SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

DUPIXENT (dupilumab) Injection 300 mg/2 mL solution in a single-use pre-filled syringe with needle shield.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each single-use pre-filled syringe with needle shield contains 300 mg dupilumab in 2 mL solution.

DUPIXENT is a fully human monoclonal antibody that inhibits interleukin-4 and interleukin-13 signaling by specifically binding to the IL-4Rα subunit of the IL-4 and IL-13 receptor complexes. DUPIXENT 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).

Dupilumab is produced by recombinant DNA technology in Chinese Hamster Ovary cell suspension culture.

Dupilumab is a covalent heterotetramer consisting of two disulfide-linked human heavy chains, each covalently linked through a disulfide bond to a human kappa light chain. There is a single N-linked glycosylation site in each heavy chain, located within the CH2 domain of the Fc constant region of the molecule. The DUPIXENT heavy chain has an immunoglobulin (Ig) G4P isotype constant region. IgG4P is an IgG4 constant region with a single amino acid substitution in the hinge region that recreates the IgG1 hinge sequence in order to stabilize IgG4 dimer formation. The variable domains of the heavy and light chains combine to form the IL-4Rα binding site within the antibody.

Dupilumab has a molecular weight of approximately 147 kDa.

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

DUPIXENT is indicated for the treatment of adult patients with moderate-to-severe atopic dermatitis whose disease is not adequately controlled with topical prescription therapies or when those therapies are not advisable. DUPIXENT can be used with or without topical corticosteroids.

4.2 Posology and method of administration

Treatment should be initiated by healthcare professionals experienced in the diagnosis and treatment of conditions for which dupilumab is indicated (see section 4.1).

Posology

General

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.

Dupilumab can be used with or without topical corticosteroids. Topical calcineurin inhibitors may be used, but should be reserved for problem 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 for atopic dermatitis. Some patients with initial partial response may subsequently improve with continued treatment beyond 16 weeks.

Patients receiving concomitant oral corticosteroids may reduce their steroid dose once clinical improvement with dupilumab has occurred (see section 5.1). Steroid reductions should be accomplished gradually (see section 4.4).

Missed dose

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 dose 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
No dose adjustment for body weight is recommended (see section 5.2).

Paediatric patients

The safety and efficacy of dupilumab in children with atopic dermatitis below the age of 18 years have not been established (see section 5.2). No data are available.

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.

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

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 may self-inject dupilumab or the patient's caregiver may administer dupilumab if their healthcare professional determines that this is appropriate. Proper training should be provided to patients and/or caregivers on the preparation and administration of dupilumab prior to use according to the Instructions for Use (IFU) section in the 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. Very rare cases of serum sickness/serum sickness-like reactions have been reported in the atopic dermatitis development program following the administration of dupilumab (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.

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 DUPIXENT consider the potential effects on other atopic conditions.

Conjunctivitis and Keratitis

Conjunctivitis and keratitis occurred more frequently in subjects who received DUPIXENT. Conjunctivitis was the most frequently reported eye disorder. Most subjects with conjunctivitis recovered or were recovering during the treatment period [see Undesirable Effects].
Keratitis was reported in <1% of the DUPIXENT group (1 per 100 subject-years) and in 0% of the placebo group (0 per 100 subject-years) in the 16-week monotherapy trials. In the 52-week DUPIXENT + topical corticosteroids (TCS) trial, keratitis was reported in 4% of the DUPIXENT + TCS group (12 per 100 subject-years) and in 0% of the placebo + TCS group (0 per 100 subject-years). Most subjects with keratitis recovered or were recovering during the treatment period. (section 4.8)
Advise patients to report new onset or worsening eye symptoms to their healthcare provider.

Vaccinations

Live and live attenuated vaccines should not be given concurrently with dupilumab 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 dose, i.e. 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.

4.6 Fertility, pregnancy and lactation

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). 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

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 reactions have been reported in the atopic dermatitis development program (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 1 are adverse reactions observed in atopic dermatitis 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 atopic dermatitis

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

Description of selected adverse reactions in atopic dermatitis

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

Conjunctivitis and related events
Conjunctivitis occurred more frequently in atopic dermatitis patients who received dupilumab. Most patients with conjunctivitis recovered or were recovering during the treatment period. (see section 4.4).

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 (≥ 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 6 % of patients with atopic dermatitis 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.

Approximately 5 % of patients in the placebo groups in the 52 week studies were also positive for antibodies to dupilumab; approximately 2 % exhibited persistent ADA response and approximately 1% had neutralizing antibodies.

Less than 0.4 % 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

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-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 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 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 2,119 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 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.

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.

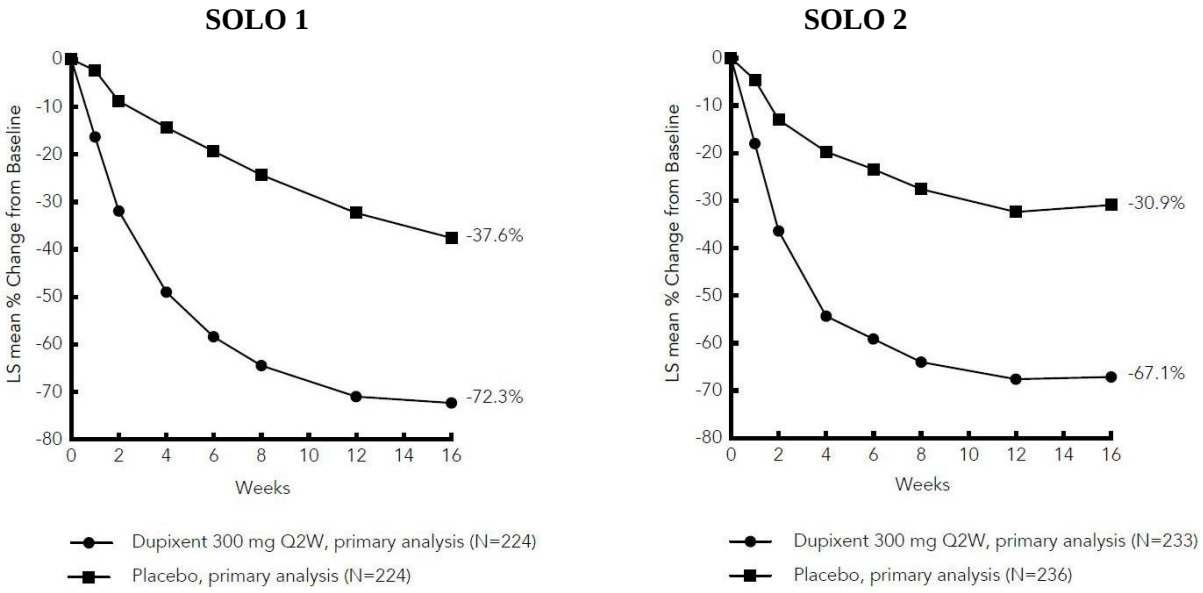
Table 2: Efficacy results of dupilumab monotherapy at week 16 (FAS)

	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]

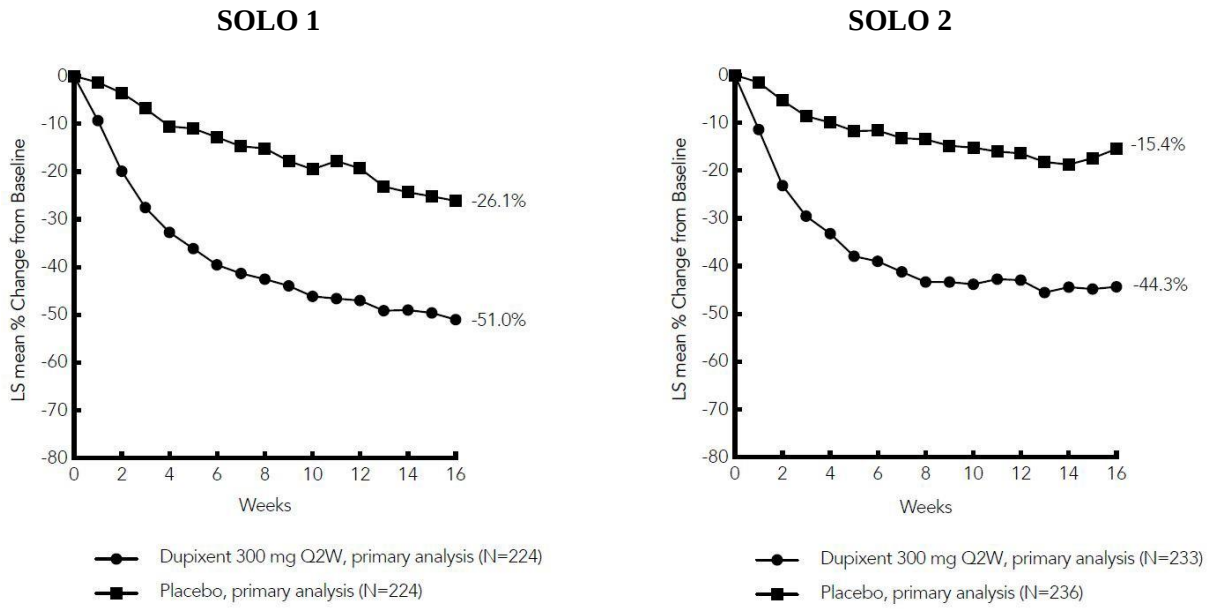
LS = least squares; SE= standard error
[a] Full analysis set (FAS) includes all patients randomized.
[b] Responder was defined as a patient with IGA 0 or 1 ("clear" or "almost clear") with a reduction of ≥ 2 points on a 0-4 IGA scale.
[c] Patients who received rescue treatment or with missing data were 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

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 pruritis NRS from baseline to week 16 and week 52 compared to placebo + TCS (see Table 3).

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 3: 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 cutoff 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 ($p < 0.05$).

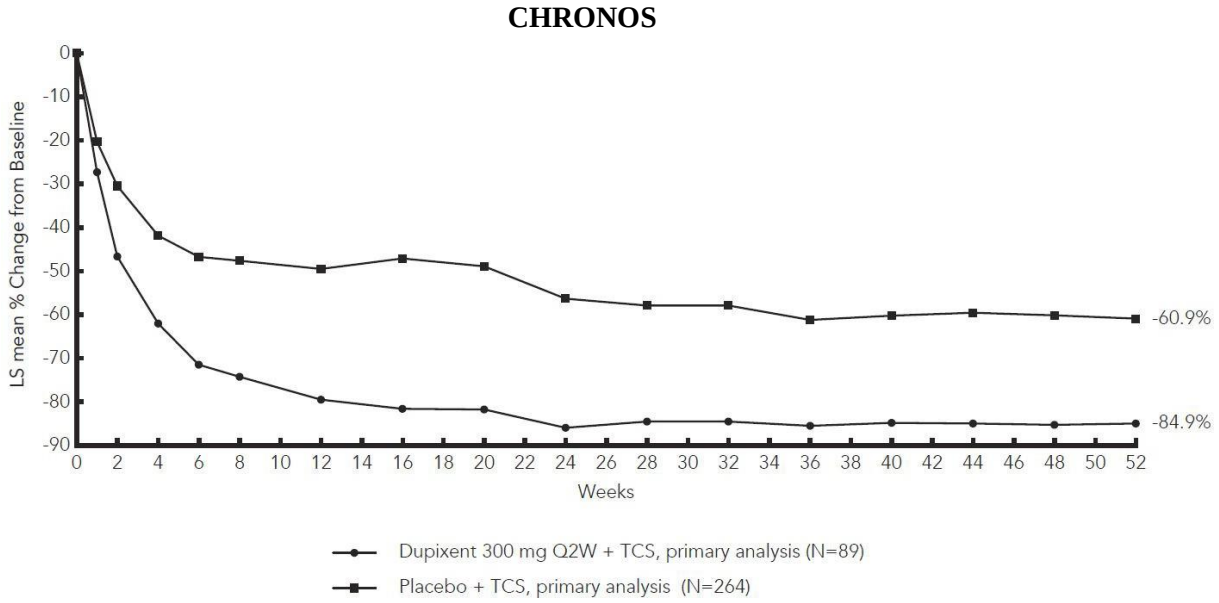
[f] p-value < 0.0001

[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]

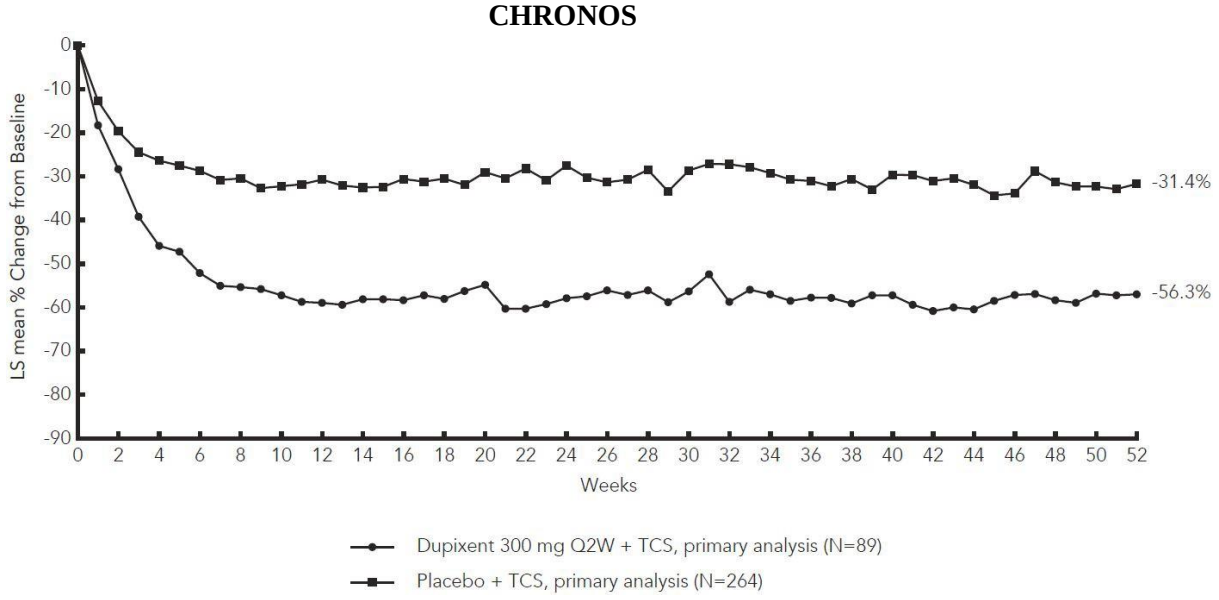


LS = least squares

[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 cutoff date of the primary analysis.

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



LS = least squares

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

[b]FAS week 52 includes all patients randomized at least one year before the cutoff 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 pruritis 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 4.

Table 4: 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 baseline (+/- SE)	-29.5 % (2.55)	-62.4 % (2.48)	-58.3 % (2.45)
DLQI, LS mean change from baseline (SE)	-4.5 (0.49)	-9.5 (0.46)	-8.8 (0.45)

(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 5.

Table 5: 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 6).

Table 6: 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 7).

Table 7: 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

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, ranging between 61% and 64 %, as determined by a population pharmacokinetics (PK) analysis.

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

Distribution

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

Biotransformation

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

Elimination

Dupilumab elimination is mediated by parallel linear and nonlinear pathways. At higher concentrations, dupilumab elimination is primarily through a non-saturable proteolytic pathway, while at lower concentrations, the non-linear saturable IL-4R α target-mediated elimination predominates. After the last steady state dose, the median time for dupilumab concentrations to decrease below the lower limit of detection, estimated 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 1,472 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 adult atopic dermatitis 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. However, there were only 61 patients over 65 years

of age included in this 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
Dupilumab trough concentrations were lower in subjects with higher body weight with no meaningful impact on efficacy.

Paediatric population
The pharmacokinetics of dupilumab in paediatric patients (< 18 years of age) with atopic dermatitis has not been studied.

5.3 Preclinical safety data

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

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

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

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

An enhanced pre- and post-natal developmental study revealed no adverse effects in maternal animals or their offspring up to 6 months post-partum/post-birth.

Fertility studies conducted in male and female mice using a surrogate antibody against IL-4Rα showed no impairment of fertility (see section 4.6).

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

arginine hydrochloride
histidine
polysorbate 80
sodium acetate trihydrate

glacial acetic acid
sucrose
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

24 months.

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

6.4 Special precautions for storage

Store refrigerated at 2°C to 8°C in the original carton to protect from light.
Do not freeze.
Do not expose to heat.
Do not shake.
Do not use beyond the expiry date stamped on the carton and container label.

6.5 Nature and contents of container

Pre-filled syringe with needle shield

DUPIXENT is supplied as a sterile, preservative-free, clear to slightly opalescent, colorless to pale yellow solution for subcutaneous injection. DUPIXENT is provided as a single dose in a 2.25-mL siliconized clear Type-1 glass pre-filled syringe with a fixed 27 gauge ½ inch, thin wall stainless steel staked needle and passive needle shield. The needle cap is not made with natural rubber latex.

Each pre-filled syringe is designed to deliver 300 mg of DUPIXENT in 2 mL (150 mg/mL) solution.

6.6 Special precautions for disposal and other handling

The instructions for the preparation and administration of DUPIXENT in a pre-filled syringe with needle shield are given in the package leaflet.

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 with needle shield from the refrigerator, it should be allowed to reach room temperature by waiting for 45 min before injecting DUPIXENT.

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 with needle shield 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. MARKETING AUTHORISATION HOLDER

sanofi-aventis (Thailand) Ltd.
Bangkok, Thailand.

8. MARKETING AUTHORISATION NUMBER(S)

1C XX/XX

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date-Month-Year

10. DATE OF REVISION OF THE TEXT