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:
http://www.gmc-uk.org/mobile/14327

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 licence 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'.

Information for the healthcare professionals:

1. NAME OF THE MEDICINAL PRODUCT

Dupilumab 300 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).

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, dupilumab is being made available to adult patients with severe atopic dermatitis who have failed to respond, or who are intolerant of or ineligible for all approved therapies. Dupilumab can be used with or without topical corticosteroids.

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 dupilumab for adult patients is an initial dose of 600 mg (two 300 mg injections), followed by 300 mg given every other week administered as subcutaneous injection.

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

Special populations

Elderly patients (≥65 years)

No dose adjustment is recommended for elderly patients (see section 5.2).

Renal impairment

No dosage adjustment is needed in patients with mild or moderate renal impairment. No 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
No dose adjustment for body weight is recommended (see section 5.2).

Paediatric patients
Not to be used in patients under 18 years of age. The safety and efficacy of dupilumab in children below the age of 18 years have not been established (see section 5.2).

Method of administration

Dupilumab is administered by subcutaneous injection.

For the initial 600 mg dose, two 300 mg dupilumab injections should be administered consecutively in different injection sites.

A patient may self-inject dupilumab or the patient's caregiver may administer dupilumab. Proper training should be provided to patients and/or caregivers on the preparation and administration of dupilumab prior to use.

Dupilumab is self-administered by subcutaneous injection into the thigh or abdomen, except for the 5 cm around the navel, using a single-use pre-filled syringe. 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.

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 of the following treatments within 5 half-lives (if known) or 12 weeks before the first anticipated date for dupilumab administration(if half-life is not known or not applicable)
    - Systemic immunosuppressive/immunomodulating drugs [e.g., corticosteroids (more than physiologic replacement doses), ciclosporine, mycophenolate-mofetil, IFN-γ, Janus kinase inhibitors, azathioprine, methotrexate, etc.]
    - Investigational drugs (other than dupilumab.)

- Is a pregnant or breast feeding women.
- 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

Hypersensitivity

If a systemic hypersensitivity reaction occurs, administration of dupilumab should be discontinued immediately and appropriate therapy initiated. One case of serum sickness-like reaction and one case of serum sickness reaction, both considered serious, have been reported in clinical trials following the administration of dupilumab (section 4.8).

Helminth infection

Patients with known helminth infections were excluded from participation in clinical studies. It is unknown if dupilumab will influence the immune response against helminth infections. Treat patients with pre-existing helminth infections before initiating dupilumab. If patients become infected while receiving treatment with dupilumab and do not respond to anti-helminth treatment, discontinue treatment with dupilumab until infection resolves.

Concomitant Atopic Conditions

Safety and efficacy have not been established in allergic or atopic conditions other than atopic dermatitis. Patients with comorbid atopic conditions (such as asthma) should be advised not to adjust their treatment without consultation with their physicians. When discontinuing dupilumab consider the potential effects on other atopic conditions.

There may be a risk of exacerbation, or a return to pre-treatment severity levels, of asthma or other concomitant atopic conditions following discontinuation of dupilumab due to the decline in circulating therapeutic antibody levels (see section 5.2). Asthma medication may need to be adjusted during this period.

Live Vaccines

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

Orofacial herpes simplex

There is an increased risk of oral herpes infection with dupilumab treatment. This should be treated promptly, including in the prodromal phase. If the herpes infection does not improve the patient should seek additional medical advice.

Patient Alert Card

All patients receiving dupilumab under the Early Access to Medicines Scheme must be provided with a Patient Alert Card which they should carry with them at all times. The prescriber must discuss the risks of dupilumab therapy with the patient.

4.5 Interaction with other medicinal products and other forms of interaction

Dupilumab has not been studied with live vaccines. Live vaccines should not 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.

The impact of dupilumab on cytochrome P450 (CYP) enzyme activity has not been studied. Published in vitro studies suggest that IL-4 and IL-13 may modulate CYP450 enzymes; however, the clinical significance of these data is not fully understood.

4.6 Fertility, pregnancy and lactation

For the purposes of the EAMS, dupilumab 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 dupilumab 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 dupilumab is excreted in human milk.

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

Summary of the safety profile

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%).

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 1 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 1 List of adverse reactions in clinical studies[a]

System Organ Class	Frequency	Adverse Reaction
Infections and infestations	Common	Conjunctivitis Oral herpes Conjunctivitis bacterial Herpes simplex[b]
Blood and lymphatic system disorders	Common	Eosinophilia
Eye disorders	Common	Conjunctivitis allergic Eye pruritus Blepharitis Dry eye
General disorders and administration site conditions	Very common	Injection site reactions

[a] Pooled data from placebo-controlled monotherapy clinical studies (SOLO 1, SOLO 2, and a phase 2, dose-ranging study data) and placebo-controlled concomitant therapy with TCS study (CHRONOS) in AD, patients exposed to 300 mg every other week or 300 mg once weekly with or without topical corticosteroids, up to 16 weeks.

[b] In clinical trials, herpes simplex cases were mucocutaneous, generally mild to moderate in severity, and did not include eczema herpecticum. Eczema herpeticum cases were reported separately and incidence was numerically lower in patients treated with dupilumab compared to placebo.

The safety profile of dupilumab + TCS through week 52 is consistent with the safety profile observed at week 16.

Description of selected adverse reactions

Conjunctivitis
During the 52-week treatment period of the concomitant therapy trial, conjunctivitis was reported in 9% of the placebo + TCS group and in 16% of the dupilumab 300 mg Q2W + TCS group.

Hypersensitivity
In the overall exposure pool, there was one case reported as serum sickness reaction and one case reported as serum sickness-like reaction following administration of dupilumab (see section 4.4).

Laboratory Abnormalities
In clinical studies, transient elevations in blood eosinophils were observed after initiating dupilumab treatment in a minority of patients. Eosinophilia was reported in <2 % of patients treated with dupilumab (see Table 1). There were no other clinically significant laboratory abnormalities.

Overall Infections
No increase was observed in the overall incidence of infections or serious infections with dupilumab compared to placebo in clinical studies. 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 dupilumab. 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 dupilumab.

Immunogenicity

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

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

ADA responses were not generally associated with impact on dupilumab exposure, safety, or 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).

4.9 Overdose

In clinical studies, no safety issues were identified with single intravenous doses up to 12 mg/kg.
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: L04AC13 ATC code: not yet assigned

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 the EAMS program is intended for adult patients with severe atopic dermatitis who have failed to respond, or who are intolerant of or ineligible for all approved therapies. Dupilumab can be used with or without topical corticosteroids (see section 4.1).

The data below are predominantly from the SOLO 1 and 2 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.

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 2).

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.

Table 2: 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

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 pruritis NRS from baseline to week 16 and week 52 compared to placebo + TCS.

The primary endpoint results at week 16 were the following:

- 39 percent of patients who received either dupilumab 300 mg weekly with TCS or dupilumab 300 mg every two weeks with TCS achieved clearing or near-clearing of skin lesions (IGA 0 or 1), compared to 12 percent of patients receiving placebo with TCS (p less than 0.0001).
- 64 percent of patients who received dupilumab 300 mg weekly with TCS, and 69 percent of patients who received dupilumab 300 mg every two weeks with TCS achievedEASI-75, a 75 percent reduction on an index measuring eczema severity, compared to 23 percent of patients receiving placebo with TCS (p less than 0.0001).

The secondary endpoint 52-week results were the following:

- 40 percent of patients who received dupilumab 300 mg weekly with TCS, and 36 percent of patients who received dupilumab 300 mg every two weeks with TCS achieved clearing or near-clearing of skin lesions (IGA 0 or 1), compared to 12.5 percent of patients receiving placebo with TCS (p less than 0.0001).
- 64 percent of patients who received 300 mg weekly with TCS, and 65 percent of patients who received 300 mg every two weeks with TCS achieved EASI-75, compared to 22 percent with placebo with TCS (p less than 0.0001).

Quality of Life/Patient-Reported Outcomes

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 3).

Table 3: 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	12.4 %	41.0 %[a]	36.3 %[b]	6.1 %	39.5 %[a]	41.2 %[a]

achieving HADS-anxiety and HADS-depression score <8, %						

LS = least squares; SE = standard error
[a] p-value <0.0001
[b] p-value <0.001

Paediatric population

The safety and efficacy of dupilumab in children below the age of 18 years have not been established (see section 4.2)

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.

Administration of a single loading dose of 600 mg on Day 1 leads to rapid attainment of clinically effective concentrations within 2 weeks.

For every two week dosing (Q2W) with 300 mg, starting with a loading dose of 600 mg, population PK analysis determined steady state concentrations to be achieved after 10 weeks in a typical patient. Mean steady state trough concentration was 74 mg/L.

For weekly dosing (QW) with 300 mg, starting with a loading dose of 600 mg, population PK analysis determined steady state concentrations to be achieved after 13 weeks in a typical patient. Mean steady state trough concentration was 189 mg/L.

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.

Elderly patients
Of the 1472 patients with atopic dermatitis exposed to dupilumab in a phase 2 dose-ranging study or phase 3 placebo-controlled studies, a total of 67 were 65 years or older. Although no differences in safety or efficacy were observed between older and younger patients, the number of patients aged 65 and over is not sufficient to determine whether they respond differently from younger patients.

Age 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.

Paediatric patients
The pharmacokinetics of dupilumab in paediatric patients has not been studied.

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. No data are available in patients with severe renal impairment.

Body Weight
No dose adjustment for body weight is recommended.

5.3 Preclinical safety data

Dupilumab does not adequately interact with the non-human IL-4Rα of animals typically utilized for the preclinical assessment of toxicology, pregnancy, lactation or fertility. Therefore, some of these assessments were conducted using surrogate antibodies against the IL-4Rα of monkeys and mice.

Dupilumab binds with high affinity to human IL-4Rα and inhibits both IL-4 and IL-13 mediated signaling in vitro and in vivo. Administration of dupilumab leads to a reduction in type 2 (including Th2) inflammation in

different mouse models using mice that express human IL-4Rα and human IL-4. In the house dust mite (HDM) allergen inflammation model, dupilumab decreases circulating levels of IgE and allergen-specific IgG1, reduces pulmonary infiltration of eosinophils, and reduces goblet cell metaplasia in this model of type 2 (including Th2)-driven inflammation.

No dose-limiting or target organ toxicity was observed in repeat-dose toxicology studies up to 5 weeks duration in mice and 6 months duration in cynomolgus monkeys conducted with surrogate antibodies. The no-observed-adverse-effect-level (NOAEL) was the highest dose administered in these studies (200 mg/kg/week in mice and 100 mg/kg/week in monkeys). Serum drug levels achieved at these dosages were sufficient to have fully saturated the IL-4Rα in both species.

No adverse effects were observed in monkeys using a surrogate antibody against IL-4Rα when administered subcutaneously at doses up to 100 mg/kg/week for 26 weeks. No juvenile toxicology studies have been conducted with dupilumab or any of its surrogates.

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 risk of cancer for dupilumab.

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

During a reproductive toxicology study conducted in monkeys, using a surrogate antibody specific to the monkey IL-4Rα, no fetal abnormalities were observed at dosages that saturate the IL-4Rα. The overall rate of embryofetal loss during gestation was 5 of 20 (25 %) in control animals, 10 of 20 (50 %) in animals treated with 25 mg/kg/week, and 3 of 18 (17 %) in animals treated with 100 mg/kg/week. The exposure at 25 mg/kg/week or greater was at least 5-fold above the concentration needed to saturate the IL-4Rα receptors. The rate of embryofetal loss observed in control animals from other studies conducted at the laboratory ranged from 7 % to 39 %. Concentrations of the surrogate antibody observed in the infant monkeys at birth were comparable to those observed in maternal serum, indicating that the surrogate antibody, like other IgG antibodies, crosses the placental barrier. There were no adverse effects of the surrogate antibody on maternal monkeys dosed with up to 100 mg/kg/week (the highest dosage administered). Serum drug levels achieved during this study were sufficient to fully saturate the IL-4Rα in monkeys at all doses.

An enhanced pre- and post-natal developmental study was performed in which pregnant cynomolgus monkeys were treated with a surrogate antibody against IL-4Rα, at doses up to 100 mg/kg/week once weekly for approximately 21 weeks, from approximately gestational day 20 through natural birth.

There were no adverse effects in maternal animals or their offspring up to 6 months post-partum/post-birth. Drug levels achieved during this study were sufficient to fully saturate the IL-4Rα in monkeys. Measurable concentrations of the surrogate antibody in serum were observed in infant monkeys, indicating that this antibody, like other IgG antibodies, crosses the placental barrier. The NOAEL for maternal and developmental toxicity was considered to be 100 mg/kg/week, the highest administered dose.

Fertility studies conducted in male and female mice using a surrogate antibody against IL-4Rα showed no impairment of fertility. The NOEL was the maximum dose studied, 200 mg/kg/week administered subcutaneously (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

24 months

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

2 ml solution in a single-use siliconised Type-1 clear glass pre-filled syringe, with a fixed 27 gauge 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 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 discoloured or contains visible particulate matter, the solution should not be used.

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

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

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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Trading as

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GU1 4SY

8. EAMS NUMBER(S)

44513/0001

9. DATE OF SCIENTIFIC OPINION

10th March 2017

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: 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 dupilumab. This will take place at baseline, after the first month, and thereafter during the 3 monthly visits.

• As each patient signs the Informed Consent Form, they must be issued with a **Patient Alert Card**. This is a wallet-card sized and patients must be instructed to carry it with them at all times. It summarises the important side effects which they need to seek assistance for. In addition it alerts any other healthcare professional that may treat the patient that they are receiving dupilumab through an early access scheme, and provides information about their dermatologist, out of hours contact details and the Company's contact information.

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

Contact information:

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