subjects were treated with subcutaneous injections of dupilumab, with or without concomitant topical corticosteroids (TCS). A total of 305 patients were treated with dupilumab for at least 1 year.

Listed in Table 2 are adverse reactions observed in clinical trials and/or postmarketing setting presented by system organ class and frequency, using the following categories: very common ($\geq 1/10$); common ($\geq 1/100$ to $< 1/10$); uncommon ($\geq 1/1,000$ to $< 1/100$); rare ($\geq 1/10,000$ to $< 1/1,000$); very rare ($< 1/10,000$); and not known (cannot be estimated from available data). Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Table 2 List of adverse reactions in atopic dermatitis

MedDRA System Organ Class	Frequency	Adverse Reaction
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Infections and infestations	Common	Conjunctivitis Oral herpes
Blood and lymphatic system disorders	Common	Eosinophilia
Immune system disorders	Very rare Not known	Serum sickness/serum sickness-like reactions Anaphylactic reaction* Angioedema*
Nervous system disorders	Common	Headache
Eye disorders	Common Uncommon	Conjunctivitis allergic Eye pruritus Blepharitis Dry eye Keratitis Ulcerative keratitis
Musculoskeletal and connective tissue disorders	Not known	Arthralgia*
General disorders and administration site conditions	Very common	Injection site reactions

* From postmarketing reporting.

Adolescents with atopic dermatitis (12 to 17 years of age)

The safety of dupilumab was assessed in a study of 250 patients 12 to 17 years ≥ 12 to < 18 years of age with moderate-to-severe atopic dermatitis (R668-AD-1526, NCT03054428). The total number of patients exposed to dupilumab was 165. The safety profile of dupilumab 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 dupilumab was assessed in an open-label extension study in patients 12 to 17 years ≥ 12 to < 18 years of age with moderate-to-severe atopic dermatitis (R668-AD-1434, NCT02612454). The safety profile of dupilumab 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 dupilumab observed in adolescents was consistent with that seen in adults with atopic dermatitis.

Paediatric patients with atopic dermatitis (6 to 11 years of age)

The safety of dupilumab was assessed in a trial of 367 patients 6 to 11 years of age with severe atopic dermatitis (R668-AD-1652). The safety profile of dupilumab + TCS in these patients through week 16 was similar to the safety profile from studies in adults and adolescents with atopic dermatitis.

The long-term safety of dupilumab + TCS was assessed in an open-label extension study of 368 subjects 6 to 11 years of age with atopic dermatitis (AD-1434). Among patients who entered this study, 110 (29.9%) had moderate and 72 (19.6%) had severe atopic dermatitis at the time of enrolment in study AD-1434. The safety profile of dupilumab + TCS in subjects followed through week 52 was similar to the safety profile observed at week 16 in AD-1652. The long-term safety profile of dupilumab + TCS observed in paediatric patients was consistent with that seen in adults and adolescents with atopic dermatitis.

Description of selected adverse reactions in atopic dermatitis indication

Hypersensitivity

Cases of anaphylactic reaction, angioedema and serum sickness/serum sickness-like reaction have been reported following administration of dupilumab (see section 4.4).

Conjunctivitis and keratitis related events

Conjunctivitis and keratitis occurred more frequently in atopic dermatitis patients who received dupilumab. Most patients with conjunctivitis or keratitis recovered or were recovering during the treatment period.

Eczema herpeticum

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

Eosinophilia

Dupilumab-treated patients had a greater mean initial increase from baseline in eosinophil count compared to patients treated with placebo. Eosinophil counts declined to near baseline levels during study treatment.

Treatment-emergent eosinophilia ($\geq 5,000$ cells/mcL) was reported in <2 % of dupilumab-treated patients and <0.5 % in placebo-treated patients.

Infections

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

Immunogenicity

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

Anti-Drug-Antibodies (ADA) responses were not generally associated with impact on dupilumab exposure, safety, or efficacy.

Approximately 5 % of patients with atopic dermatitis, asthma, or Chronic rhinosinusitis with nasal polyp (CRSwNP) who received dupilumab 300 mg Q2W for 52 weeks developed ADA to dupilumab; approximately 2 % exhibited persistent ADA responses and approximately 2 % had neutralizing antibodies. Similar results were observed in paediatric patients (6 to 11 years of age) with atopic dermatitis who received dupilumab 200 mg Q2W or 300 mg Q4W for 16 weeks.

Approximately 16% of adolescent patients with atopic dermatitis who received dupilumab 300 mg or 200 mg Q2W for 16 weeks developed antibodies to dupilumab; approximately 3% exhibited persistent ADA responses, and approximately 5% had neutralizing antibodies.

Regardless of age or population, approximately 2 to 4 % of patients in the placebo groups were positive for antibodies to dupilumab; approximately 2 % exhibited persistent ADA response and approximately 1% had neutralizing antibodies.

Less than 1% of patients who received dupilumab at approved dosing regimens 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).

Paediatric population

The safety profile observed in the paediatric population (6 to 17 years) in atopic dermatitis clinical trials was similar to that seen in adults.

4.9 Overdose

There is no specific treatment for dupilumab 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

Pharmacotherapeutic group: Other dermatological preparations, agents for dermatitis, excluding corticosteroids, ATC code: D11AH05

Mechanism of action

Dupilumab is a recombinant human IgG4 monoclonal antibody that inhibits interleukin-4 and interleukin-13 signaling. Dupilumab inhibits IL-4 signaling via the Type I receptor (IL-4R α / γ c), and both IL-4 and IL-13 signaling through the Type II receptor (IL-4R α /IL-13R α). IL-4 and IL-13 are major drivers of human type 2 inflammatory

disease, such as atopic dermatitis. Blocking the IL-4/IL-13 pathway with dupilumab in patients decreases many of the mediators of type 2 inflammation.

Pharmacodynamic effects

In atopic dermatitis clinical trials, treatment with dupilumab was associated with decreases from baseline in concentrations of type 2 immunity 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 in atopic dermatitis

The efficacy and safety of dupilumab have been assessed in clinical studies in adults and adolescents with moderate-to-severe atopic dermatitis. In addition, efficacy and safety have been assessed in a pivotal phase 3 clinical trial in children (≥ 6 to < 12 years of age) with severe AD not adequately controlled with currently available treatments. Efficacy assessments included measurements of the extent and intensity of AD signs, severity of AD symptoms, the impact of AD on QOL, as well as anxiety and depression scores.

Adults with atopic dermatitis

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 of atopic dermatitis, patients were permitted to receive rescue treatment (which included higher potency topical steroids or systemic immunosuppressants) 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.

Baseline Characteristics

In the monotherapy studies (SOLO 1 and SOLO 2), across all treatment groups, the mean age was 38.3, the mean weight was 76.9 kg, 42.1% were female, 68.1% were white, 21.8% were Asian, and 6.8% were black. In these studies, 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.

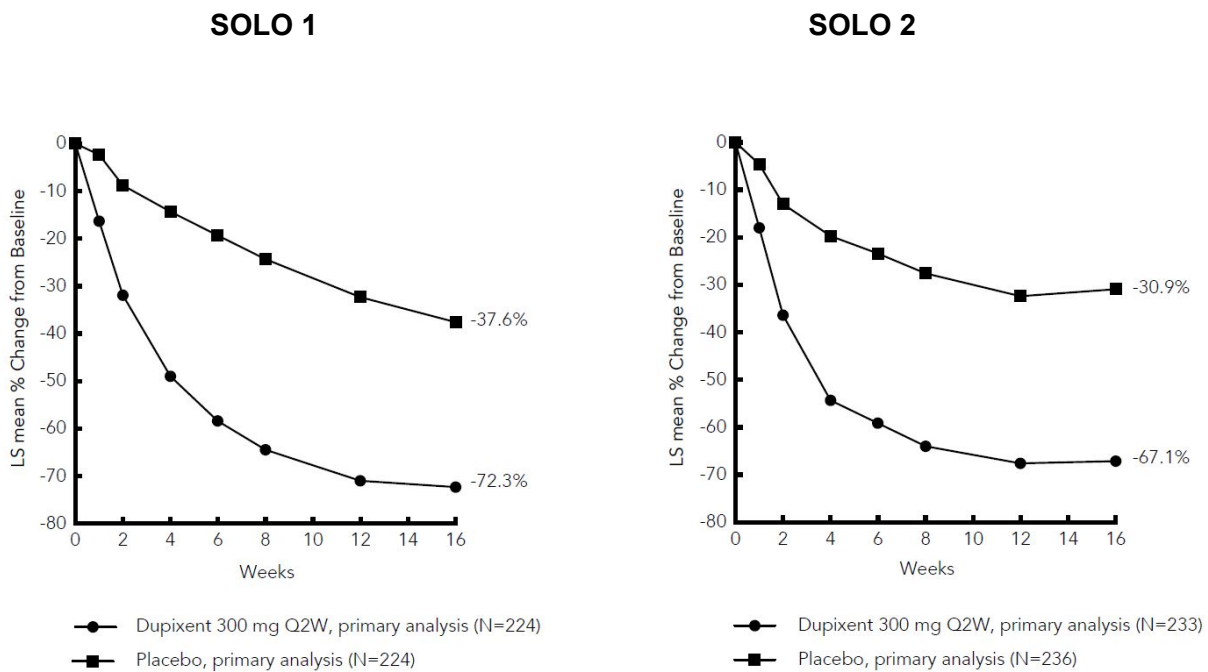
^b Responder was defined as a patient with IGA 0 or 1 (“clear” or “almost clear”) with a reduction of ≥ 2 points on a 0-4 IGA scale.

^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

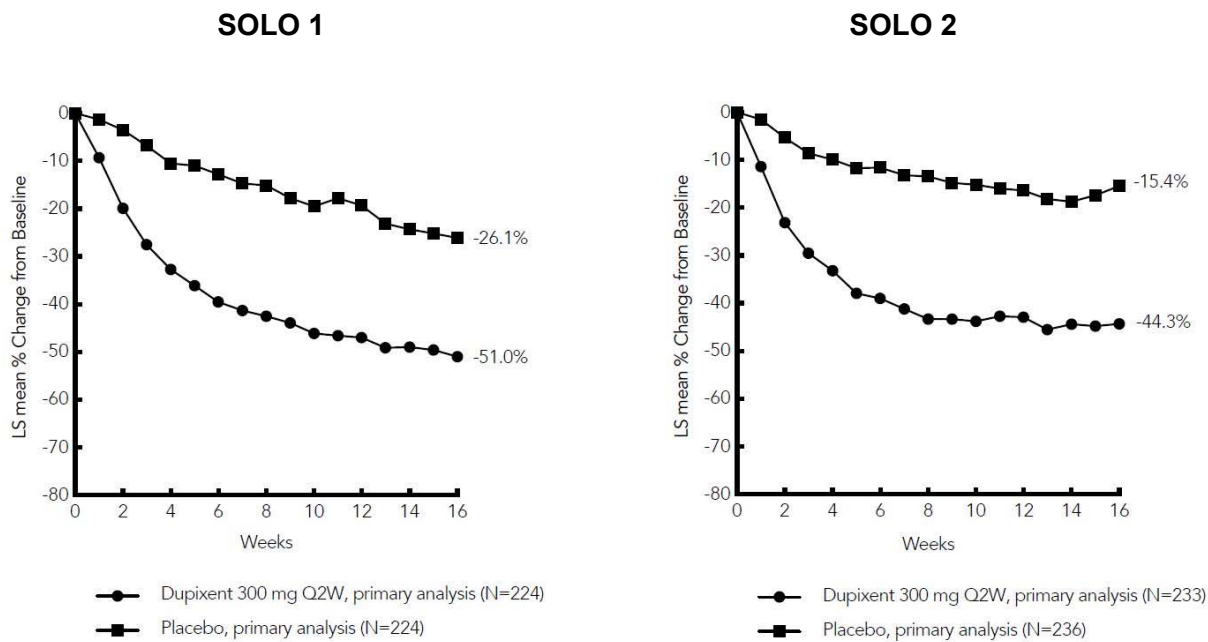


LS = least squares

^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



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 dupilumab 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 dupilumab + 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 Dupilumab with concomitant TCS^a at Week 16 and Week 52 in CHRONOS

	Week 16 (FAS) ^b			Week 52 (FAS Week 52) ^b		
	Placebo + TCS	Dupilumab 300 mg Q2W + TCS	Dupilumab 300 mg QW + TCS	Placebo + TCS	Dupilumab 300 mg Q2W + TCS	Dupilumab 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 Dupilumab had improvement in pruritus NRS of ≥4 points compared to placebo at week 2 (p <0.05).

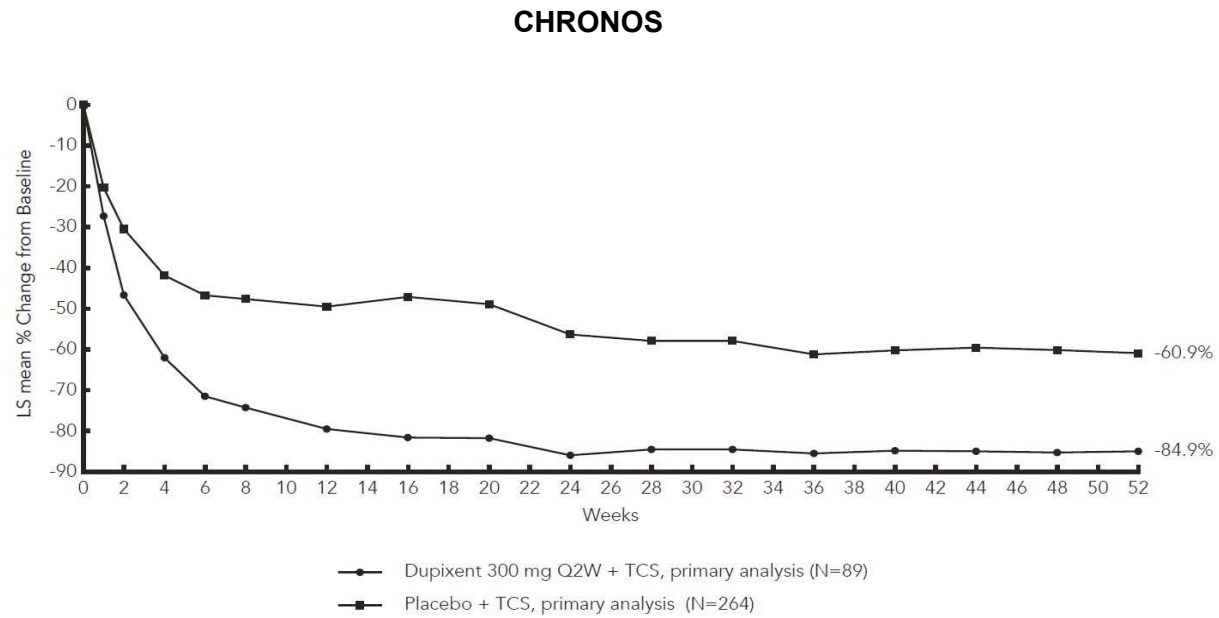
^f p-value <0.0001

^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

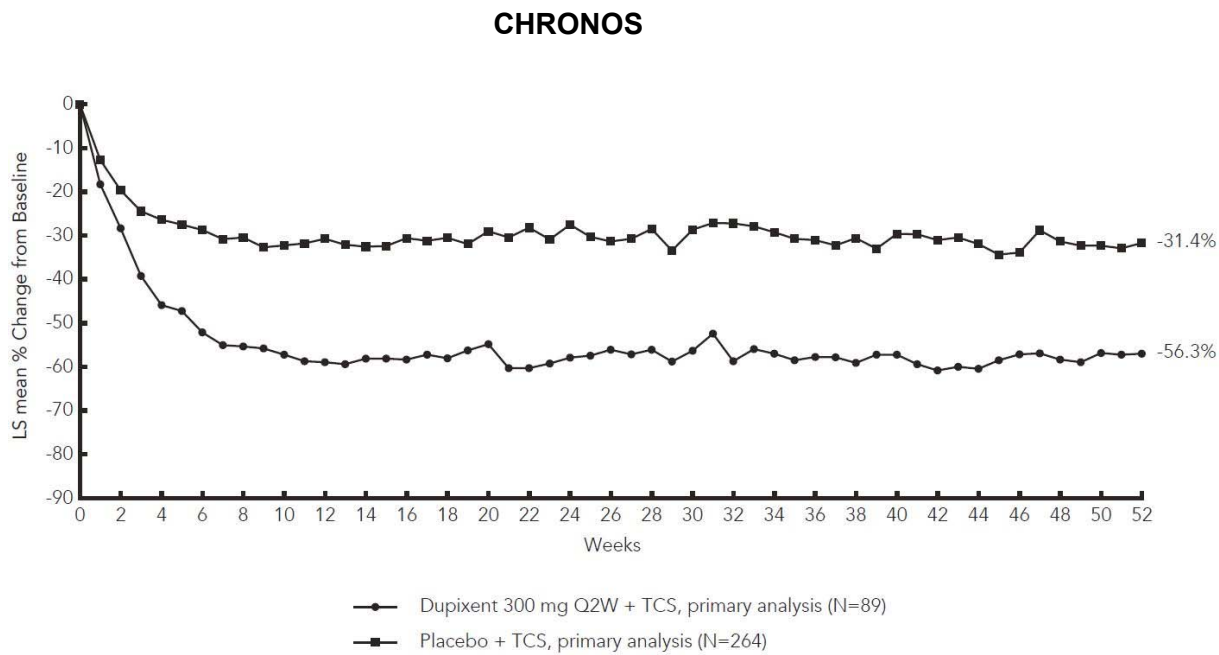


LS = least squares

^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

^aIn the primary analyses of the efficacy endpoints, patients who received rescue treatment or with missing data were considered non-responders.

^bFAS 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 dupilumab 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	Dupilumab 300 mg Q2W + TCS	Dupilumab 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	-29.5 %	-62.4 %	-58.3 %

baseline (+/- SE)	(2.55)	(2.48)	(2.45)
DLQI, LS mean change from baseline (SE)	-4.5 (0.49)	-9.5 (0.46)	-8.8 (0.45)

(all p values <0.0001)

In the subgroup of patients resembling the CAFE study population within the 52 week CHRONOS study, 69.6 % of dupilumab 300 mg Q2W-treated patients reached EASI-75 vs 18.0 % placebo-treated patients at week 16, and 52.4 % of dupilumab 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 dupilumab 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 dupilumab 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 dupilumab 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 Atopic Dermatitis

In both monotherapy studies (SOLO 1 and SOLO 2), both dupilumab 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 dupilumab 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 dupilumab 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 dupilumab 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 Dupilumab monotherapy at Week 16

	Monotherapy					
	SOLO 1 at Week 16			SOLO 2 at Week 16		
	Placebo	Dupilumab 300 mg Q2W	Dupilumab 300 mg QW	Placebo	Dupilumab 300 mg Q2W	Dupilumab 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), dupilumab 300 mg Q2W + TCS and dupilumab 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 dupilumab 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, dupilumab 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 dupilumab 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 dupilumab with concomitant TCS at Week 16 and Week 52 in CHRONOS

	Concomitant Use of TCS					
	CHRONOS at Week 16			CHRONOS at Week 52		
	Placebo	Dupilumab 300 mg Q2W + TCS	Dupilumab 300 mg QW + TCS	Placebo +TCS	Dupilumab 300 mg Q2W + TCS	Dupilumab 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 (12 to 17 years of age)

The efficacy and safety of dupilumab 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 $\geq 10\%$. Eligible patients enrolled into this study had previous inadequate response to topical medication.

Patients received 1) an initial dose of 400 mg dupilumab (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 dupilumab (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 dupilumab (two 300 mg injections) on day 1, followed by 300 mg every 4 weeks (Q4W) regardless of baseline body weight; or 3) matching placebo. Dupilumab 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 dupilumab in the adolescent atopic dermatitis study at Week 16 (FAS)

	AD-1526(FAS) ^a	
	Placebo	Dupilumab 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.

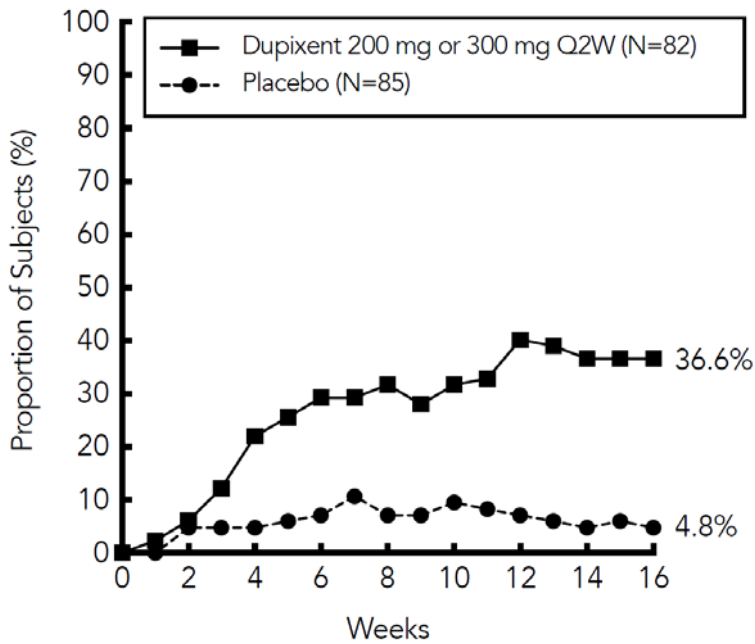
^c Patients who received rescue treatment or with missing data were considered as non-responders (58.8% and 20.7% in the placebo and dupilumab arms, respectively).

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 dupilumab group (58.8% and 20.7%, respectively).

A significantly greater proportion of patients randomised to dupilumab 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 dupilumab 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 dupilumab in adolescent patients with moderate-to-severe AD who had participated in previous clinical trials of dupilumab 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.

Paediatric population 6 to 11 years of age

The efficacy and safety of dupilumab in paediatric patients concomitantly with TCS was evaluated in a multicentre, randomised, double-blind, placebo-controlled study (AD-1652) in 367 subjects 6 to 11 years of age, with AD defined by an IGA score of 4 (scale of 0 to 4), an EASI score ≥ 21 (scale of 0 to 72), and a minimum BSA involvement of $\geq 15\%$. Eligible patients enrolled into this trial had previous inadequate response to topical medication. Enrolment was stratified by baseline weight (<30 kg; ≥ 30 kg).

Patients in the dupilumab Q2W + TCS group with baseline weight of <30 kg received an initial dose of 200 mg on Day 1, followed by 100 mg Q2W from Week 2 to Week 14, and patients with baseline weight of ≥ 30 kg received an initial dose of 400 mg on Day 1, followed by 200 mg Q2W from week 2 to week 14. Patients in the dupilumab Q4W + TCS group received an initial dose of 600 mg on Day 1, followed by 300 mg Q4W from week 4 to week 12, regardless of weight. 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 8.5 years, the median weight was 29.8 kg, 50.1% of patients were female, 69.2% were White, 16.9% were Black, and 7.6% were Asian. At baseline, the mean BSA involvement was 57.6%, and 16.9% had received prior systemic non-steroidal immunosuppressants.

Also, at baseline the mean EASI score was 37.9, and the weekly average of daily worst itch score was 7.8 on a scale of 0-10, the baseline mean SCORAD score was 73.6, the baseline POEM score was 20.9, and the baseline mean CDLQI was 15.1. Overall, 91.7% of subjects had at least one co-morbid allergic condition; 64.4% had food allergies, 62.7% had other allergies, 60.2% had allergic rhinitis, and 46.7% had asthma.

The primary endpoint was the proportion of patients with an IGA 0 (clear) or 1 (almost clear) at week 16. Other evaluated outcomes included the proportion of patients with EASI-75 or EASI-90 (improvement of at least 75% or 90% in EASI from baseline, respectively), percent change in EASI score from baseline to week 16, and reduction in itch as measured by the peak pruritus NRS (≥ 4 -point improvement). Additional secondary endpoints included mean change from baseline to week 16 in the POEM and CDLQI scores.

Clinical response

Table 10 presents the results by baseline weight strata for the proposed dose regimens

Table 10 Efficacy Results of Dupilumab with Concomitant TCS in AD-1652 at Week 16 (FAS)^a

	Dupilumab 300 mg Q4W ^d + TCS	Placebo +TCS	Dupilumab 200 mg Q2W ^e + TCS	Placebo + TCS
	(N=61)	(N=61)	(N=59)	(N=62)
	<30 kg	<30 kg	≥30 kg	≥30 kg
IGA 0 or 1 ^b , % responders ^c	29.5%	13.1%	39.0%	9.7%
EASI-50, % responders ^c	95.1%	42.6%	86.4%	43.5%
EASI-75, % responders ^c	75.4%	27.9%	74.6%	25.8%
EASI-90, % responders ^c	45.9%	6.6%	35.6%	8.1%
EASI, LS mean % change from baseline (+/-SE)	-84.3% (3.08)	-49.1% (3.30)	-80.4% (3.61)	-48.3% (3.63)
SCORAD, LS mean % change from baseline (+/- SE)	-65.3% (2.87)	-28.9% (3.05)	-62.7% (3.14)	-30.7% (3.28)
Pruritus NRS, LS mean % change from baseline (+/- SE)	-55.1% (3.94)	-27.0% (4.24)	-58.2% (4.01)	-25.0% (3.95)
Pruritus NRS (≥4-point improvement), % responders ^c	54.1%	11.7%	61.4%	12.9%
BSA LS mean change from baseline (+/- SE)	-43.2 (2.16)	-23.9 (2.34)	-38.4 (2.47)	-19.8 (2.50)
CDLQI, LS mean change from baseline (+/-SE)	-11.5 (0.69)	-7.2 (0.76)	-9.8 (0.63)	-5.6 (0.66)
CDLQI, (≥6-point improvement), % responders	81.8%	48.3%	80.8%	35.8%
POEM, LS mean change from baseline (+/- SE)	-14.0 (0.95)	-5.9 (1.04)	-13.6 (0.90)	-4.7 (0.91)
POEM, (≥6-point improvement), % responders	81.4%	32.8%	79.3%	31.1%

Full Analysis Set (FAS) includes all patients randomised.

^b Responder was defined as a patient with an IGA 0 or 1 ("clear" or "almost clear").

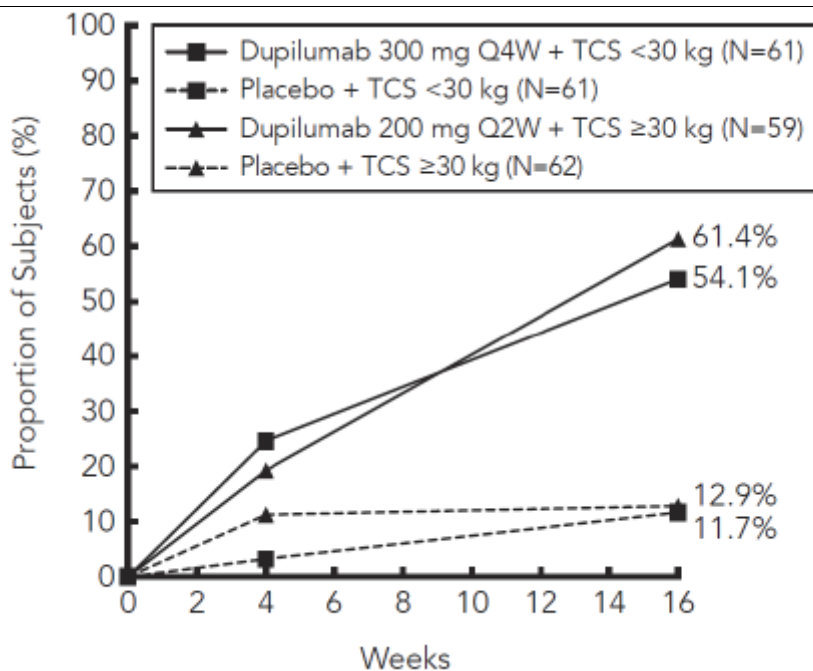
^c Patients who received rescue treatment or with missing data were considered as non-responders.

^d At Day 1, patients received 600 mg of dupilumab (see section 5.2).

^e At Day 1, patients received 200 mg (baseline weight <30 kg) or 400 mg (baseline weight ≥30 kg) of dupilumab.

A greater proportion of patients randomised to dupilumab + TCS achieved an improvement in the peak pruritus NRS compared to placebo + TCS (defined as ≥4-point improvement at week 4). See Figure 6.

Figure 6: Proportion of Paediatric Subjects with ≥4-point Improvement on the Peak Pruritus NRS in AD-1652a (FAS)^b



^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 randomised.

^c At Day 1, patients received 600 mg of dupilumab (see section 5.2)

^d At day 1, patients received 200 mg (baseline weight <30 kg) or 400 mg (baseline weight ≥30 kg) of dupilumab

The dupilumab groups 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 dupilumab + TCS in paediatric patients with atopic dermatitis who had participated in the previous clinical trials of dupilumab + TCS was assessed in an open-label extension study (AD-1434). Efficacy data from this trial suggests that clinical benefit provided at week 16 was sustained through week 52.

Paediatric population

Atopic dermatitis

The safety and efficacy of dupilumab have been established in 12 to 17 years old with moderate-to severe atopic dermatitis in study AD-1526 which included 251 adolescents. The efficacy of dupilumab has been demonstrated in patients 6 to 11 years of age with severe atopic dermatitis in study AD-1652 which enrolled 367 paediatric patients. At data cut-off for the analysis of the 6-11 year old patients, 115 patients had received treatment for 52 weeks or more. The safety and efficacy were generally consistent between paediatric, adolescent, and adult patients (see section 4.8). Safety and efficacy in paediatric patients (<6 years of age) with atopic dermatitis have not been established.

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 ranges between 61% and 64%.

Steady-state concentrations were achieved by Week 16 following the administration of 600 mg starting dose and 300 mg dose every other week or 300 mg dose every other week without a loading dose. Across clinical trials, the mean \pm SD steady-state trough concentrations ranged from 69.2 \pm 36.9 mcg/ml to 80.2 \pm 35.3 mcg/ml for 300 mg dose and from 29.2 \pm 18.7 to 36.5 \pm 22.2 mcg/ml for 200 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

Paediatric population

The pharmacokinetics of dupilumab in paediatric patients (< 6 years of age) with atopic dermatitis has not been studied.

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 \pm SD steady state trough concentration of dupilumab was 54.5 \pm 27.0 mcg/mL.

For children 6 to 11 years of age with atopic dermatitis receiving every other week dosing (Q2W) with 200 mg (≥ 30 kg) or every four week dosing (Q4W) with 300 mg (<30 kg), mean \pm SD steady-state trough concentration was 86.0 \pm 34.6 mcg/mL and 98.7 \pm 33.2 mcg/mL, respectively. For children 6 to 11 years of age with body weight of <30 kg receiving 300 mg Q4W, initial doses of 300 mg on Days 1 and 15 produce similar steady-state exposure as an initial dose of 600 mg on Day 1, based on PK simulations

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-4R α 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-4R α , no foetal abnormalities were observed at dosages that saturate the IL-4R α .

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-4R α showed no impairment of fertility (see section 4.6).

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

- Sucrose
- L-arginine hydrochloride
- L-histidine
- Polysorbate 80 (E433)
- Sodium acetate trihydrate
- Glacial acetic acid (E260)(for pH adjustment)
- Water for injections

6.2 Incompatibilities

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

6.3 Shelf life

Dupilumab 200 mg solution for injection in pre-filled syringe

2 years

Dupilumab 300 mg solution for injection in pre-filled syringe

3 years

If necessary, pre-filled syringes (200 and 300 mg) 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, Dupilumab 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

Dupilumab 200 mg solution for injection in pre-filled syringe

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
- 2 pre-filled syringes
- Multipack containing 3 (3 packs of 1) pre-filled syringes
- Multipack containing 6 (3 packs of 2) pre-filled syringes

Dupilumab 300 mg solution for injection in pre-filled syringe

2 ml solution in a siliconised type-1 clear glass pre-filled syringe with or without needle shield, with a fixed 27 gauge 12.7 mm (½ inch), thin wall stainless steel staked needle.

Pack size:

- 1 pre-filled syringes
- 2 pre-filled syringes
- Multipack containing 3 (3 packs of 1) pre-filled syringes
- Multipack containing 6 (3 packs of 2) pre-filled syringes

6.6 Special precautions for disposal and other handling

The instructions for the administration of dupilumab 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 up to 25°C by waiting for 45 min before injecting dupilumab.

After removing the 200 mg pre-filled syringe from the refrigerator, it should be allowed to reach room temperature up to 25°C by waiting for 30 min before injecting dupilumab.

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

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

Aventis Pharma Limited t/a Sanofi
410 Thames Valley Park Drive,
Reading, Berkshire, RG6 1PT, UK

8. EAMS NUMBER

04425/0003

9. DATE OF SCIENTIFIC OPINION

14 August 2020.

Additional information

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

The schedule of follow up visits is: 4 weeks from the initial administration (i.e. from the initial dose), 8 weeks from the initial administration and 3 monthly (or more frequently, based on the clinician's assessment) follow-up in outpatient clinic. Pharmacovigilance data collection will take place at baseline, after the 4 weeks, after 8 weeks 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.

Contact information

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