SmPC

DUPIXENT 200mg

1. NAME OF THE MEDICINAL PRODUCT

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

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Dupilumab 200 mg solution for injection in pre-filled syringe

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

Dupilumab 200 mg solution for injection in pre-filled pen

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

Dupilumab is a fully human monoclonal antibody 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 Therapeutic indications

Atopic dermatitis

Adults and adolescents
Dupixent is indicated for the treatment of moderate-to-severe atopic dermatitis in adults and adolescents 12 years and older who are candidates for systemic therapy.

Children 6 months to 11 years of age
Dupixent is indicated for the treatment of severe atopic dermatitis in children 6 months to 11 years old who are candidates for systemic therapy.

Asthma

Adults and adolescents
Dupixent is indicated in adults and adolescents 12 years and older as add-on maintenance treatment for severe asthma with type 2 inflammation characterised by raised blood eosinophils and/or raised fraction of exhaled nitric oxide (FeNO), see section 5.1, who are inadequately controlled with high dose inhaled corticosteroids (ICS) plus another medicinal product for maintenance treatment.

Children 6 to 11 years of age
Dupixent is indicated in children 6 to 11 years old as add-on maintenance treatment for severe asthma with type 2 inflammation characterised by raised blood eosinophils and/or raised fraction of exhaled nitric oxide (FeNO), see section 5.1, who are inadequately controlled with medium to high dose inhaled corticosteroids (ICS) plus another medicinal product for maintenance treatment.

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

Atopic dermatitis

Adults
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.

Adolescents (12 to 17 years of age)
The recommended dose of dupilumab for adolescent patients 12 to 17 years of age is specified in Table 1.

Table 1: Dose of dupilumab for subcutaneous administration in adolescent patients 12 to 17 years of age with atopic dermatitis

Body weight of patient	Initial dose	Subsequent doses (every other week)
less than 60 kg	400 mg (two 200 mg injections)	200 mg
60 kg or more	600 mg (two 300 mg injections)	300 mg

Children 6 to 11 years of age
The recommended dose of dupilumab for children 6 to 11 years of age is specified in Table 2.

Table 2: Dose of dupilumab for subcutaneous administration in children 6 to 11 years of age with atopic dermatitis

Body weight of patient	Initial dose	Subsequent doses
15 kg to less than 60 kg	300 mg (one 300 mg injection) on Day 1, followed by 300 mg on Day 15	300 mg every 4 weeks (Q4W)*, starting 4 weeks after Day 15 dose
60 kg or more	600 mg (two 300 mg injections)	300 mg every other week (Q2W)

*the dose may be increased to 200 mg Q2W in patients with body weight of 15 kg to less than 60 kg based on physician's assessment.

Children 6 months to 5 years of age
The recommended dose of dupilumab for children 6 months to 5 years of age is specified in Table 3.

Table 3: Dose of dupilumab for subcutaneous administration in children 6 months to 5 years of age with atopic dermatitis

Body Weight of Patient	Initial Dose	Subsequent Doses
5 kg to less than 15 kg	200 mg (one 200 mg injection)	200 mg every 4 weeks (Q4W)
15 kg to less than 30 kg	300 mg (one 300 mg injection)	300 mg every 4 weeks (Q4W)

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

Asthma

Adults and adolescents
The recommended dose of dupilumab for adults and adolescents (12 years of age and older) is:

- An initial dose of 400 mg (two 200 mg injections), followed by 200 mg given every other week administered as subcutaneous injection.
- For patients with severe asthma and who are on oral corticosteroids or for patients with severe asthma and co-morbid moderate-to-severe atopic dermatitis or adults with co-morbid severe chronic rhinosinusitis with nasal polyposis, an initial dose of 600 mg (two 300 mg injections), followed by 300 mg every other week administered as subcutaneous injection.

Children 6 to 11 years of age
The recommended dose of dupilumab for paediatric patients 6 to 11 years of age is specified in Table 4.

Table 4: Dose of dupilumab for subcutaneous administration in children 6 to 11 years of age with asthma

Body weight	Initial and subsequent doses
15 to less than 30 kg	300 mg every four weeks (Q4W)
30 kg to less than 60 kg	200 mg every other week (Q2W) or 300 mg every four weeks (Q4W)
60 kg or more	200 mg every other week (Q2W)

For paediatric patients (6 to 11 years old) with asthma and co-morbid severe atopic dermatitis, as per approved indication, the recommended dose should be followed in Table 2.

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).

Dupilumab is intended for long-term treatment. The need for continued therapy should be considered at least on an annual basis as determined by physician assessment of the patient's level of asthma control.

Missed dose

If a weekly dose is missed, administer the dose as soon as possible, starting a new schedule based on this date.

If an every other week dose is missed, administer the injection within 7 days from the missed dose and then resume the patient's original schedule. If the missed dose is not administered within 7 days, wait until the next dose on the original schedule.

If an every 4 week dose is missed, administer the injection within 7 days from the missed dose and then resume the patient's original schedule. If the missed dose is not administered within 7 days, administer the dose, starting a new schedule based on this date.

Special populations

Elderly (≥ 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 for patients with asthma 12 years of age and older or in adults with atopic dermatitis (see section 5.2).

Paediatric population
The safety and efficacy of dupilumab in children with atopic dermatitis below the age of 6 months have not been established. The safety and efficacy of dupilumab in children with a body weight < 5 kg have not been established. No data are available.

The safety and efficacy of dupilumab in children with severe asthma below the age of 6 years have not been established. No data are available.

Method of administration

Subcutaneous use

The dupilumab pre-filled pen is not intended for use in children below 12 years of age. For children 6 months to 11 years of age with atopic dermatitis, and asthma, the dupilumab pre-filled syringe is the presentation appropriate for administration to this population.

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.

Each pre-filled syringe or pre-filled pen is for single use only.

For the initial 400 mg dose, two 200 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 at the end of 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

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.

Acute asthma exacerbations

Dupilumab should not be used to treat acute asthma symptoms or acute exacerbations. Dupilumab should not be used to treat acute bronchospasm or status asthmaticus.

Corticosteroids

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).

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 (see section 4.8).

Eosinophilic conditions

Cases of eosinophilic pneumonia and cases of vasculitis consistent with eosinophilic granulomatosis with polyangiitis (EGPA) have been reported with dupilumab in adult patients who participated in the asthma development program. Cases of vasculitis consistent with EGPA have been reported with dupilumab and placebo in adult patients with co-morbid asthma in the CRSwNP development program. Physicians should be alert to vasculitic rash, worsening pulmonary symptoms, cardiac complications, and/or neuropathy presenting in their patients with eosinophilia. Patients being treated for asthma may present with serious systemic eosinophilia sometimes presenting with clinical features of eosinophilic pneumonia or vasculitis consistent with eosinophilic granulomatosis with polyangiitis, conditions which are often treated with systemic corticosteroid therapy. These events usually, but not always, may be associated with the reduction of oral corticosteroid therapy.

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. Cases of enterobiasis were reported in children 6 to 11 years old who participated in the paediatric asthma development program (see section 4.8).

Conjunctivitis and keratitis related events

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

Patients with comorbid asthma

Patients on dupilumab 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

Concurrent use of live and live attenuated vaccines with dupilumab should be avoided as clinical safety and efficacy have not been established. 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. Clinical data are not available to support more specific guidance for live or live attenuated vaccines administration in patients treated with dupilumab. Immune responses to TdaP vaccine and meningococcal polysaccharide vaccine were assessed (see section 4.5).

Sodium content

This medicinal product contains less than 1 mmol sodium (23 mg) per 200 mg dose, that is to say 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 atopic dermatitis 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 medicinal products is not expected. Based on the population analysis, commonly co-administered medicinal products had no effect on dupilumab pharmacokinetics on patients with moderate to severe asthma.

4.6 Fertility, pregnancy and lactation

Pregnancy

There is a 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 and use machines.

4.8 Undesirable effects

Summary of the safety profile

The most common adverse reactions in atopic dermatitis, asthma, and CRSwNP are injection site reactions (includes erythema, oedema, pruritus, pain and swelling), conjunctivitis, conjunctivitis allergic, arthralgia, oral herpes, and eosinophilia. An additional adverse reaction of injection site bruising was reported in EoE. Rare cases of serum sickness, serum sickness-like reaction, anaphylactic reaction, and ulcerative keratitis have been reported (see section 4.4).

Tabulated list of adverse reactions

The dupilumab safety data presented in Table 5 were predominantly derived from 12 randomised, placebo-controlled trials, including atopic dermatitis, asthma, and CRSwNP patients. These studies involved 4,206 patients receiving dupilumab and 2,326 patients receiving placebo during the controlled period are representative of the overall safety profile for dupilumab.

Listed in Table 5 are adverse reactions observed in clinical trials and/or postmarketing setting 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, adverse reactions are presented in order of decreasing seriousness.

Table 5: List of adverse reactions

MedDRA System Organ Class	**Frequency**	**Adverse Reaction**
Infections and infestations	Common	Conjunctivitis* Oral herpes*
Blood and lymphatic system disorders	Common	Eosinophilia
Immune system disorders	Uncommon Rare	Angioedema[#] Anaphylactic reaction Serum sickness reaction Serum sickness-like reaction
Eye disorders	Common Uncommon Rare	Conjunctivitis allergic* Keratitis*[#] Blepharitis*[†] Eye pruritus*[†] Dry eye*[†] Ulcerative keratitis*[†#]
Skin and subcutaneous tissue disorders	Uncommon	Facial rash[#]

Musculoskeletal and connective tissue disorders	Common	Arthralgia[#]
General disorders and administration site conditions	Common	Injection site reactions (includes erythema, oedema, pruritus, pain, swelling, and bruising)

*eye disorders and oral herpes occurred predominately in atopic dermatitis studies.
[†]the frequencies for eye pruritus, blepharitis, and dry eye were common and ulcerative keratitis was uncommon in atopic dermatitis studies.
[#]from postmarketing reporting.

Description of selected adverse reactions

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 compared to placebo in atopic dermatitis studies. Most patients with conjunctivitis or keratitis recovered or were recovering during the treatment period. In the long-term OLE atopic dermatitis study (AD-1225) at 5 years, the respective rates of conjunctivitis and keratitis remained similar to those in the dupilumab arm in the placebo controlled atopic dermatitis studies. Among asthma patients frequency of conjunctivitis and keratitis was low and similar between dupilumab and placebo. Among CRSwNP and Prurigo Nodularis (PN) patients the frequency of conjunctivitis was higher in dupilumab than placebo, though lower than that observed in atopic dermatitis patients. There were no cases of keratitis reported in the CRSwNP or PN development program. Among patients with EoE, the frequency of conjunctivitis was low and similar between dupilumab and placebo groups. There were no cases of keratitis in the EoE development program (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 adult studies. In the 52-week atopic dermatitis dupilumab + TCS adult study, eczema herpeticum was reported in 0.2 % of the dupilumab + TCS group and 1.9 % of the placebo + TCS group. These rates remained stable at 5 years in the long-term OLE study (AD-1225).

Eosinophilia
Dupilumab-treated patients had a greater mean initial increase from baseline in eosinophil count compared to patients treated with placebo in the atopic dermatitis, asthma, and CRSwNP indications. Eosinophil counts declined to near baseline levels during study treatment and returned to baseline during the asthma open-label extension safety study (TRAVERSE). The mean blood eosinophil levels decreased to below baseline by week 20 and was maintained up to 5 years in the long-term OLE study (AD-1225). Compared to placebo, no increase in mean blood eosinophil counts was observed in PN (PRIME and PRIME2). Mean and median blood eosinophil counts declined to near baseline or remained below baseline levels in EoE (TREET Parts A and B) during study treatment.

Treatment-emergent eosinophilia (≥ 5,000 cells/mcL) was reported in < 3 % of dupilumab-treated patients and < 0.5 % in placebo-treated patients (SOLO1, SOLO2, AD-1021, DRI12544, QUEST, and VOYAGE; SINUS-24 and SINUS-52; PRIME and PRIME2; TREET Parts A and B studies) .

Treatment-emergent eosinophilia (≥5,000 cells/mcL) was reported in 8.4% of dupilumab-treated patients and 0% in placebo-treated patients in study AD-1539, with median eosinophil counts declining below baseline at end of treatment period.

Infections
In the 16-week atopic dermatitis monotherapy clinical adult 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 adult study, serious infections were reported in 0.6 % of patients treated with placebo and 0.2 % of patients treated with dupilumab. The rates of serious infections remained stable at 5 years in the long-term OLE study (AD-1225).

No increase was observed in the overall incidence of infections with dupilumab compared to placebo in the safety pool for asthma clinical studies. In the 24-week safety pool, serious infections were reported in 1.0% of patients treated with dupilumab and 1.1% of patients treated with placebo. In the 52-week QUEST study, serious infections were reported in 1.3% of patients treated with dupilumab and 1.4% of patients treated with placebo.

No increase was observed in the overall incidence of infections with dupilumab compared to placebo in the safety pool for CRSwNP clinical studies. In the 52-week SINUS-52 study, serious infections were reported in 1.3% of patients treated with dupilumab and 1.3 % of patients treated with placebo. No increase was observed in the overall incidence of infections with dupilumab compared to placebo in the safety pool for PN clinical studies. In the safety pool, serious infections were reported in 1.3% of patients treated with dupilumab and 1.3% of patients treated with placebo.

The overall incidence of infections was numerically higher with dupilumab (32.0%) compared to placebo (24.8%) in the safety pool for EoE TREET (Parts A and B) studies. In the 24-week safety pool, serious infections were reported in 0.5% of patients treated with dupilumab and 0% of patients treated with placebo.

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 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 adult patients with PN who received dupilumab 300 mg Q2W for 24 weeks, paediatric patients (6 months to 11 years of age) with atopic dermatitis who received either dupilumab 200 mg Q2W, 200 mg Q4W or 300 mg Q4W for 16 weeks and patients (6 to 11 years of age) with asthma who received dupilumab 100 mg Q2W or 200 mg Q2W for 52 weeks. Similar ADA responses were observed in adult patients with atopic dermatitis treated with dupilumab for up to 5 years in the long-term OLE study (AD-1225).

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.

Approximately 9 % of patients with asthma who received dupilumab 200 mg Q2W for 52 weeks developed antibodies to dupilumab; approximately 4 % exhibited persistent ADA responses and approximately 4 % had neutralizing antibodies.

Approximately 1% of patients with EoE who received dupilumab 300 mg QW or 300 mg Q2W for 24 weeks developed antibodies to dupilumab; 0% exhibited persistent ADA responses and approximately 0.5% had neutralizing antibodies.

Regardless of age or population, upto 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

Atopic dermatitis

Adolescents (12 t o17 years of age)
The safety of dupilumab was assessed in a study of 250 patients 12 to 17 years of age with moderate-to-severe atopic dermatitis (AD-1526). 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.

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

Children 6 months to 5 years of age
The safety of dupilumab with concomitant TCS was assessed in a study of 161 patients 6 months to 5 years of age with moderate-to-severe atopic dermatitis, which included a subgroup of 124 patients with severe atopic dermatitis (AD-1539). The safety profile of dupilumab with concomitant TCS in these patients, through week 16 was similar to the safety profile from studies in adults and paediatric patients 6 to 17 years of age with atopic dermatitis.

Atopic Hand and Foot Dermatitis
The safety of dupilumab was assessed in 27 paediatric patients 12 to 17 years of age with moderate-to-severe atopic hand and foot dermatitis (AD-1924). The safety profile of dupilumab in these patients through Week 16 was consistent with the safety profile from studies in adult and paediatric patients 6 months of age and older with moderate-to-severe AD.

Asthma

Adolescents (12 t o17 years of age)
A total of 107 adolescents aged 12 to 17 years with asthma were enrolled in the 52 week QUEST study. The safety profile observed was similar to that seen in adults.

The long-term safety of dupilumab was assessed in 89 adolescent patients who were enrolled in an open-label extension study in moderate-to-severe asthma (TRAVERSE). In this study, patients were followed for up to 96 weeks. The safety profile of dupilumab in TRAVERSE was consistent with the safety profile observed in pivotal asthma studies for up to 52 weeks of treatment.

Children 6 to 11 years of age
In children 6 to 11 years of age with moderate-to-severe asthma (VOYAGE), the additional adverse reaction of enterobiasis was reported in 1.8 % (5 patients) in the dupilumab groups and none in the placebo group. All enterobiasis cases were mild to moderate and patients recovered with anti-helminth treatment without dupilumab treatment discontinuation.

In children 6 to 11 years of age with moderate-to-severe asthma, eosinophilia (blood eosinophils ≥ 3,000 cells/mcL or deemed by the investigator to be an adverse event) was reported in 6.6 % of the dupilumab groups and 0.7% in the placebo group. Most eosinophilia cases were mild to moderate and not associated with clinical symptoms. These cases were transient, decreased over time, and did not lead to dupilumab treatment discontinuation.

The long-term safety of dupilumab was assessed in an open-label extension study (EXCURSION) in children 6 to 11 years of age with moderate-to-severe asthma who previously participated in VOYAGE. Among 365 patients who entered EXCURSION, 350 completed 52 weeks of treatment and 228 patients completed a cumulative treatment duration of 104 weeks (VOYAGE and EXCURSION). The long-term safety profile of dupilumab in EXCURSION was consistent with the safety profile observed in the pivotal asthma study (VOYAGE) for 52 weeks of treatment.

EoE
A total of 99 adolescents aged 12 to 17 years with EoE were enrolled in the TREET (Parts A and B) studies. The safety profile observed was similar to that seen in adults.

Long-term safety

Atopic dermatitis
The safety profile of dupilumab + TCS (CHRONOS) in adult atopic dermatitis patients) through week 52 was consistent with the safety profile observed at week 16. The long-term safety of dupilumab was assessed in an open-label extension study in patients 6 months to 17 years of age with moderate-to-severe atopic dermatitis (AD-1434). The safety profile of dupilumab in patients followed through week 52 was similar to the safety profile observed at week 16 in the AD-1526, AD-1652, and AD-1539 studies. The long-term safety profile of dupilumab observed in children and adolescents was consistent with that seen in adults with atopic dermatitis.

In a phase 3, multicentre, open label extension (OLE) study (AD-1225), the long-term safety of repeat doses of dupilumab was assessed in 2,677 adults with moderate-to-severe AD exposed to 300 mg weekly dosing (99.7 %), including 179 who completed at least 260 weeks of the study. The long-term safety profile observed in this study up to 5 years was generally consistent with the safety profile of dupilumab observed in controlled studies.

Asthma
The safety profile of dupilumab in the 96 weeks long term safety study (TRAVERSE) was consistent with the safety profile observed in pivotal asthma studies for up to 52 weeks of treatment.

The safety profile of dupilumab in children with asthma 6 to 11 years of age who participated in the 52 weeks long-term safety study (EXCURSION) was consistent with the safety profile observed in the pivotal asthma study (VOYAGE) for 52 weeks of treatment.

CRSwNP
The safety profile of dupilumab in adults with CRSwNP through week 52 was consistent with the safety profile observed at week 24.

Eosinophilic esophagitis

The safety profile of dupilumab through week 52 was generally consistent with the safety profile observed at week 24.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via:

Belgium: Federal Agency for Medicines and Health Products: www.afmps.be – Vigilance Division: Website: www.notifieruneffetindesirable.be – E-mail: adr@fagg-afmps.be
Luxembourg: Centre Régional de Pharmacovigilance de Nancy ou Division de la pharmacie et des médicaments de la Direction de la santé – Website: www.guichet.lu/pharmacovigilance

The Netherlands: Nederlands Bijwerkingen Centrum Lareb – Website: www.lareb.nl

4.9 Overdose

There is no specific treatment for dupilumab overdose. In the event of overdose, the patient should be monitored 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 and asthma. 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 in adults and adolescents with atopic dermatitis.

In adult and adolescent patients with asthma, dupilumab treatment relative to placebo markedly decreased FeNO and circulating concentrations of eotaxin-3, total IgE, allergen specific IgE, TARC, and periostin, the type 2 biomarkers evaluated in clinical trials. These reductions in type 2 inflammatory biomarkers were comparable for the 200 mg Q2W and 300 mg Q2W regimens. In paediatric (6 to 11 years of age) patients with asthma, dupilumab treatment relative to placebo markedly decreased FeNO and circulating concentrations of total IgE, allergen specific IgE, and TARC, the type 2 biomarkers evaluated in clinical trials. These markers were near maximal suppression after 2 weeks of treatment, except for IgE which declined more slowly. These effects were sustained throughout treatment.

Clinical efficacy and safety in atopic dermatitis

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 ≥10 %. Eligible patients enrolled into this study had previous inadequate response to topical medication.

Patients received dupilumab was administered by subcutaneous (SC) injections either as: 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; or 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. 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 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.

Clinical Response

The efficacy results at week 16 for adolescent atopic dermatitis study are presented in Table 6.

Table 6: 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 randomised	**85[a]**	**82[a]**
IGA 0 or 1[b], % responders[c]	2.4 %	24.4 %[d]
EASI-50, % responders[c]	12.9 %	61.0 %[d]
EASI-75, % responders[c]	8.2 %	41.5 %[d]
EASI-90, % responders[c]	2.4 %	23.2 %[d]
EASI, LS mean % change from baseline (+/-SE)	-23.6 % (5.49)	-65.9 %[d] (3.99)
Pruritus NRS, LS mean % change from baseline (+/-SE)	-19.0 % (4.09)	-47.9 %[d] (3.43)
Pruritus NRS (≥ 4-point improvement), % responders[c]	4.8 %	36.6 %[d]
CDLQI, LS mean change from baseline (+/-SE)	-5.1 (0.62)	-8.5[d] (0.50)
CDLQI, (≥ 6-point improvement), % responders	19.7 %	60.6 %[e]
POEM, LS mean change from baseline (+/- SE)	-3.8 (0.96)	-10.1[d] (0.76)
POEM, (≥ 6-point improvement), % responders	9.5 %	63.4 %[e]

[a]full Analysis Set (FAS) includes all patients randomised.

[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).

[d]p –value < 0.0001(statistically significant vs placebo with adjustment for multiplicity)

[e]nominal p-value < 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.

The dupilumab group significantly improved patient-reported symptoms, the impact of AD on sleep and health-related quality of life as measured by POEM 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.

Paediatrics (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 severe 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 ≥ 15 %. Eligible patients enrolled into this trial had previous inadequate response to topical medication. Enrollment 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.

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 co-primary endpoint was the proportion of patients with IGA 0 or 1 (“clear” or “almost clear”) at 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.

Clinical Response

Table 7 presents the results by baseline weight strata for the approved dose regimens.

Table 7: 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=122)	(N=123)	(N=59)	(N=62)
	≥ 15 kg	≥ 15 kg	≥ 30 kg	≥ 30 kg
IGA 0 or 1[b], % responders[c]	32.8 %[f]	11.4 %	39.0 %[h]	9.7 %
EASI-50, % responders[c]	91.0 %[f]	43.1 %	86.4 %[g]	43.5 %
EASI-75, % responders[c]	69.7 %[f]	26.8 %	74.6 %[g]	25.8 %
EASI-90, % responders[c]	41.8 %[f]	7.3 %	35.6 %[h]	8.1 %
EASI, LS mean % change from baseline (+/-SE)	-82.1 %[f] (2.37)	-48.6 % (2.46)	-80.4 %[g] (3.61)	-48.3 % (3.63)
Pruritus NRS, LS mean % change from baseline (+/- SE)	-54.6 %[f] (2.89)	-25.9 % (2.90)	-58.2 %[g] (4.01)	-25.0 % (3.95)
Pruritus NRS (≥ 4-point improvement), % responders[c]	50.8 %[f]	12.3 %	61.4 %[g]	12.9 %
CDLQI, LS mean change from baseline (+/-SE)	-10.6[f] (0.47)	-6.4 (0.51)	-9.8[g] (0.63)	-5.6 (0.66)
CDLQI, (≥ 6-point improvement), % responders	77.3 %[g]	38.8 %	80.8 %[g]	35.8 %
POEM, LS mean change from baseline (+/- SE)	-13.6[f] (0.65)	-5.3 (0.69)	-13.6[g] (0.90)	-4.7 (0.91)
POEM, (≥ 6-point improvement), % responders	81.7 %[g]	32.0 %	79.3 %[g]	31.1 %

[a]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 400 mg (baseline weight ≥ 30 kg) of dupilumab.
[f]p-value < 0.0001 (statistically significant vs placebo with adjustment for multiplicity)
[g]nominal p-values < 0.0001
[h]nominal p-value = 0.0002

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).

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

The long-term efficacy and safety of dupilumab + TCS in paediatric patients with moderate to severe 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. Some patients receiving dupilumab 300 mg Q4W + TCS showed further clinical benefit when escalated to dupilumab 200 mg Q2W + TCS. The safety profile of dupilumab in patients followed through week 52 was similar to the safety profile observed at week 16 in the AD-1526 and AD-1652 studies.

Paediatrics (6 Months to 5 years of age)

The efficacy and safety of dupilumab + TCS in paediatric patients was evaluated in a multicentre, randomised, double-blind, placebo-controlled study (AD-1539) in 162 patients 6 months to 5 years of

age, with moderate-to-severe AD (ITT population) defined by an IGA score ≥ 3 (scale of 0 to 4), an EASI score ≥ 16 (scale of 0 to 72), and a minimum BSA involvement of ≥ 10. Of the 162 patients, 125 patients had severe AD defined by an IGA score of 4. Eligible patients enrolled into this study had previous inadequate response to topical medication. Enrollment was stratified by baseline weight (≥ 5 to < 15 kg and ≥ 15 to < 30 kg).

Patients in the dupilumab Q4W + TCS group with baseline weight of ≥ 5 to < 15 kg received an initial dose of 200 mg on Day 1, followed by 200 mg Q4W from week 4 to week 12, and patients with baseline weight of ≥ 15 to < 30 kg received an initial dose of 300 mg on Day 1, followed by 300 mg Q4W from week 4 to week 12. Patients were permitted to receive rescue treatment at the discretion of the investigator. Patients who received rescue treatment were considered non-responders.

In AD-1539, the mean age was 3.8 years, the median weight was 16.5 kg, 38.9% of patients were female, 68.5% were White, 18.5% were Black, and 6.2% were Asian. At baseline, the mean BSA involvement was 58.4%, and 15.5% had received prior systemic non-steroidal immunosuppressants. Also, at baseline the mean EASI score was 34.1, and the weekly average of daily worst itch score was 7.6 on a scale of 0-10. Overall, 81.4% of patients had at least one co-morbid allergic condition; 68.3% had food allergies, 52.8% had other allergies, 44.1% had allergic rhinitis, and 25.5% had asthma.

These baseline disease characteristics were comparable between moderate-to-severe and severe AD populations.

The co-primary endpoint was the proportion of patients with IGA 0 or 1 ("clear" or "almost clear") at 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. The primary endpoint was the proportion of patients with an IGA 0 (clear) or 1 (almost clear) at week 16.

Clinical Response

The efficacy results at week 16 for AD-1539 are presented in Table 8.

Table 8: Efficacy results of dupilumab with concomitant TCS in AD-1539 at Week 16 (FAS)[a]

	Dupilumab 200 mg (5 to < 15kg) or 300 mg (15 to < 30 kg) Q4W[d]+ TCS (ITT population)(N=83)[a]	**Placebo + TCS (ITT population) (N=79)**	**Dupilumab 200 mg (5 to < 15kg) or 300 mg (15 to < 30 kg) Q4W[d]+ TCS (severe AD population) (N=63)**	**Placebo + TCS (severe AD population) (N=62)**
IGA 0 or 1[b,c]	27.7%[e]	3.9%	14.3%[f]	1.7%
EASI-50, % responders[c]	68.7%[e]	20.2%	60.3%[g]	19.2%
EASI-75[c]	53.0%[e]	10.7%	46.0%[g]	7.2%
EASI-90[c]	25.3%[e]	2.8%	15.9%[h]	0%
EASI, LS mean % change from baseline (+/-SE)	-70.0%[e] (4.85)	-19.6% (5.13)	-55.4%[g] (5.01)	-10.3% (5.16)
Worst scratch/itch NRS, LS mean % change from baseline (+/-SE) *	-49.4%[e] (5.03)	-2.2% (5.22)	-41.8[g] (5.35)	0.5 (5.40)
Worst Scratch/Itch NRS (≥4-point improvement)[c] *	48.1%[e]	8.9%	42.3%[i]	8.8%
Patient's sleep quality NRS, LS mean change from baseline (+/-SE)*	2.0[e] (0.25)	0.3 (0.26)	1.7[g] (0.25)	0.2 (0.25)

Patient's skin pain NRS, LS mean change from baseline (+/- SE)*	-3.9[e] (0.30)	-0.6 (0.30)	-3.4[g] (0.29)	-0.3 (0.29)
POEM, LS mean change from baseline (+/- SE)*	-12.9[e] (0.89)	-3.8 (0.92)	-10.6[g] (0.93)	-2.5 (0.95)

[a]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 (62% and 19% in the placebo and dupilumab arms, respectively) or with missing data were considered as non-responders.

[d]At Day 1, patients received 200 mg (5 to <15kg) or 300 mg (15 to <30 kg) of dupilumab.

[e]p–values < 0.0001,[f]nominal p-value < 0.05, [g]nominal p-value < 0.0001, [h]nominal p-value < 0.005, [i]nominal p-value < 0.001

*Caregiver reported outcome

A significantly greater proportion of patients randomised to dupilumab + TCS achieved a rapid improvement in the Worst Scratch/Itch NRS compared to placebo + TCS (defined as ≥ 4-point improvement as early as week 3, nominal p< 0.005) and the proportion of patients responding on the Worst Scratch/Itch NRS continued to increase through the treatment period.

In this study, dupilumab significantly improved health-related quality of life as measured by the CDLQI (in 85 patients 4 to 5 years old) and IDQOL (in 77 patients 6 months to 3 years old). In the ITT population, greater LS mean changes in CDLQI and IDQOL scores from baseline to week 16 were observed in the dupilumab + TCS (-10.0 and -10.9) group compared to the placebo + TCS group (-2.5 and -2.0), respectively (p< 0.0001). Similar improvements in both CDLQI and IDQOL were observed in the severe AD population.

The long-term efficacy and safety of dupilumab + TCS in paediatric patients with moderate to severe atopic dermatitis who had participated in the previous clinical trials of dupilumab + TCS were assessed in an open-label extension study (AD-1434). Efficacy data from this trial suggest that clinical benefit provided at week 16 was sustained through week 52. The safety profile of dupilumab in patients followed through week 52 was similar to the safety profile observed at week 16 in the AD-1539 study.

Atopic Hand and Foot Dermatitis (adults and adolescents)

The efficacy and safety of dupilumab was evaluated in a 16-week multicenter, randomized, double-blind, parallel-group, placebo-controlled trial (AD-1924) in 133 adult and paediatric patients 12 to 17 years of age with moderate-to-severe atopic hand and foot dermatitis, defined by an IGA (hand and foot) score ≥3 (scale of 0 to 4) and a hand and foot Peak Pruritus Numeric Rating Scale (NRS) score for maximum itch intensity ≥4 (scale of 0 to 10). Eligible patients had previous inadequate response or intolerance to treatment of hand and foot dermatitis with topical AD medications.

In AD-1924, 38% of patients were male, 80% were White, 72% of subjects had a baseline IGA (hand and foot) score of 3 (moderate atopic hand and foot dermatitis), and 28% of patients had a baseline IGA (hand and foot) score of 4 (severe atopic hand and foot dermatitis). The baseline weekly averaged hand and foot Peak Pruritus NRS score was 7.1.

The primary endpoint was the proportion of patients with an IGA hand and foot score of 0 (clear) or 1 (almost clear) at Week 16. The key secondary endpoint was reduction of itch as measured by the hand and foot Peak Pruritus NRS (≥4-point improvement). Other patient reported outcomes included assessment of hand and foot skin pain NRS (0-10), quality of sleep NRS (0-10), quality of life in Hand Eczema Questionnaire (0-117) (QoLHEQ) and work productivity and impairment (WPAI) (0-100%).

The proportion of patients with an IGA (hand and foot) 0 to 1 at Week 16 was 40.3% for dupilumab and 16.7% for placebo (treatment difference 23.6, 95% CI: 8.84, 38.42). The proportion of patients with improvement (reduction) of weekly averaged hand and foot Peak Pruritus NRS ≥4 at Week 16 was 52.2% for dupilumab and 13.6% for placebo (treatment difference 38.6, 95% CI: 24.06, 53.15).

Greater improvements for hand and foot skin pain NRS, quality of sleep NRS, QoLHEQ score and WPAI overall work impairment and routine activity impairment from baseline to week 16 were seen in the dupilumab group as compared to the placebo group (LS mean change of dupilumab vs placebo: -4.66 vs -1.93 [$p < 0.0001$], 0.88 vs -0.00 [$p < 0.05$], -40.28 vs -16.18 [$p < 0.0001$], -38.57% vs -22.83% [nominal $p<0.001$] and -36.39% vs -21.26% [nominal $p < 0.001$] respectively).

Adults with atopic dermatitis

For clinical data in adults with atopic dermatitis please refer to the dupilumab 300 mg Summary of Product Characteristics.

Clinical efficacy and safety in asthma

The asthma development program included three randomised, double-blind, placebo-controlled, parallel-group, multi-centre studies (DRI12544, QUEST, and VENTURE) of 24 to 52 weeks in treatment duration which enrolled a total of 2,888 patients (12 years of age and older). Patients were enrolled without requiring a minimum baseline blood eosinophil or other type 2 inflammatory biomarkers (e.g. FeNO or IgE) level. Asthma treatment guidelines define type 2 inflammation as eosinophilia ≥ 150 cells/mcL and/or FeNO ≥ 20 ppb. In DRI12544 and QUEST, the pre-specified subgroup analyses included blood eosinophils ≥ 150 and ≥ 300 cells/mcL, FeNO ≥ 25 and ≥ 50 ppb.

DRI12544 was a 24-week dose-ranging study which included 776 patients (18 years of age and older). Dupilumab compared with placebo was evaluated in adult patients with moderate to severe asthma on a medium-to-high dose inhaled corticosteroid and a long acting beta agonist. The primary endpoint was change from baseline to week 12 in FEV_1 (L). Annualised rate of severe asthma exacerbation events during the 24-week placebo controlled treatment period was also determined. Results were evaluated in the overall population (unrestricted by minimum baseline eosinophils or other type 2 inflammatory biomarkers) and subgroups based on baseline blood eosinophil count.

QUEST was a 52-week confirmatory study which included 1,902 patients (12 years of age and older). Dupilumab compared with placebo was evaluated in 107 adolescent and 1,795 adult patients with persistent asthma on a medium-to-high dose inhaled corticosteroid (ICS) and a second controller medication. Patients requiring a third controller were allowed to participate in this trial. The primary endpoints were the annualised rate of severe exacerbation events during the 52-week placebo controlled period and change from baseline in pre-bronchodilator FEV_1 at week 12 in the overall population (unrestricted by minimum baseline eosinophils or other type 2 inflammatory biomarkers) and subgroups based on baseline blood eosinophil count and FeNO.

VENTURE was a 24-week oral corticosteroid-reduction study in 210 patients with asthma unrestricted by baseline type 2 biomarker levels who required daily oral corticosteroids in addition to regular use of high dose inhaled corticosteroids plus an additional controller. The OCS dose was optimized during the screening period. Patients continued to receive their existing asthma medicine during the study; however their OCS dose was reduced every 4 weeks during the OCS reduction phase (week 4-20), as long as asthma control was maintained. The primary endpoint was the percent reduction in oral corticosteroid dose assessed in the overall population, based on a comparison of the oral corticosteroid dose at weeks 20 to 24 that maintained asthma control with the previously optimized (at baseline) oral corticosteroid dose.

The demographics and baseline characteristics of these 3 studies are provided in Table 9 below.

Table 9: Demographics and baseline characteristics of asthma trials

Parameter	DRI12544 (n = 776)	QUEST (n = 1902)	VENTURE (n=210)
Mean age (years) (SD)	48.6 (13.0)	47.9 (15.3)	51.3 (12.6)
% Female	63.1	62.9	60.5
% White	78.2	82.9	93.8
Duration of Asthma (years), mean ± SD	22.03 (15.42)	20.94 (15.36)	19.95 (13.90)
Never smoked, (%)	77.4	80.7	80.5
Mean exacerbations in previous year ± SD	2.17 (2.14)	2.09 (2.15)	2.09 (2.16)
High dose ICS use (%)[a]	49.5	51.5	88.6
Pre-dose FEV_1 (L) at baseline ± SD	1.84 (0.54)	1.78 (0.60)	1.58 (0.57)
Mean percent predicted FEV_1 at baseline (%)(± SD)	60.77 (10.72)	58.43 (13.52)	52.18 (15.18)
% Reversibility (± SD)	26.85 (15.43)	26.29 (21.73)	19.47 (23.25)
Mean ACQ-5 score (± SD)	2.74 (0.81)	2.76 (0.77)	2.50 (1.16)
Mean AQLQ score (± SD)	4.02 (1.09)	4.29 (1.05)	4.35 (1.17)
Atopic Medical History % Overall (AD %, NP %, AR %)	72.9 (8.0, 10.6, 61.7)	77.7 (10.3, 12.7, 68.6)	72.4 (7.6, 21.0, 55.7)
Mean FeNO ppb (± SD)	39.10 (35.09)	34.97 (32.85)	37.61 (31.38)
% patients with FeNO ppb ≥ 25 ≥ 50	 49.9 21.6	 49.6 20.5	 54.3 25.2
Mean total IgE IU/mL **(±** SD)	435.05 (753.88)	432.40 (746.66)	430.58 (775.96)
Mean baseline Eosinophil count (± SD) cells/mcL	350 (430)	360 (370)	350 (310)
% patients with EOS ≥ 150 cells/mcL ≥ 300 cells/mcL	 77.8 41.9	 71.4 43.7	 71.4 42.4

ICS = inhaled corticosteroid; FEV_1 = Forced expiratory volume in 1 second; ACQ-5 = Asthma Control Questionnaire-5; AQLQ = Asthma Quality of Life Questionnaire; AD = atopic dermatitis; NP = nasal polyposis; AR = allergic rhinitis; FeNO = fraction of exhaled nitric oxide; EOS = blood eosinophil

[a]the population in dupilumab asthma trials included patients on medium and high dose ICS. The medium ICS dose was defined as equal to 500 mcg fluticasone or equivalent per day.

Exacerbations

In the overall population in DRI12544 and QUEST subjects receiving either dupilumab 200 mg or 300 mg every other week had significant reductions in the rate of severe asthma exacerbations compared to placebo. There were greater reductions in exacerbations in subjects with higher baseline levels of type 2 inflammatory biomarkers such as blood eosinophils or FeNO (Table 10 and Table 11).

Table 10: Rate of severe exacerbations in DRI12544 and QUEST (baseline blood eosinophil levels ≥ 150 and ≥ 300 cells/mcL)

Treatment	Baseline blood EOS							
	≥150 cells/mcL				≥300 cells/mcL			
	Exacerbations per Year			% reduction	Exacerbations per Year			% reduction
	N	Rate (95% CI)	Rate ratio (95%CI)		N	Rate (95% CI)	Rate ratio (95%CI)	
All Severe Exacerbations								
DRI12544 study								
Dupilumab 200 mg Q2W	120	0.29 (0.16, 0.53)	0.28[a] (0.14, 0.55)	72 %	65	0.30 (0.13, 0.68)	0.29[c] (0.11, 0.76)	71 %
Dupilumab 300 mg Q2W	129	0.28 (0.16, 0.50)	0.27[b] (0.14, 0.52)	73 %	64	0.20 (0.08, 0.52)	0.19[d] (0.07, 0.56)	81 %
Placebo	127	1.05 (0.69, 1.60)			68	1.04 (0.57, 1.90)		
QUEST study								
Dupilumab 200 mg Q2W	437	0.45 (0.37, 0.54)	0.44[f] (0.34,0.58)	56 %	264	0.37 (0.29, 0.48)	0.34[f] (0.24,0.48)	66 %
Placebo	232	1.01 (0.81, 1.25)			148	1.08 (0.85, 1.38)		
Dupilumab 300 mg Q2W	452	0.43 (0.36, 0.53)	0.40 [e] (0.31,0.53)	60 %	277	0.40 (0.32, 0.51)	0.33[e] (0.23,0.45)	67 %
Placebo	237	1.08 (0.88, 1.33)			142	1.24 (0.97, 1.57)		

[a]p-value = 0.0003, [b]p-value = 0.0001, [c]p-value = 0.0116, [d]p-value = 0.0024, [e]p-value < 0.0001 (all statistically significant vs placebo with adjustment for multiplicity); [f]nominal p-value < 0.0001

Table 11: Rate of severe exacerbations in QUEST defined by baseline FeNO subgroups

Treatment	Exacerbations per Year			% reduction
	N	Rate (95% CI)	Rate ratio (95%CI)	
FeNO ≥ 25 ppb				
Dupilumab 200 mg Q2W	299	0.35 (0.27, 0.45)	0.35 (0.25, 0.50)[a]	65 %
Placebo	162	1.00 (0.78, 1.30)		
Dupilumab 300 mg Q2W	310	0.43 (0.35, 0.54)	0.39 (0.28, 0.54) [a]	61 %
Placebo	172	1.12 (0.88, 1.43)		
FeNO ≥ 50 ppb				
Dupilumab 200 mg Q2W	119	0.33 (0.22, 0.48)	0.31 (0.18, 0.52) [a]	69 %
Placebo	71	1.057 (0.72, 1.55)		
Dupilumab 300 mg Q2W	124	0.39 (0.27, 0.558)	0.31 (0.19, 0.49) [a]	69 %
Placebo	75	1.27 (0.90, 1.80)		

[a]nominal p-value < 0.0001

In the pooled analysis of DRI12544 and QUEST, hospitalisations and/or emergency room visits due to severe exacerbations were reduced by 25.5 % and 46.9 % with dupilumab 200 mg or 300 mg every other week, respectively.

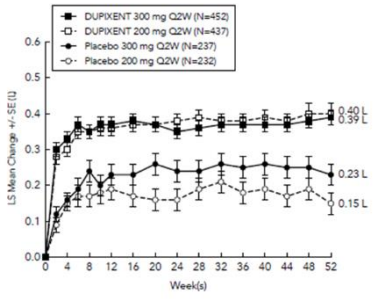
Lung function

Clinically significant increases in pre-bronchodilator FEV_1 were observed at week 12 for DRI12544 and QUEST. There were greater improvements in FEV_1 in the subjects with higher baseline levels of type 2 inflammatory biomarkers such as blood eosinophils or FeNO (Table 12 and Table 13).

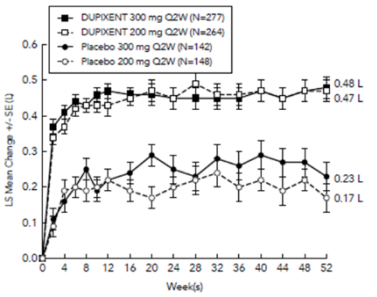
Significant improvements in FEV_1 were observed as early as week 2 following the first dose of dupilumab for both the 200 mg and 300 mg dose strengths and were maintained through week 24 (DRI12544) and week 52 in QUEST (see Figure 1).

Figure 1: Mean change from baseline in pre-bronchodilator FEV_1 (L) over time (baseline eosinophils ≥ 150 and ≥ 300 cells/mcL and FeNO ≥25 ppb) in QUEST

QUEST: blood eosinophils ≥ 150 cells/mcL



QUEST: blood eosinophils ≥ 300 cells/mcL



QUEST: FeNO ≥ 25 ppb

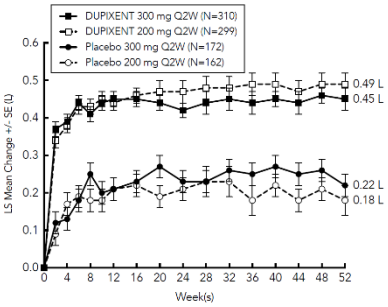


Table 12: Mean change from baseline in pre-bronchodilator FEV_1 at week 12 in DRI12544 and QUEST (baseline blood eosinophil Levels ≥ 150 and ≥ 300 cells/mcL)

Treatment	Baseline blood EOS					
	≥ 150 cells/mcL			≥ 300 cells/mcL		
	N	LS mean Δ from baseline L (%)	LS mean difference vs. placebo (95% CI)	N	LS mean Δ from baseline L (%)	LS mean difference vs. placebo (95% CI)
DRI12544 study						
Dupilumab 200 mg Q2W	120	0.32 (18.25)	0.23[a] (0.13, 0.33)	65	0.43 (25.9)	0.26[c] (0.11, 0.40)
Dupilumab 300 mg Q2W	129	0.26 (17.1)	0.18[b] (0.08, 0.27)	64	0.39 (25.8)	0.21[d] (0.06, 0.36)
Placebo	127	0.09 (4.36)		68	0.18 (10.2)	
QUEST study						
Dupilumab 200 mg Q2W	437	0.36 (23.6)	0.17[f] (0.11, 0.23)	264	0.43 (29.0)	0.21[f] (0.13, 0.29)
Placebo	232	0.18 (12.4)		148	0.21 (15.6)	
Dupilumab 300 mg Q2W	452	0.37 (25.3)	0.15[e] (0.09, 0.21)	277	0.47 (32.5)	0.24[e] (0.16, 0.32)
Placebo	237	0.22 (14.2)		142	0.22 (14.4)	

[a]p-value < 0.0001, [b]p-value = 0.0004, [c]p-value = 0.0008, [d]p-value = 0.0063, [e]p-value < 0.0001 (all statistically significant vs placebo with adjustment for multiplicity); [f]nominal p-value < 0.0001

Table 13: Mean change from baseline in pre-bronchodilator FEV_1 at week 12 and week 52 in QUEST by baseline FeNO subgroups

Treatment		At week 12		At week 52	
	N	LS mean Δ from baseline L (%)	LS mean difference vs. placebo (95% CI)	LS mean Δ from baseline L (%)	LS mean difference vs. placebo (95% CI)
FeNO ≥ 25 ppb					
Dupilumab 200 mg Q2W	288	0.44 (29.0 %)	0.23 (0.15, 0.31)[a]	0.49 (31.6 %)	0.30 (0.22, 0.39)[a]
Placebo	157	0.21 (14.1 %)		0.18 (13.2 %)	
Dupilumab 300 mg Q2W	295	0.45 (29.8 %)	0.24 (0.16, 0.31)[a]	0.45 (30.5 %)	0.23 (0.15, 0.31)[a]
Placebo	167	0.21 (13.7 %)		0.22 (13.6 %)	
FeNO ≥ 50 ppb					
Dupilumab 200 mg Q2W	114	0.53 (33.5 %)	0.30 (0.17, 0.44)[a]	0.59 (36.4 %)	0.38 (0.24, 0.53)[a]
Placebo	69	0.23 (14.9 %)		0.21 (14.6 %)	
Dupilumab 300 mg Q2W	113	0.59 (37.6 %)	0.39 (0.26, 0.52)[a]	0.55 (35.8 %)	0.30 (0.16, 0.44)[a]
Placebo	73	0.19 (13.0 %)		0.25 (13.6 %)	

[a]nominal p-value < 0.0001

Quality of life/patient-reported outcomes in asthma

Pre-specified secondary endpoint of ACQ-5 and AQLQ(S) responder rates were analysed at 24 weeks (DRI12544 and VENTURE) and at 52 weeks (QUEST, Table 14). The responder rate was defined as an improvement in score of 0.5 or more (scale range 0-6 for ACQ-5 and 1-7 for AQLQ(S)). Improvements in ACQ-5 and AQLQ(S) were observed as early as week 2 and maintained for 24 weeks in DRI12544 study and 52 weeks in QUEST study. Similar results were observed in VENTURE.

Table 14: ACQ-5 and AQLQ(S) responder rates at week 52 in QUEST

PRO	**Treatment**	**EOS ≥ 150 cells/mcL**		**EOS ≥ 300 cells/mcL**		**FeNO ≥ 25 ppb**	
		N	**Responder rate %**	**N**	**Responder rate (%)**	**N**	**Responder rate (%)**
ACQ-5	Dupilumab 200 mg Q2W	395	72.9	239	74.5	262	74.4
	Placebo	201	64.2	124	66.9	141	65.2
	Dupilumab 300 mg Q2W	408	70.1	248	71.0	277	75.8
	Placebo	217	64.5	129	64.3	159	64.2
AQLQ(S)	Dupilumab 200 mg Q2W	395	66.6	239	71.1	262	67.6
	Placebo	201	53.2	124	54.8	141	54.6
	Dupilumab 300 mg Q2W	408	62.0	248	64.5	277	65.3
	Placebo	217	53.9	129	55.0	159	58.5

Oral corticosteroid reduction study (VENTURE)

VENTURE evaluated the effect of dupilumab on reducing the use of maintenance oral corticosteroids. Baseline characteristics are presented in Table 9. All patients were on oral corticosteroids for at least 6 months prior to the study initiation. The baseline mean oral corticosteroid use was 11.75 mg in the placebo group and 10.75 mg in the group receiving dupilumab.

In this 24-week trial, asthma exacerbations (defined as a temporary increase in oral corticosteroid dose for at least 3 days) were reduced by 59 % in subjects receiving dupilumab compared with those receiving placebo (annualised rate 0.65 and 1.60 for the dupilumab and placebo group, respectively; rate ratio 0.41 [95% CI 0.26, 0.63]) and improvement in pre-bronchodilator FEV_1 from baseline to week 24 was greater in subjects receiving dupilumab compared with those receiving placebo (LS mean difference for dupilumab versus placebo of 0.22 L [95% CI: 0.09 to 0.34 L]). Effects on lung function, on oral steroid and exacerbation reduction were similar irrespective of baseline levels of type 2 inflammatory biomarkers (e.g. blood eosinophils, FeNO). The ACQ-5 and AQLQ(S) were also assessed in VENTURE and showed improvements similar to those in QUEST.

The results for VENTURE by baseline biomarkers are presented in the Table 15.

Table 15: Effect of dupilumab on OCS dose reduction, VENTURE (baseline blood eosinophil levels ≥ 150 and ≥ 300 cells/mcL and FeNO ≥ 25 ppb)

	Baseline blood EOS ≥ 150 cells/mcL		**Baseline blood EOS ≥ 300 cells/mcL**		**FeNO ≥ 25 ppb**	
	Dupilumab 300 mg Q2W N=81	**Placebo N=69**	**Dupilumab 300 mg Q2W N=48**	**Placebo N=41**	**Dupilumab 300 mg Q2W N=57**	**Placebo N=57**
Primary endpoint (week 24)						
Percent reduction in OCS from baseline						
Mean overall percent reduction from baseline (%)	75.91	46.51	79.54	42.71	77.46	42.93
Difference (% [95% CI]) (Dupilumab vs. placebo)	29.39[b] (15.67, 43.12)		36.83[b] (18.94, 54.71)		34.53[b] (19.08, 49.97)	

Median % reduction in daily OCS dose from baseline	100	50	100	50	100	50
Percent reduction from baseline						
100% %	54.3	33.3	60.4	31.7	52.6	28.1
≥ 90 %	58.0	34.8	66.7	34.1	54.4	29.8
≥ 75 %	72.8	44.9	77.1	41.5	73.7	36.8
≥ 50 %	82.7	55.1	85.4	53.7	86.0	50.9
> 0 %	87.7	66.7	85.4	63.4	89.5	66.7
No reduction or any increase in OCS dose, or dropped out of study	12.3	33.3	14.6	36.6	10.5	33.3
Secondary endpoint (week 24)[a]						
Proportion of patients achieving a reduction of OCS dose to < 5 mg/day	77	44	84	40	79	34
Odds ratio (95% CI)	4.29[c] (2.04, 9.04)		8.04[d] (2.71, 23.82)		7.21[b] (2.69, 19.28)	

[a]model estimates by logistic regression, [b]nominal p-value < 0.0001, [c]nominal p-value = 0.0001, [d]nominal p-value = 0.0002

Long-term extension study (TRAVERSE)

The long-term safety of dupilumab in 2,193 adults and 89 adolescents with moderate-to-severe asthma, including 185 adults with oral corticosteroid-dependent asthma, who had participated in previous clinical trials of dupilumab (DRI12544, QUEST, and VENTURE), was assessed in the open-label extension study (TRAVERSE) (see section 4.8). Efficacy was measured as a secondary endpoint, was similar to results observed in the pivotal studies and was sustained up to 96 weeks. In the adults with oral-corticosteroid-dependent asthma, there was sustained reduction in exacerbations and improvement in lung function up to 96 weeks, despite decrease or discontinuation of oral corticosteroid dose.

Paediatric study (6 to 11 years of age; VOYAGE)

The efficacy and safety of dupilumab in paediatric patients was evaluated in a 52-week multicentre, randomised, double-blind, placebo-controlled study (VOYAGE) in 408 patients 6 to 11 years of age, with moderate-to-severe asthma on a medium- or high- dose ICS and one controller medication or high dose ICS alone. Patients were randomised to dupilumab (N=273) or matching placebo (N=135) every other week based on body weight ≤ 30 kg or > 30 kg, respectively. The efficacy was evaluated in populations with type 2 inflammation defined as blood eosinophil levels of ≥ 150 cells/mcL or FeNO ≥ 20 ppb.

The primary endpoint was the annualised rate of severe exacerbation events during the 52-week placebo-controlled period and the key secondary endpoint was the change from baseline in pre-bronchodilator FEV_1 percent predicted at week 12. Additional secondary endpoints included mean change from baseline and responder rates in the ACQ-7-IA and PAQLQ(S)-IA scores.
The demographics and baseline characteristics for VOYAGE are provided in Table 16 below.

Table 16. Demographics and baseline characteristics for VOYAGE

Parameter	**EOS ≥ 150 cells/mcL or FeNO ≥ 20 ppb (N = 350)**	**EOS ≥ 300 cells/mcL (N = 259)**
Mean age (years) (SD)	8.9 (1.6)	9.0 (1.6)
% Female	34.3	32.8

Table 16. Demographics and baseline characteristics for VOYAGE

Parameter	**EOS ≥ 150 cells/mcL or FeNO ≥ 20 ppb (N = 350)**	**EOS ≥ 300 cells/mcL (N = 259)**
% White	88.6	87.3
Mean body weight (kg)	36.09	35.94
Mean exacerbations in previous year (± SD)	2.47 (2.30)	2.64 (2.58)
ICS dose (%) Medium High	 55.7 43.4	 54.4 44.4
Pre-dose FEV_1 (L) at baseline (± SD)	1.49 (0.41)	1.47 (0.42)
Mean percent predicted FEV_1 (%) (±SD)	77.89 (14.40)	76.85 (14.78)
Mean % Reversibility *(*± SD)	27.79 (19.34)	22.59 (20.78)
Mean ACQ-7-IA score (± SD)	2.14 (0.72)	2.16 (0.75)
Mean PAQLQ(S)-IA score (± SD)	4.94 (1.10)	4.93 (1.12)
Atopic Medical History % Overall (AD %, AR %)	94 (38.9, 82.6)	96.5 (44.4, 85.7)
Median total IgE IU/mL (± SD)	905.52 (1140.41)	1077.00 (1230.83)
Mean FeNO ppb (± SD)	30.71 (24.42)	33.50 (25.11)
% patients with FeNO≥ 20 ppb	58	64.1
Mean baseline Eosinophil count (± SD) cells/mcL	570 (380)	710 (360)
% patients with EOS ≥ 150 cells/mcL ≥ 300 cells/mcL	 94.6 74	 0 100

ICS = inhaled corticosteroid; FEV_1 = Forced expiratory volume in 1 second; ACQ-7-IA = Asthma Control Questionnaire-7 Interviewer Administered; PAQLQ(S)-IA = Paediatric Asthma Quality of Life Questionnaire with Standardised Activities–Interviewer Administered; AD = atopic dermatitis; AR = allergic rhinitis; EOS = blood eosinophil; FeNO = fraction of exhaled nitric oxide

Dupilumab significantly reduced the annualised rate of severe asthma exacerbation events during the 52-week treatment period compared to placebo in the population with the type 2 inflammation and in population defined by baseline blood eosinophils ≥ 300 cells/mcL or by baseline FeNO ≥ 20 ppb. Clinically significant improvements in percent predicted pre-bronchodilator FEV_1 were observed at week 12. Improvements were also observed for ACQ-7-IA and PAQLQ(S)-IA at week 24 and were sustained at week 52. Greater responder rates were observed for ACQ-7-IA and PAQLQ(S)-IA compared to placebo at week 24. The efficacy results for VOYAGE are presented in Table 17.

In the population with the type 2 inflammation, the LS mean change from baseline in pre-bronchodilator FEV_1 at week 12 was 0.22 L in the dupilumab group and 0.12 L in the placebo group, with an LS mean difference versus placebo of 0.10 L (95% CI: 0.04, 0.16). The treatment effect was sustained over the 52-week treatment period, with an LS mean difference versus placebo at week 52 of 0.17 L (95% CI: 0.09, 0.24).

In the population defined by baseline blood eosinophils ≥ 300 cells/mcL, the LS mean change from baseline in pre-bronchodilator FEV_1 at week 12 was 0.22 L in the dupilumab group and 0.12 L in the placebo group, with an LS mean difference versus placebo of 0.10 L (95% CI: 0.03, 0.17). The

treatment effect was sustained over the 52-week treatment period, with an LS mean difference versus placebo at week 52 of 0.17 L (95% CI: 0.09, 0.26).

In both primary efficacy populations, there was a rapid improvement in FEF25-75% and FEV_1/FVC (onset of a difference was observed as early as week 2) and sustained over the 52-week treatment period, see Table 17.

Table 17: Rate of severe exacerbations, mean change from baseline in FEV_1, ACQ-7-IA and PAQLQ(S)-IA responder rates in VOYAGE

Treatment	**EOS ≥ 150 cells/mcL or FeNO ≥ 20 ppb**			**EOS ≥ 300 cells/mcL**			**FeNO ≥20 ppb**		
Annualised severe exacerbations rate over 52 weeks									
	N	**Rate (95% CI)**	**Rate ratio (95% CI)**	**N**	**Rate (95% CI)**	**Rate ratio (95% CI)**	**N**	**Rate (95% CI)**	**Rate ratio (95% CI)**
Dupilumab 100 mg Q2W (<30 kg)/ 200 mg Q2W (≥30 kg)	236	0.305 (0.223, 0.416)	0.407[b] (0.274, 0.605)	175	0.235 (0.160, 0.345)	0.353[b] (0.222, 0.562)	141	0.271 (0.170, 0.432)	0.384[c] (0.227, 0.649)
Placebo	114	0.748 (0.542, 1.034)		84	0.665 (0.467, 0.949)		62	0.705 (0.421, 1.180)	
Mean change from baseline in percent predicted FEV_1 at week 12									
	N	**LS mean Δ from baseline**	**LS mean difference vs. placebo (95% CI)**	**N**	**LS mean Δ from baseline**	**LS mean difference vs. placebo (95% CI)**	**N**	**LS mean Δ from baseline**	**LS mean difference vs. placebo (95% CI)**
Dupilumab 100 mg Q2W (<30 kg)/ 200 mg Q2W (≥30 kg)	229	10.53	5.21[c] (2.14, 8.27)	168	10.15	5.32[d] (1.76, 8.88)	141	11.36	6.74[d] (2.54, 10.93)
Placebo	110	5.32		80	4.83		62	4.62	
Mean change from baseline in percent predicted FEF 25-75% at week 12									
	N	**LS mean Δ from baseline**	**LS mean difference vs. placebo (95% CI)**	**N**	**LS mean Δ from baseline**	**LS mean difference vs. placebo (95% CI)**	**N**	**LS mean Δ from baseline**	**LS mean difference vs. placebo (95% CI)**
Dupilumab 100 mg Q2W (<30 kg)/ 200 mg Q2W (≥30 kg)	229	16.70	11.93[e] (7.44, 16.43)	168	16.91	13.92[e] (8.89, 18.95)	141	17.96	13.97[e] (8.30, 19.65)
Placebo	110	4.76		80	2.99		62	3.98	
Mean change from baseline in FEV_1/FVC % at week 12									
	N	**LS mean Δ from baseline**	**LS mean difference vs. placebo (95% CI)**	**N**	**LS mean Δ from baseline**	**LS mean difference vs. placebo (95% CI)**	**N**	**LS mean Δ from baseline**	**LS mean difference vs. placebo (95% CI)**
Dupilumab 100 mg Q2W (<30 kg)/ 200 mg Q2W (≥30 kg)	229	5.67	3.73[e] (2.25, 5.21)	168	6.10	4.63[e] (2.97, 6.29)	141	6.84	4.95[e] (3.08, 6.81)
Placebo	110	1.94		80	1.47		62	1.89	
ACQ-7-IA at week 24[a]									

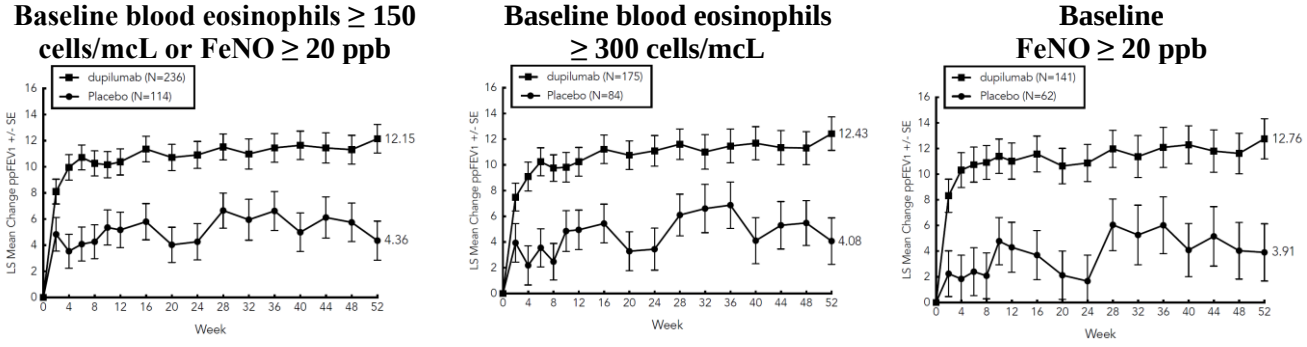
	N	Responder rate %	OR vs. placebo (95% CI)	N	Responder rate %	OR vs. placebo (95% CI)	N	Responder rate %	OR vs. placebo (95% CI)
Dupilumab 100 mg Q2W (<30 kg)/ 200 mg Q2W (≥30 kg)	236	79.2	1.82[g] (1.02, 3.24)	175	80.6	2.79[f] (1.43, 5.44)	141	80.9	2.60[g] (1.21, 5.59)
Placebo	114	69.3		84	64.3		62	66.1	
PAQLQ(S)-IA at week 24[a]									
	N	**Responder rate %**	**OR vs. placebo (95% CI)**	**N**	**Responder rate %**	**OR vs. placebo (95% CI)**	**N**	**Responder rate %**	**OR vs. placebo (95% CI)**
Dupilumab 100 mg Q2W (<30 kg)/ 200 mg Q2W (≥30 kg)	211	73.0	1.57 (0.87, 2.84)	158	72.8	1.84 (0.92, 3.65)	131	75.6	2.09 (0.95, 4.61)
Placebo	107	65.4		81	63.0		61	67.2	

[a]the responder rate was defined as an improvement in score of 0.5 or more (scale range 0-6 for ACQ-7-IA and 1-7 for PAQLQ(S))
[b]p-value < 0.0001; [c]p-value < 0.001, [d]p-value < 0.01 (all statistically significant vs placebo with adjustment for multiplicity);
[e]nominal p-value < 0.0001, [f]nominal p-value < 0.01, [g]nominal p-value < 0.05

Significant improvements in percent predicted FEV1 were observed as early as week 2 and were maintained through week 52 in VOYAGE study.

Improvements in percent predicted FEV_1 over time in VOYAGE are shown in Figure 2.

Figure 2: Mean change from baseline in percent predicted pre-bronchodilator FEV_1 (L) over time in VOYAGE (baseline blood eosinophils ≥ 150 cells/mcL or FeNO ≥ 20 ppb, baseline eosinophils ≥ 300 cells/mcL, and baseline FeNO ≥ 20 ppb)



In VOYAGE, in the population with the type 2 inflammation, the mean annualised total number of systemic corticosteroid courses due to asthma was reduced by 59.3% versus placebo (0.350 [95% CI: 0.256, 0.477] versus 0.860 [95% CI: 0.616, 1.200]). In the population defined by baseline blood eosinophils ≥ 300 cells/mcL, the mean annualised total number of systemic corticosteroid courses due to asthma was reduced by 66.0% versus placebo (0.274 [95% CI: 0.188, 0.399] versus 0.806 [95% CI: 0.563, 1.154]).

Dupilumab improved the overall health status as measured by the European Quality of Life 5-Dimension Youth Visual Analog Scale (EQ-VAS) in both the type 2 inflammation and the baseline blood eosinophil count of ≥ 300 cells/mcL populations at week 52; the LS mean difference versus placebo was 4.73 (95% CI: 1.18, 8.28), and 3.38 (95% CI: -0.66, 7.43), respectively.

Dupilumab reduced the impact of paediatric patient's asthma on the caregiver quality of life as measured by the Paediatric Asthma Quality of Life Questionnaire (PACQLQ) in both the type 2

inflammation and the baseline blood eosinophil count of ≥ 300 cells/mcL population at week 52; the LS mean difference versus placebo was 0.47 (95% CI: 0.22, 0.72), and 0.50 (95% CI: 0.21, 0.79), respectively.

Long-term extension study (EXCURSION)

The efficacy of dupilumab, measured as a secondary endpoint, was assessed in 365 paediatric asthma patients (6 to 11 years of age) in the long-term extension study (EXCURSION). There were sustained reductions in exacerbations requiring hospitalization and/or emergency room visits and a reduction in exposure to systemic oral corticosteroids. Sustained improvements in lung function were observed across multiple parameters including percent predicted FEV_1, percent predicted FVC, FEV_1/FVC ratio and percent predicted FEF 25-75%. Furthermore, 75% of patients achieved and/or maintained normal lung function with pre-bronchodilator percent predicted FEV_1 > 80% by the end of EXCURSION. Efficacy was sustained for a cumulative treatment duration of up to 104 weeks (VOYAGE and EXCURSION).

Paediatric population

Atopic dermatitis
The safety and efficacy of dupilumab have been established in paediatric patients 6 months of age and older with atopic dermatitis. Use of dupilumab in this age group is supported by study AD-1526 which included 251 adolescents aged 12 to 17 years old with moderate-to-severe atopic dermatitis, in study AD-1652 which included 367 paediatric patients aged 6 to 11 years old with severe atopic dermatitis, and study AD-1539 which included 162 children ages 6 months to 5 years old with moderate-to-severe atopic dermatitis (125 of whom had severe atopic dermatitis). Long termuse is supported by study AD-1434 which enrolled 823 paediatric patients aged 6 months to 17 years of age; this included 275 adolescents, 368 children 6 to 11 years of age, and 180 children 6 months to 5 years of age. The safety and efficacy were generally consistent between children 6 months to 5 years old, 6 to 11 years old, adolescent (12 to 17 years old), and adult patients with atopic dermatitis (see section 4.8). Safety and efficacy in paediatric patients < 6 monthsof age with atopic dermatitis have not been established.

Asthma
A total of 107 adolescents aged 12 to 17 years with moderate to severe asthma were enrolled in QUEST study and received either 200 mg (N=21) or 300 mg (N=18) dupilumab (or matching placebo either 200 mg [N=34] or 300 mg [N=34]) every other week. Efficacy with respect to severe asthma exacerbations and lung function was observed in both adolescents and adults. For both the 200 mg and 300 mg every other week doses, significant improvements in FEV_1 (LS mean change from baseline at week 12) were observed (0.36 L and 0.27 L, respectively). For the 200 mg every other week dose, patients had a reduction in the rate of severe exacerbations that was consistent with adults. The safety profile in adolescents was generally similar to the adults.

A total of 89 adolescents aged 12 to 17 years with moderate-to-severe asthma were enrolled in the open label long-term study (TRAVERSE). In this study, efficacy was measured as a secondary endpoint, was similar to results observed in the pivotal studies and was sustained up to 96 weeks.

A total of 408 children aged 6 to 11 years with moderate-to-severe asthma was enrolled in the VOYAGE study, which evaluated doses of 100 mg Q2W and 200 mg Q2W. The efficacy of dupilumab 300 mg Q4W in children aged 6 to 11 years is extrapolated from the efficacy of 100 mg and 200 mg Q2W in VOYAGE and 200 mg and 300 mg Q2W in adults and adolescents (QUEST). Patients who completed the treatment period of the VOYAGE study could participate in the open label extension study (EXCURSION). Eighteen patients (≥ 15 kg to < 30 kg) out of 365 patients were exposed to 300 mg Q4W in this study, and the safety profile was similar to that seen in VOYAGE. Safety and efficacy in paediatric patients < 6 years of age with asthma have not been established.

The European Medicines Agency has deferred the obligation to submit the results of studies with dupilumab in one or more subset of the paediatric population in asthma (see section 4.2 for

information on paediatric use). Obligations related to the paediatric investigation plans for atopic dermatitis have been fulfilled.

5.2 Pharmacokinetic properties

The pharmacokinetics of dupilumab is similar in patients with atopic dermatitis and asthma.

Absorption

After a single subcutaneous (SC) dose of 75-600 mg dupilumab to adults, median times to maximum concentration in serum (t_{max}) were 3-7 days. The absolute bioavailability of dupilumab following a SC dose is similar between AD and asthma patients, 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 69.2±36.9 mcg/mL to 80.2±35.3 mcg/mL for 300 mg dose and from 29.2±18.7 to 36.5±22.2 mcg/mL for 200 mg dose administered every other week to adults.

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 of 300 mg QW, 300 mg Q2W, 200 mg Q2W, 300 mg Q4W, or 200 mg Q4W dupilumab, the median times to decrease below the lower limit of detection, estimated by population PK analysis, ranged from 9-13 weeks in adults and adolescents and are approximately 1.5 times and 2.5 times longer in paediatric patients 6 to 11 years of age and paediatric subjects less than 6 years of age, respectively.

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
Of the 1,539 patients with atopic dermatitis, including patients with atopic hand and foot dermatitis exposed to dupilumab in a phase 2 dose-ranging study or phase 3 placebo-controlled studies, a total of 71 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.

Of the 1,977 patients with asthma exposed to dupilumab, a total of 240 patients were 65 years or older and 39 patients were 75 years or older. Efficacy and safety in this age group were similar to the overall study population.

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

Atopic dermatitis
Based on population pharmacokinetic analysis, age did not affect dupilumab clearance in adults and in paediatric patients 6 to 17 years of age. In paediatric patients from 6 months to 5 years of age, clearance increased with age but is accommodated in the recommended dose regimen.

The pharmacokinetics of dupilumab in paediatric patients (< 6 monthsof age) or body weight < 5 kg with atopic dermatitis has not been studied.

For adolescents 12 to 17 years of age with atopic dermatitis receiving every other week dosing (Q2W) with either 200 mg (<60 kg) or 300 mg (≥60 kg), the mean ±SD steady state trough concentration of dupilumab was 54.5±27.0 mcg/mL.

For children 6 to 11 years of age with atopic dermatitis receiving every four week dosing (Q4W) with 300 mg (≥ 15 kg) in AD-1652, the mean ± SD steady-state trough concentration was 76.3±37.2 mcg/mL. At week 16 in AD-1434 in children 6 to 11 years of age who initiated every four week dosing (Q4W) with 300 mg (≥ 15 kg), and whose dose was increased to every other week dosing (Q2W) with 200 mg (≥ 15 to < 60 kg) or 300 mg (≥ 60 kg), the mean±SD steady-state trough concentration was 108±53.8 mcg/mL. For children 6 to 11 years of age 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.

For children 6 months to 5 years of age with atopic dermatitis receiving every four week dosing (Q4W) with 300 mg (≥ 15 to < 30 kg) or 200 mg (≥ 5 to < 15 kg) mean ± SD steady-state trough concentration was 110±42.8 mcg/mL and 109±50.8 mcg/mL, respectively.

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

A total of 107 adolescents aged 12 to 17 years with asthma were enrolled in QUEST study. The mean ±SD steady-state trough concentrations of dupilumab were 107±51.6 mcg/mL and 46.7±26.9 mcg/mL, respectively, for 300 mg or 200 mg administered every other week. No age-related pharmacokinetic difference was observed in adolescent patients after correction for body weight.

In the VOYAGE study, dupilumab pharmacokinetics was investigated in 270 patients with moderate-to-severe asthma following subcutaneous administration of either 100 mg Q2W (for 91 children weighing < 30 kg) or 200 mg Q2W (for 179 children weighing ≥ 30 kg). The volume of distribution for dupilumab of approximately 3.7 L was estimated by population PK analysis. Steady-state concentrations were achieved by week 12. The mean ± SD steady-state trough concentration was 58.4±28.0 mcg/mL and 85.1±44.9 mcg/mL, respectively. Simulation of a 300 mg Q4W subcutaneous dose in children aged 6 to 11 years with body weight of ≥ 15 kg to < 30 kg and ≥ 30 kg to < 60 kg resulted in predicted steady-state trough concentrations similar to the observed trough concentrations of 200 mg Q2W (≥ 30 kg) and 100 mg Q2W (< 30 kg), respectively. In addition, simulation of a 300 mg Q4W subcutaneous dose in children aged 6 to 11 years with body weight of ≥ 15 kg to < 60 kg resulted in predicted steady-state trough concentrations similar to those demonstrated to be efficacious in adults and adolescents. 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 14 to 18 weeks for 100 mg Q2W, 200 mg Q2W or 300 mg Q4W.

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 doses 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

L-Arginine monohydrochloride
L-Histidine
L-Histidine monohydrochloride monohydrate
Polysorbate 80 (E 433)
Sodium acetate trihydrate
Acetic acid, glacial (E 260)

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

3 years.

If necessary, the pre-filled syringe or pre-filled pen can be removed from the refrigerator and kept in the pack for up to 14 days at room temperature up to 25°C, while protected from light. The date of removal from the refrigerator shall be recorded in the space provided on the outer carton. The pack must be discarded if left out of the refrigerator for more than 14 days or if the expiry date has passed.

6.4 Special precautions for storage

Store in a refrigerator (2°C - 8°C).

Do not freeze.

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

6.5 Nature and contents of container

Dupixent 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 6 (3 packs of 2) pre-filled syringes

Dupixent 200 mg solution for injection in pre-filled pen

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

The pre-filled pen is available either with a round cap and oval viewing window encircled with an arrow or with a square cap with ridges and an oval viewing window without an arrow.

Pack size:
- 1 pre-filled pen
- 2 pre-filled pens
- 6 pre-filled pens
- Multipack containing 6 (2 packs of 3) pre-filled pens

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Comprehensive instructions for the administration of Dupixent in a pre-filled syringe or in a pre-filled pen are given at the end of 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 200 mg pre-filled syringe or pre-filled pen from the refrigerator, it should be allowed to reach room temperature up to 25°C by waiting for 30 min before injecting Dupixent.

The pre-filled syringe or the pre-filled pen 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 or the pre-filled pen into a puncture-resistant container and discard as required by local regulations. Do not recycle the container.

7. MARKETING AUTHORISATION HOLDER

Sanofi Winthrop Industrie
82 avenue Raspail
94250 Gentilly
France

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/17/1229/009
EU/1/17/1229/010
EU/1/17/1229/012
EU/1/17/1229/013
EU/1/17/1229/014
EU/1/17/1229/016
EU/1/17/1229/023
EU/1/17/1229/024
EU/1/17/1229/025

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 26 September 2017
Date of latest renewal: 02 September 2022

10. DATE OF REVISION OF THE TEXT

03/2024

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu

SmPC

DUPIXENT 300mg

1. NAME OF THE MEDICINAL PRODUCT

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

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Dupilumab 300 mg solution for injection in pre-filled syringe

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

Dupilumab 300 mg solution for injection in pre-filled pen

Each single-use pre-filled pen contains 300 mg of dupilumab in 2 mL solution (150 mg/mL).

Dupilumab is a fully human monoclonal antibody 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 Therapeutic indications

Atopic dermatitis

Adults and adolescents
Dupixent is indicated for the treatment of moderate-to-severe atopic dermatitis in adults and adolescents 12 years and older who are candidates for systemic therapy.

Children 6 months to 11 years of age
Dupixent is indicated for the treatment of severe atopic dermatitis in children 6 months to 11 years old who are candidates for systemic therapy.

Asthma

Adults and adolescents
Dupixent is indicated in adults and adolescents 12 years and older as add-on maintenance treatment for severe asthma with type 2 inflammation characterised by raised blood eosinophils and/or raised fraction of exhaled nitric oxide (FeNO), see section 5.1, who are inadequately controlled with high dose inhaled corticosteroids (ICS) plus another medicinal product for maintenance treatment.

Children 6 to 11 years of age
Dupixent is indicated in children 6 to 11 years old as add-on maintenance treatment for severe asthma with type 2 inflammation characterised by raised blood eosinophils and/or raised fraction of exhaled nitric oxide (FeNO), see section 5.1, who are inadequately controlled with medium to high dose inhaled corticosteroids (ICS) plus another medicinal product for maintenance treatment.

Chronic rhinosinusitis with nasal polyposis (CRSwNP)

Dupixent is indicated as an add-on therapy with intranasal corticosteroids for the treatment of adults with severe CRSwNP for whom therapy with systemic corticosteroids and/or surgery do not provide adequate disease control.

Prurigo Nodularis (PN)

Dupixent is indicated for the treatment of adults with moderate-to-severe prurigo nodularis (PN) who are candidates for systemic therapy.

Eosinophilic esophagitis (EoE)

Dupixent is indicated for the treatment of eosinophilic esophagitis in adults and adolescents 12 years and older, weighing at least 40 kg, who are inadequately controlled by, are intolerant to, or who are not candidates for conventional medicinal therapy (see section 5.1).

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

Atopic dermatitis

Adults
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.

Adolescents (12 to 17 years of age)
The recommended dose of dupilumab for adolescent patients 12 to 17 years of age is specified in Table 1.

Table 1: Dose of dupilumab for subcutaneous administration in adolescent patients 12 to 17 years of age with atopic dermatitis

Body weight of patient	Initial dose	Subsequent doses (every other week)
less than 60 kg	400 mg (two 200 mg injections)	200 mg
60 kg or more	600 mg (two 300 mg injections)	300 mg

Children 6 to 11 years of age
The recommended dose of dupilumab for children 6 to 11 years of age is specified in Table 2.

Table 2: Dose of dupilumab for subcutaneous administration in children 6 to 11 years of age with atopic dermatitis

Body weight of patient	Initial dose	Subsequent doses
15 kg to less than 60 kg	300 mg (one 300 mg injection) on Day 1, followed by 300 mg on Day 15	300 mg every 4 weeks (Q4W)*, starting 4 weeks after Day 15 dose
60 kg or more	600 mg (two 300 mg injections)	300 mg every other week (Q2W)

*the dose may be increased to 200 mg Q2W in patients with body weight of 15 kg to less than 60 kg based on physician's assessment.

Children 6 months to 5 years of age
The recommended dose of dupilumab for children 6 months to 5 years of age is specified in Table 3.

Table 3: Dose of dupilumab for subcutaneous administration in children 6 months to 5 years of age with atopic dermatitis

Body Weight of Patient	Initial Dose	Subsequent Doses
5 kg to less than 15 kg	200 mg (one 200 mg injection)	200 mg every 4 weeks (Q4W)
15 kg to less than 30 kg	300 mg (one 300 mg injection)	300 mg every 4 weeks (Q4W)

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

Asthma

Adults and adolescents
The recommended dose of dupilumab for adults and adolescents (12 years of age and older) is:

- For patients with severe asthma and who are on oral corticosteroids or for patients with severe asthma and co-morbid moderate-to-severe atopic dermatitis or adults with co-morbid severe chronic rhinosinusitis with nasal polyposis, an initial dose of 600 mg (two 300 mg injections), followed by 300 mg every other week administered as subcutaneous injection.
- For all other patients, an initial dose of 400 mg (two 200 mg injections), followed by 200 mg every other week administered as subcutaneous injection.

Children 6 to 11 years of age
The recommended dose of dupilumab for paediatric patients 6 to 11 years of age is specified in Table 4.

Table 4: Dose of dupilumab for subcutaneous administration in children 6 to 11 years of age with asthma

Body weight	Initial and subsequent doses
15 to less than 30 kg	300 mg every four weeks (Q4W)
30 kg to less than 60 kg	200 mg every other week (Q2W) or 300 mg every four weeks (Q4W)
60 kg or more	200 mg every other week (Q2W)

For paediatric patients (6 to 11 years old) with asthma and co-morbid severe atopic dermatitis, as per approved indication, the recommended dose should be followed in Table 2.

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).

Dupilumab is intended for long-term treatment. The need for continued therapy should be considered at least on an annual basis as determined by physician assessment of the patient's level of asthma control.

Chronic rhinosinusitis with nasal polyposis (CRSwNP)

The recommended dose of dupilumab for adult patients is an initial dose of 300 mg followed by 300 mg given every other week.

Dupilumab is intended for long-term treatment. Consideration should be given to discontinuing treatment in patients who have shown no response after 24 weeks of treatment for CRSwNP. Some patients with initial partial response may subsequently improve with continued treatment beyond 24 weeks.

Prurigo Nodularis (PN)

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.
Dupilumab can be used with or without topical corticosteroids.

PN clinical trial data are available for patients treated up to 24 weeks. Consideration should be given to discontinuing treatment in patients who have shown no response after 24 weeks of treatment for PN.

Eosinophilic esophagitis (EoE)

The recommended dose of dupilumab for patients 12 years of age and older is 300 mg given every week (QW).

Dupilumab 300 mg QW has not been studied in patients with EoE weighing less than 40 kg.

Dupilumab is intended for long-term treatment. Dupilumab 300 mg QW has been studied up to 52 weeks. Dosing beyond 52 weeks has not been studied.

Missed dose

If a weekly dose is missed, administer the dose as soon as possible, starting a new schedule based on this date.

If an every other week dose is missed, administer the injection within 7 days from the missed dose and then resume the patient's original schedule. If the missed dose is not administered within 7 days, wait until the next dose on the original schedule.

If an every 4 week dose is missed, administer the injection within 7 days from the missed dose and then resume the patient's original schedule. If the missed dose is not administered within 7 days, administer the dose, starting a new schedule based on this date.

Special populations

Elderly (≥ 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 for patients with asthma and EoE 12 years of age and older or in adults with atopic dermatitis or CRSwNP, or PN (see section 5.2).

Paediatric population
The safety and efficacy of dupilumab in children with atopic dermatitis below the age of 6 months have not been established. The safety and efficacy of dupilumab in children with a body weight < 5 kg have not been established. No data are available.

The safety and efficacy of dupilumab in children with severe asthma below the age of 6 years have not been established. No data are available.

The safety and efficacy in children with CRSwNP below the age of 18 years have not been established. No data are available.

The safety and efficacy of dupilumab in children with PN below the age of 18 years have not been established. No data are available.

The safety and efficacy of dupilumab in children with EoE below the age of 12 years have not been established.

Method of administration

Subcutaneous use

The dupilumab pre-filled pen is not intended for use in children below 12 years of age. For children 6 months to 11 years of age with atopic dermatitis and asthma, the dupilumab pre-filled syringe is the presentation appropriate for administration to this population.

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.

Each pre-filled syringe or pre-filled pen is for single use only.

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 at the end of 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

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.

Acute asthma exacerbations

Dupilumab should not be used to treat acute asthma symptoms or acute exacerbations. Dupilumab should not be used to treat acute bronchospasm or status asthmaticus.

Corticosteroids

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).

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 (see section 4.8).

Eosinophilic conditions

Cases of eosinophilic pneumonia and cases of vasculitis consistent with eosinophilic granulomatosis with polyangiitis (EGPA) have been reported with dupilumab in adult patients who participated in the asthma development program. Cases of vasculitis consistent with EGPA have been reported with dupilumab and placebo in adult patients with co-morbid asthma in the CRSwNP development program. Physicians should be alert to vasculitic rash, worsening pulmonary symptoms, cardiac complications, and/or neuropathy presenting in their patients with eosinophilia. Patients being treated for asthma may present with serious systemic eosinophilia sometimes presenting with clinical features of eosinophilic pneumonia or vasculitis consistent with eosinophilic granulomatosis with polyangiitis, conditions which are often treated with systemic corticosteroid therapy. These events usually, but not always, may be associated with the reduction of oral corticosteroid therapy.

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. Cases of enterobiasis were reported in children 6 to 11 years old who participated in the paediatric asthma development program (see section 4.8).

Conjunctivitis and keratitis related events

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

Patients with comorbid asthma

Patients on dupilumab who also have co-morbid 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

Concurrent use of live and live attenuated vaccines with dupilumab should be avoided as clinical safety and efficacy have not been established. 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. Clinical data are not available to support more specific guidance for live or live attenuated vaccines administration in patients treated with dupilumab. Immune responses to TdaP vaccine and meningococcal polysaccharide vaccine were assessed (see section 4.5).

Sodium content

This medicinal product contains less than 1 mmol sodium (23 mg) per 300 mg dose, that is to say 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 atopic dermatitis 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 medicinal products is not expected. Based on the population analysis, commonly co-administered medicinal products had no effect on dupilumab pharmacokinetics on patients with moderate to severe asthma.

4.6 Fertility, pregnancy and lactation

Pregnancy

There is a 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 and use machines.

4.8 Undesirable effects

Summary of the safety profile

The most common adverse reactions in atopic dermatitis, asthma, and CRSwNP are injection site reactions (includes erythema, oedema, pruritus, pain, and swelling), conjunctivitis, conjunctivitis allergic, arthralgia, oral herpes, and eosinophilia. An additional adverse reaction of injection site bruising was reported in EoE. Rare cases of serum sickness, serum sickness-like reaction, anaphylactic reaction, and ulcerative keratitis have been reported (see section 4.4).

Tabulated list of adverse reactions

The dupilumab safety data presented in Table 5 were predominantly derived from 12 randomised, placebo-controlled trials, including atopic dermatitis, asthma, and CRSwNP patients. These studies involved 4,206 patients receiving dupilumab and 2,326 patients receiving placebo during the controlled period are representative of the overall safety profile for dupilumab.

Listed in Table 5 are adverse reactions observed in clinical trials and/or postmarketing setting 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, adverse reactions are presented in order of decreasing seriousness.

Table 5: List of adverse reactions

MedDRA System Organ Class	Frequency	Adverse Reaction
Infections and infestations	Common	Conjunctivitis* Oral herpes*
Blood and lymphatic system disorders	Common	Eosinophilia
Immune system disorders	Uncommon Rare	Angioedema[#] Anaphylactic reaction Serum sickness reaction Serum sickness-like reaction
Eye disorders	Common Uncommon Rare	Conjunctivitis allergic* Keratitis*[#] Blepharitis*[†] Eye pruritus*[†] Dry eye*[†] Ulcerative keratitis*[†#]
Skin and subcutaneous tissue disorders	Uncommon	Facial rash[#]
Musculoskeletal and connective tissue disorders	Common	Arthralgia[#]
General disorders and administration site conditions	Common	Injection site reactions (includes erythema, oedema, pruritus, pain, swelling, and bruising)

*eye disorders and oral herpes occurred predominately in atopic dermatitis studies.
[†]the frequencies for eye pruritus, blepharitis, and dry eye were common and ulcerative keratitis was uncommon in atopic dermatitis studies.
[#]from postmarketing reporting.

Description of selected adverse reactions

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 compared to placebo in atopic dermatitis studies. Most patients with conjunctivitis or keratitis recovered or were recovering during the treatment period. In the long-term OLE atopic dermatitis study (AD-1225) at 5 years, the respective rates of conjunctivitis and keratitis remained similar to those in the dupilumab arm in the placebo controlled atopic dermatitis studies. Among asthma patients frequency of conjunctivitis and keratitis was low and similar between dupilumab and placebo. Among CRSwNP and Prurigo Nodularis (PN) patients the frequency of conjunctivitis was higher in dupilumab than placebo, though lower than that observed in atopic dermatitis patients. There were no cases of keratitis reported in the CRSwNP or PN development program. Among patients with EoE, the frequency of conjunctivitis was low and similar between dupilumab and placebo groups. There were no cases of keratitis in the EoE development program (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 adult studies. In the 52-week atopic dermatitis dupilumab + TCS adult study, eczema herpeticum was reported in 0.2 % of the dupilumab + TCS group and 1.9 % of the placebo + TCS group. These rates remained stable at 5 years in the long-term OLE study (AD-1225).

Eosinophilia
Dupilumab-treated patients had a greater mean initial increase from baseline in eosinophil count compared to patients treated with placebo in the atopic dermatitis, asthma, and CRSwNP indications. Eosinophil counts declined to near baseline levels during study treatment and returned to baseline during the asthma open-label extension safety study (TRAVERSE). The mean blood eosinophil levels decreased to below baseline by week 20 and was maintained up to 5 years in the long-term OLE study (AD-1225). Compared to placebo, no increase in mean blood eosinophil counts was observed in PN (PRIME and PRIME2). Mean and median blood eosinophil counts declined to near baseline or remained below baseline levels in EoE (TREET Parts A and B) during study treatment.

Treatment-emergent eosinophilia (≥ 5,000 cells/mcL) was reported in < 3 % of dupilumab-treated patients and < 0.5 % in placebo-treated patients (SOLO1, SOLO2, AD-1021, DRI12544, QUEST, and VOYAGE; SINUS-24 and SINUS-52, PRIME, and PRIME2 studies; TREET Parts A and B).

Treatment-emergent eosinophilia (≥5,000 cells/mcL) was reported in 8.4% of dupilumab-treated patients and 0% in placebo-treated patients in study AD-1539, with median eosinophil counts declining below baseline at end of treatment period.

Infections
In the 16-week atopic dermatitis monotherapy clinical adult 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 adult study, serious infections were reported in 0.6 % of patients treated with placebo and 0.2 % of patients treated with dupilumab. The rates of serious infections remained stable at 5 years in the long-term OLE study (AD-1225).

No increase was observed in the overall incidence of infections with dupilumab compared to placebo in the safety pool for asthma clinical studies. In the 24-week safety pool, serious infections were reported in 1.0% of patients treated with dupilumab and 1.1% of patients treated with placebo. In the 52-week QUEST study, serious infections were reported in 1.3% of patients treated with dupilumab and 1.4% of patients treated with placebo.

No increase was observed in the overall incidence of infections with dupilumab compared to placebo in the safety pool for CRSwNP clinical studies. In the 52-week SINUS-52 study, serious infections were reported in 1.3 % of patients treated with dupilumab and 1.3 % of patients treated with placebo.

No increase was observed in the overall incidence of infections with dupilumab compared to placebo in the safety pool for PN clinical studies. In the safety pool, serious infections were reported in 1.3% of patients treated with dupilumab and 1.3% of patients treated with placebo.

The overall incidence of infections was numerically higher with dupilumab (32.0%) compared to placebo (24.8%) in the safety pool for EoE TREET (Parts A and B) studies. In the 24-week safety pool, serious infections were reported in 0.5% of patients treated with dupilumab and 0% of patients treated with placebo.

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 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 adult patients with PN who received dupilumab 300 mg Q2W for 24 weeks, paediatric patients (6 months to 11 years of age) with atopic dermatitis who received either dupilumab 200 mg Q2W, 200 mg Q4W, or 300 mg Q4W for 16 weeks and patients (6 to 11 years of age) with asthma who received dupilumab 100 mg Q2W or 200 mg Q2W for 52 weeks. Similar ADA responses were observed in

adult patients with atopic dermatitis treated with dupilumab for up to 5 years in the long-term OLE study (AD-1225).

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.

Approximately 9 % of patients with asthma who received dupilumab 200 mg Q2W for 52 weeks developed antibodies to dupilumab; approximately 4 % exhibited persistent ADA responses and approximately 4 % had neutralizing antibodies.

Approximately 1% of patients with EoE who received dupilumab 300 mg QW or 300 mg Q2W for 24 weeks developed antibodies to dupilumab; 0% exhibited persistent ADA responses and approximately 0.5% had neutralizing antibodies.

Regardless of age or population, up 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

Atopic dermatitis

Adolescents (12 to 17 years of age)
The safety of dupilumab was assessed in a study of 250 patients 12 to 17 years of age with moderate-to-severe atopic dermatitis (AD-1526). 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.

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

Children 6 months to 5 years of age
The safety of dupilumab with concomitant TCS was assessed in a study of 161 patients 6 months to 5 years of age with moderate-to-severe atopic dermatitis, which included a subgroup of 124 patients with severe atopic dermatitis (AD-1539). The safety profile of dupilumab with concomitant TCS in these patients through week 16 was similar to the safety profile from studies in adults and paediatric patients 6 to 17 years of age with atopic dermatitis.

Atopic Hand and Foot Dermatitis
The safety of dupilumab was assessed in 27 paediatric patients 12 to 17 years of age with moderate-to-severe atopic hand and foot dermatitis (AD-1924). The safety profile of dupilumab in these patients through Week 16 was consistent with the safety profile from studies in adult and paediatric patients 6 months of age and older with moderate-to-severe AD.

Asthma

Adolescents (12 to 17 years of age)
A total of 107 adolescents aged 12 to 17 years with asthma were enrolled in the 52 week QUEST study. The safety profile observed was similar to that seen in adults.

The long-term safety of dupilumab was assessed in 89 adolescent patients who were enrolled in an open-label extension study in moderate-to-severe asthma (TRAVERSE). In this study, patients were followed for up to 96 weeks. The safety profile of dupilumab in TRAVERSE was consistent with the safety profile observed in pivotal asthma studies for up to 52 weeks of treatment.

Children 6 to 11 years of age
In children 6 to 11 years of age with moderate-to-severe asthma (VOYAGE), the additional adverse reaction of enterobiasis was reported in 1.8 % (5 patients) in the dupilumab groups and none in the placebo group. All enterobiasis cases were mild to moderate and patients recovered with anti-helminth treatment without dupilumab treatment discontinuation.

In children 6 to 11 years of age with moderate-to-severe asthma, eosinophilia (blood eosinophils ≥ 3,000 cells/mcL or deemed by the investigator to be an adverse event) was reported in 6.6 % of the dupilumab groups and 0.7% in the placebo group. Most eosinophilia cases were mild to moderate and not associated with clinical symptoms. These cases were transient, decreased over time, and did not lead to dupilumab treatment discontinuation.

The long-term safety of dupilumab was assessed in an open-label extension study (EXCURSION) in children 6 to 11 years of age with moderate-to-severe asthma who previously participated in VOYAGE. Among 365 patients who entered EXCURSION, 350 completed 52 weeks of treatment and 228 patients completed a cumulative treatment duration of 104 weeks (VOYAGE and EXCURSION). The long-term safety profile of dupilumab in EXCURSION was consistent with the safety profile observed in the pivotal asthma study (VOYAGE) for 52 weeks of treatment.

EoE
A total of 99 adolescents aged 12 to 17 years with EoE were enrolled in the TREET (Parts A and B) studies. The safety profile observed was similar to that seen in adults.

Long-term safety

Atopic dermatitis
The safety profile of dupilumab + TCS (CHRONOS) in adult atopic dermatitis patients) through week 52 was consistent with the safety profile observed at week 16. The long-term safety of dupilumab was assessed in an open-label extension study in patients 6 months to 17 years of age with moderate-to-severe atopic dermatitis (AD-1434). The safety profile of dupilumab in patients followed through week 52 was similar to the safety profile observed at week 16 in the AD-1526, AD-1652, and AD-1539 studies. The long-term safety profile of dupilumab observed in children and adolescents was consistent with that seen in adults with atopic dermatitis.

In a phase 3, multicentre, open label extension (OLE) study (AD-1225), the long-term safety of repeat doses of dupilumab was assessed in 2,677 adults with moderate-to-severe AD exposed to 300 mg weekly dosing (99.7 %), including 179 who completed at least 260 weeks of the study. The long-term safety profile observed in this study up to 5 years was generally consistent with the safety profile of dupilumab observed in controlled studies.

Asthma
The safety profile of dupilumab in the 96 weeks long term safety study (TRAVERSE) was consistent with the safety profile observed in pivotal asthma studies for up to 52 weeks of treatment.

The safety profile of dupilumab in children with asthma 6 to 11 years of age who participated in the 52 weeks long-term safety study (EXCURSION) was consistent with the safety profile observed in the pivotal asthma study (VOYAGE) for 52 weeks of treatment.

CRSwNP
The safety profile of dupilumab in adults with CRSwNP through week 52 was consistent with the safety profile observed at week 24.

Eosinophilic esophagitis

The safety profile of dupilumab through week 52 was generally consistent with the safety profile observed at week 24.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via:

Belgium: Federal Agency for Medicines and Health Products: www.afmps.be – Vigilance Division: Website: www.notifieruneffetindesirable.be – E-mail: adr@fagg-afmps.be
Luxembourg: Centre Régional de Pharmacovigilance de Nancy ou Division de la pharmacie et des médicaments de la Direction de la santé – Website: www.guichet.lu/pharmacovigilance
The Netherlands: Nederlands Bijwerkingen Centrum Lareb – Website: www.lareb.nl

4.9 Overdose

There is no specific treatment for dupilumab overdose. In the event of overdose, the patient should be monitored 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, asthma, CRSwNP, PN, and EoE. 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 in adults and adolescents with atopic dermatitis.

In adult and adolescent patients with asthma, dupilumab treatment relative to placebo markedly decreased FeNO and circulating concentrations of eotaxin-3, total IgE, allergen specific IgE, TARC, and periostin, the type 2 biomarkers evaluated in clinical trials. These reductions in type 2 inflammatory biomarkers were comparable for the 200 mg Q2W and 300 mg Q2W regimens. In paediatric (6 to 11 years of age) patients with asthma, dupilumab treatment relative to placebo markedly decreased FeNO and circulating concentrations of total IgE, allergen specific IgE, and TARC, the type 2 biomarkers evaluated in clinical trials. These markers were near maximal suppression after 2 weeks of treatment, except for IgE which declined more slowly. These effects were sustained throughout treatment.

Clinical efficacy and safety in atopic dermatitis

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 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 dupilumab subcutaneous (SC) injections administered as 1) an initial dose of 600 mg dupilumab (two 300 mg injections) on day 1, followed by 300 mg once every two weeks (Q2W); or 2) an initial dose of 600 mg dupilumab on day 1, followed by 300 mg once weekly (QW); or 3) matching placebo. 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.

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). Key secondary and other clinically relevant secondary endpoints are presented in Table 5.

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 Numerical Rating Scale (NRS) was 7.4, 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 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) and 52-week concomitant TCS study (CHRONOS)

In SOLO 1,SOLO 2, and CHRONOS from baseline to week 16, a significantly greater proportion of patients randomised to dupilumab achieved an IGA 0 or 1 response, EASI-75, and/or an improvement of $\geq$ 4 points on the pruritus NRS (key secondary endpoint) compared to placebo (see Table 5).

A significantly greater proportion of patients randomised to dupilumab alone or with TCS achieved a rapid improvement in the pruritus NRS compared to placebo or placebo + TCS (defined as $\geq$ 4-point improvement as early as week 2, $p < 0.01$ and $p < 0.05$, respectively).

A persistent treatment effect of dupilumab was observed in the CHRONOS study up to week 52 (see Table 6).

The efficacy results for co-primary, key secondary and other clinically relevant secondary endpoints for all three studies are presented in Table 6.

Table 6: Efficacy results of dupilumab monotherapy at week 16 (FAS) and with concomitant TCS[a] at week 16 and week 52

	SOLO 1 Week 16 (FAS)[b]		SOLO 2 Week 16 (FAS)[b]		CHRONOS Week 16 (FAS)[h]		CHRONOS Week 52 (FAS Week 52)[h]	
	Placebo	**Dupilumab 300 mg Q2W**	**Placebo**	**Dupilumab 300 mg Q2W**	**Placebo + TCS**	**Dupilumab 300 mg Q2 W + TCS**	**Placebo + TCS**	**Dupilumab 300 mg Q2W + TCS**
Patients randomised	224	224	236	233	315	106	264	89
IGA 0 or 1[c], % responders[d]	10.3 %	37.9 %[g]	8.5 %	36.1 %[g]	12.4 %	38.7 %[g]	12.5 %	36.0 %[g]
EASI-50, % responders[d]	24.6 %	68.8 %[g]	22.0 %	65.2 %[g]	37.5 %	80.2 %[j]	29.9 %	78.7 %[j]
EASI-75, % responders[d]	14.7 %	51.3 %[g]	11.9 %	44.2 %[g]	23.2 %	68.9 %[g]	21.6 %	65.2 %[g]
EASI-90, % responders[d]	7.6 %	35.7 %[g]	7.2 %	30.0 %[g]	11.1 %	39.6 %[j]	15.5 %	50.6 %[j]
Pruritus NRS, LS mean % change from baseline (+/- SE)	-26.1 % (3.02)	-51.0 %[g] (2.50)	-15.4 % (2.98)	-44.3 %[g] (2.28)	-30.3 % (2.36)	-56.6 %[g] (3.95)	-31.7 % (3.95)	-57.0 %[i] (6.17)
Pruritus NRS (≥ 4-point improvement), % responders[d, e, f]	12.3 % (26/212)	40.8 %[g] (87/213)	9.5% (21/221)	36.0 %[g] (81/225)	19.7 % (59/299)	58.8 %[g] (60/102)	12.9 % (32/249)	51.2 %[g] (44/86)

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 randomised.

[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]the number of patients with baseline pruritus NRS ≥ 4 as denominator.

[f]a significantly greater proportion of patients on dupilumab had improvement in pruritus NRS of ≥ 4 points compared to placebo at week 2 ($p < 0.01$).

[g]p-value < 0.0001, statistically significant vs placebo with adjustment for multiplicity.

[h]full analysis set (FAS) includes all patients randomised. FAS week 52 includes all patients randomised at least one year before the cutoff date of the primary analysis.

[i]nominal p-value = 0.0005

[j]nominal p-value < 0.0001

In SOLO1, SOLO2 and CHRONOS similar results were observed in patients receiving Dupilumab 300 mg QW.

Figure 1a and Figure 1b show the mean percent change from baseline in EASI and the mean percent change from baseline in NRS respectively up to week 16 in SOLO1 and SOLO2.

Figure 2a and Figure 2b 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.

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

Figure 1a. SOLO 1 and SOLO 2 EASI

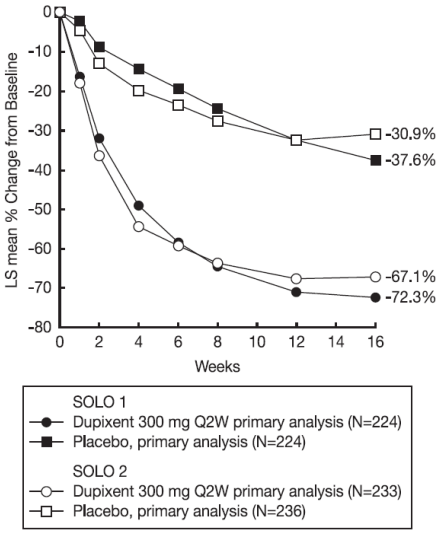
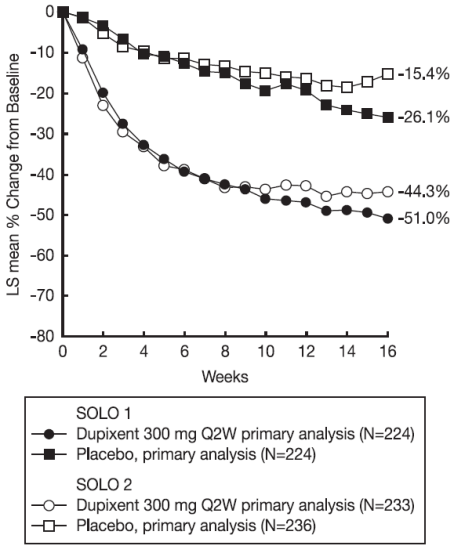


Figure 1b. SOLO 1 and SOLO 2 NRS



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 randomised.

Figure 2: Mean percent change from baseline in EASI and pruritus NRS in CHRONOS[a] (FAS Week 52)[b]

Figure 2a. CHRONOS EASI

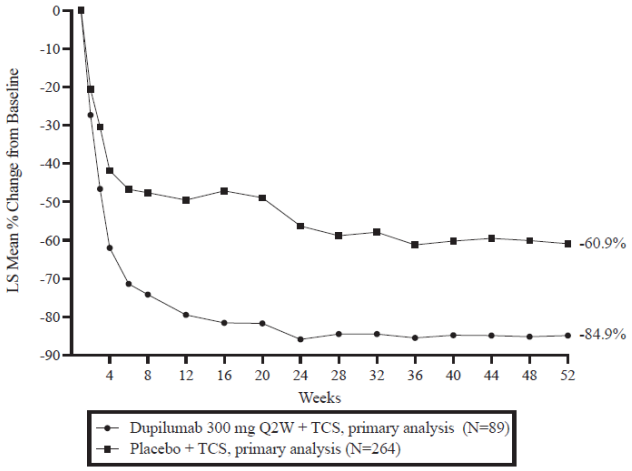
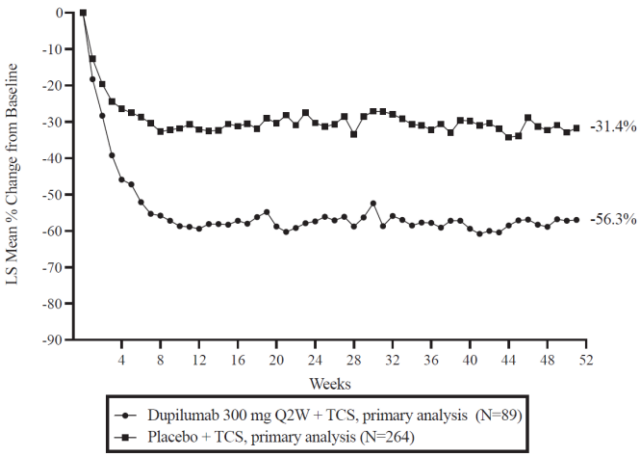


Figure 2b. CHRONOS NRS



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 randomised 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 SOLO 1, SOLO 2, and CHRONOS were consistent with the results in the overall study population within each of these studies.

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, and the baseline mean DLQI was 13.8.

Primary endpoint (proportion of patients with EASI-75) and secondary endpoints for the 16 week CAFE study are summarized in Table 7.

Table 7: 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)
DLQI, LS mean change from baseline (SE)	-4.5 (0.49)	-9.5 (0.46)	-8.8 (0.45)

(all p-values < 0.0001, statistically significant vs placebo with adjustment for multiplicity.)

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-randomised 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 8.

Table 8: 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-value < 0.05, *p-value < 0.01, **p-value < 0.001, ***p-value ≤ 0.0001 (all statistically significant vs placebo with adjustment for multiplicity.)

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, anxiety and depression symptoms as measured by HADS, and health-related quality of life as measured by POEM and DLQI total scores, respectively, at 16 weeks compared to placebo (see Table 9).

Similarly, 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 (see Table 9).

Table 9: Additional secondary endpoint results of dupilumab monotherapy at week 16 and concomitant use of TCS at week 16 and week 52

	SOLO 1 Week 16 (FAS)		SOLO 2 Week 16 (FAS)		CHRONOS Week 16 (FAS)		CHRONOS Week 52 (FAS Week 52)	
	Placebo	**Dupilumab 300 mg Q2W**	**Placebo**	**Dupilumab 300 mg Q2W**	**Placebo +TCS**	**Dupilumab 300 mg Q2W + TCS**	**Placebo +TCS**	**Dupilumab 300 mg Q2W + TCS**
Patients randomized	224	224	236	233	315	106	264	89
DLQI, LS mean change from baseline (SE)	-5.3 (0.50)	-9.3[a] (0.40)	-3.6 (0.50)	-9.3[a] (0.38)	-5.8 (0.34)	-10.0[f] (0.50)	-7.2 (0.40)	-11.4[f] (0.57)
POEM, LS mean change from baseline (SE)	-5.1 (0.67)	-11.6[a] (0.49)	-3.3 (0.55)	-10.2[a] (0.49)	-5.3 (0.41)	-12.7[f] (0.64)	-7.0 (0.57)	-14.2[f] (0.78)
HADS, LS mean change from baseline (SE)	-3.0 (0.65)	-5.2[b] (0.54)	-0.8 (0.44)	-5.1[a] (0.39)	-4.0 (0.37)	-4.9[c] (0.58)	-3.8 (0.47)	-5.5[e] (0.71)
DLQI (≥ 4-point improvement), % responders[d]	30.5 % (65/213)	64.1 %[f] (134/209)	27.6 % (62/225)	73.1 %[f] (163/223)	43.0 % (129/300)	74.3 %[f] (231/311)	30.3 % (77/254)	80.0 %[f] (68/85)
POEM (≥ 4-point improvement), % responders[d]	26.9 % (60/223)	67.6 %[f] (150/222)	24.4 % (57/234)	71.7 %[f] (167/233)	36.9 % (115/312)	77.4 %[f] (246/318)	26.1 % (68/261)	76.4 %[f] (68/89)
Patients achieving HADS-anxiety and HADS-depression score < 8, %[d]	12.4 % (12/97)	41.0 %[f] (41/100)	6.1 % (7/115)	39.5 %[f] (51/129)	26.4 % (39/148)	47.4 %[g] (73/154)	18.0 % (24/133)	43.4 %[g] (23/53)

LS = least squares; SE = standard error

[a]p-value < 0.0001,[b]p-value < 0.001, [c]p-value < 0.05 (all statistically significant vs placebo with adjustment for multiplicity.

[d]the number of patients with baseline pruritus DLQI, POEM, and HADS as denominator.

[e]nominal p-value < 0.05, [f]nominal p-value < 0.0001, [g]nominal p-value < 0.001

In SOLO1, SOLO2 and CHRONOS similar results were observed in patients receiving Dupilumab 300 mg QW.

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 ≥10 %. Eligible patients enrolled into this study had previous inadequate response to topical medication.

Patients received dupilumab was administered by subcutaneous (SC) injections either as: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; or 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. 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 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.

Clinical Response

The efficacy results at week 16 for adolescent atopic dermatitis study are presented in Table 10.

Table 10: 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 randomised	**85**[a]	**82**[a]
IGA 0 or 1[b], % responders[c]	2.4 %	24.4 %[d]
EASI-50, % responders[c]	12.9 %	61.0 %[d]
EASI-75, % responders[c]	8.2 %	41.5 %[d]
EASI-90, % responders[c]	2.4 %	23.2 %[d]
EASI, LS mean % change from baseline (+/-SE)	-23.6 % (5.49)	-65.9 %[d] (3.99)
Pruritus NRS, LS mean % change from baseline (+/- SE)	-19.0 % (4.09)	-47.9 %[d] (3.43)
Pruritus NRS (≥ 4-point improvement), % responders[c]	4.8 %	36.6 %[d]
CDLQI, LS mean change from baseline (+/-SE)	-5.1 (0.62)	-8.5[d] (0.50)
CDLQI, (≥ 6-point improvement), % responders	19.7 %	60.6 %[e]
POEM, LS mean change from baseline (+/- SE)	-3.8 (0.96)	-10.1[d] (0.76)
POEM, (≥ 6-point improvement), % responders	9.5 %	63.4 %[e]

[a]full Analysis Set (FAS) includes all patients randomised.
[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).
[d]p–value < 0.0001 (statistically significant vs placebo with adjustment for multiplicity)
[e]nominal p-value < 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.

The dupilumab group significantly improved patient-reported symptoms, the impact of AD on sleep and health-related quality of life as measured by POEM 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.

Paediatrics (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 severe 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 ≥ 15 %. Eligible patients enrolled into this trial had previous inadequate response to topical medication. Enrollment 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.

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 co-primary endpoint was the proportion of patients with IGA 0 or 1 (“clear” or “almost clear”) at 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.

Clinical Response

Table 11 presents the results by baseline weight strata for the approved dose regimens.

Table 11: 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=122)	(N=123)	(N=59)	(N=62)
	≥ 15 kg	≥ 15 kg	≥ 30 kg	≥ 30 kg
IGA 0 or 1[b], % responders[c]	32.8 %[f]	11.4 %	39.0 %[h]	9.7 %
EASI-50, % responders[c]	91.0 %[f]	43.1 %	86.4 %[g]	43.5 %
EASI-75, % responders[c]	69.7 %[f]	26.8 %	74.6 %[g]	25.8 %
EASI-90, % responders[c]	41.8 %[f]	7.3 %	35.6 %[h]	8.1 %
EASI, LS mean % change from baseline (+/-SE)	-82.1 %[f] (2.37)	-48.6 % (2.46)	-80.4 %[g] (3.61)	-48.3 % (3.63)
Pruritus NRS, LS mean % change from baseline (+/- SE)	-54.6 %[f] (2.89)	-25.9 % (2.90)	-58.2 %[g] (4.01)	-25.0 % (3.95)
Pruritus NRS (≥4-point improvement), % responders[c]	50.8 %[f]	12.3 %	61.4 %[g]	12.9 %
CDLQI, LS mean change from baseline (+/-SE)	-10.6[f] (0.47)	-6.4 (0.51)	-9.8[g] (0.63)	-5.6 (0.66)
CDLQI, (≥ 6-point improvement), % responders	77.3 %[g]	38.8 %	80.8 %[g]	35.8 %
POEM, LS mean change from baseline (+/- SE)	-13.6[f] (0.65)	-5.3 (0.69)	-13.6[g] (0.90)	-4.7 (0.91)
POEM, (≥ 6-point improvement), % responders	81.7 %[g]	32.0 %	79.3 %[g]	31.1 %

[a]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 400 mg (baseline weight ≥ 30 kg) of dupilumab.
[f]p-value < 0.0001 (statistically significant vs placebo with adjustment for multiplicity)
[g]nominal p-values < 0.0001
[h]nominal p-value = 0.0002

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).

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

The long-term efficacy and safety of dupilumab + TCS in paediatric patients with moderate to severe 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. Some patients receiving dupilumab 300 mg Q4W + TCS showed further clinical benefit when escalated to dupilumab 200 mg Q2W + TCS. The safety profile of dupilumab in patients followed through week 52 was similar to the safety profile observed at week 16 in the AD-1526 and AD-1652 studies.

Paediatrics (6 Months to 5 years of age)

The efficacy and safety of dupilumab + TCS in paediatric patients was evaluated in a multicentre, randomised, double-blind, placebo-controlled study (AD-1539) in 162 patients 6 months to 5 years of age, with moderate-to-severe AD (ITT population) defined by an IGA score ≥ 3 (scale of 0 to 4), an EASI score ≥ 16 (scale of 0 to 72), and a minimum BSA involvement of ≥ 10. Of the 162 patients, 125 patients had severe AD defined by an IGA score of 4. Eligible patients enrolled into this study had

previous inadequate response to topical medication. Enrollment was stratified by baseline weight (≥ 5 to < 15 kg and ≥ 15 to < 30 kg).

Patients in the dupilumab Q4W + TCS group with baseline weight of ≥ 5 to < 15 kg received an initial dose of 200 mg on Day 1, followed by 200 mg Q4W from week 4 to week 12, and patients with baseline weight of ≥ 15 to < 30 kg received an initial dose of 300 mg on Day 1, followed by 300 mg Q4W from week 4 to week 12. Patients were permitted to receive rescue treatment at the discretion of the investigator. Patients who received rescue treatment were considered non-responders.

In AD-1539, the mean age was 3.8 years, the median weight was 16.5 kg, 38.9% of patients were female, 68.5% were White, 18.5% were Black, and 6.2% were Asian. At baseline, the mean BSA involvement was 58.4%, and 15.5% had received prior systemic non-steroidal immunosuppressants. Also, at baseline the mean EASI score was 34.1, and the weekly average of daily worst itch score was 7.6 on a scale of 0-10. Overall, 81.4% of patients had at least one co-morbid allergic condition; 68.3% had food allergies, 52.8% had other allergies, 44.1% had allergic rhinitis, and 25.5% had asthma.

These baseline disease characteristics were comparable between moderate-to-severe and severe AD populations.

The co-primary endpoint was the proportion of patients with IGA 0 or 1 ("clear" or "almost clear", at 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. The primary endpoint was the proportion of patients with an IGA 0 (clear) or 1 (almost clear) at week 16.

Clinical Response

The efficacy results at week 16 for AD-1539 are presented in Table 12.

Table 12: Efficacy results of dupilumab with concomitant TCS in AD-1539 at Week 16 (FAS)[a]

	Dupilumab 200 mg (5 to < 15kg) or 300 mg (15 to < 30 kg) Q4W[d]+ TCS (ITT population)(N=83)[a]	**Placebo + TCS (ITT population) (N=79)**	**Dupilumab 200 mg (5 to < 15kg) or 300 mg (15 to < 30 kg) Q4W[d]+ TCS (severe AD population) (N=63)**	**Placebo + TCS (severe AD population) (N=62)**
IGA 0 or 1[b,c]	27.7%[e]	3.9%	14.3%[f]	1.7%
EASI-50, % responders[c]	68.7%[e]	20.2%	60.3%[g]	19.2%
EASI-75[c]	53.0%[e]	10.7%	46.0%[g]	7.2%
EASI-90[c]	25.3%[e]	2.8%	15.9%[h]	0%
EASI, LS mean % change from baseline (+/-SE)	-70.0%[e] (4.85)	-19.6% (5.13)	-55.4%[g] (5.01)	-10.3% (5.16)
Worst scratch/itch NRS, LS mean % change from baseline (+/-SE)*	-49.4%[e] (5.03)	-2.2% (5.22)	-41.8[g] (5.35)	0.5 (5.40)
Worst Scratch/Itch NRS (≥4-point improvement)[c] *	48.1%[e]	8.9%	42.3%[i]	8.8%
Patient's sleep quality NRS, LS mean change from baseline (+/-SE)*	2.0[e] (0.25)	0.3 (0.26)	1.7[g] (0.25)	0.2 (0.25)
Patient's skin pain NRS, LS mean change from baseline (+/-SE)*	-3.9[e] (0.30)	-0.6 (0.30)	-3.4[g] (0.29)	-0.3 (0.29)

POEM, LS mean change from baseline (+/- SE)*	-12.9[e] (0.89)	-3.8 (0.92)	-10.6[g] (0.93)	-2.5 (0.95)

[a]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 (62% and 19% in the placebo and dupilumab arms, respectively) or with missing data were considered as non-responders.

[d]At Day 1, patients received 200 mg (5 to <15kg) or 300 mg (15 to <30 kg) of dupilumab.

[e]p–values < 0.0001,[f]nominal p-value < 0.05, [g]nominal p-value < 0.0001, [h]nominal p-value < 0.005, [i]nominal p-value < 0.001

*Caregiver reported outcome

A significantly greater proportion of patients randomised to dupilumab + TCS achieved a rapid improvement in the Worst Scratch/Itch NRS compared to placebo + TCS (defined as ≥ 4-point improvement as early as week 3, nominal p< 0.005) and the proportion of patients responding on the Worst Scratch/Itch NRS continued to increase through the treatment period.

In this study, dupilumab significantly improved health-related quality of life as measured by the CDLQI (in 85 patients 4 to 5 years old) and IDQOL (in 77 patients 6 months to 3 years old). In the ITT population, greater LS mean changes in CDLQI and IDQOL scores from baseline to week 16 were observed in the dupilumab + TCS (-10.0 and -10.9) group compared to the placebo + TCS group (-2.5 and -2.0), respectively (p< 0.0001). Similar improvements in both CDLQI and IDQOL were observed in the severe AD population.

The long-term efficacy and safety of dupilumab + TCS in paediatric patients with moderate to severe atopic dermatitis who had participated in the previous clinical trials of dupilumab + TCS were assessed in an open-label extension study (AD-1434). Efficacy data from this trial suggest that clinical benefit provided at week 16 was sustained through week 52. The safety profile of dupilumab in patients followed through week 52 was similar to the safety profile observed at week 16 in the AD-1539 study.

Atopic Hand and Foot Dermatitis (adults and adolescents)

The efficacy and safety of dupilumab was evaluated in a 16-week multicenter, randomized, double-blind, parallel-group, placebo-controlled trial (AD-1924) in 133 adult and paediatric patients 12 to 17 years of age with moderate-to-severe atopic hand and foot dermatitis, defined by an IGA (hand and foot) score ≥3 (scale of 0 to 4) and a hand and foot Peak Pruritus Numeric Rating Scale (NRS) score for maximum itch intensity ≥4 (scale of 0 to 10). Eligible patients had previous inadequate response or intolerance to treatment of hand and foot dermatitis with topical AD medications.

In AD-1924, 38% of patients were male, 80% were White, 72% of subjects had a baseline IGA (hand and foot) score of 3 (moderate atopic hand and foot dermatitis), and 28% of patients had a baseline IGA (hand and foot) score of 4 (severe atopic hand and foot dermatitis). The baseline weekly averaged hand and foot Peak Pruritus NRS score was 7.1.

The primary endpoint was the proportion of patients with an IGA hand and foot score of 0 (clear) or 1 (almost clear) at Week 16. The key secondary endpoint was reduction of itch as measured by the hand and foot Peak Pruritus NRS (≥4-point improvement). Other patient reported outcomes included assessment of hand and foot skin pain NRS (0-10), quality of sleep NRS (0-10), quality of life in Hand Eczema Questionnaire (0-117) (QoLHEQ) and work productivity and impairment (WPAI) (0-100%).

The proportion of patients with an IGA (hand and foot) 0 to 1 at Week 16 was 40.3% for dupilumab and 16.7% for placebo (treatment difference 23.6, 95% CI: 8.84, 38.42). The proportion of patients with improvement (reduction) of weekly averaged hand and foot Peak Pruritus NRS ≥4 at Week 16 was 52.2% for dupilumab and 13.6% for placebo (treatment difference 38.6, 95% CI: 24.06, 53.15).

Greater improvements for hand and foot skin pain NRS, quality of sleep NRS, QoLHEQ score and WPAI overall work impairment and routine activity impairment from baseline to week 16 were seen in the dupilumab group as compared to the placebo group (LS mean change of dupilumab vs placebo: -4.66 vs -1.93 [$p < 0.0001$], 0.88 vs -0.00 [$p < 0.05$], -40.28 vs -16.18 [$p < 0.0001$], -38.57% vs -22.83% [nominal $p<0.001$] and -36.39% vs -21.26% [nominal $p < 0.001$] respectively).

Clinical efficacy and safety in asthma

The asthma development program included three randomised, double-blind, placebo-controlled, parallel-group, multi-centre studies (DRI12544, QUEST, and VENTURE) of 24 to 52 weeks in treatment duration which enrolled a total of 2,888 patients (12 years of age and older). Patients were enrolled without requiring a minimum baseline blood eosinophil or other type 2 inflammatory biomarkers (e.g. FeNO or IgE) level. Asthma treatment guidelines define type 2 inflammation as eosinophilia ≥ 150 cells/mcL and/or FeNO ≥ 20 ppb. In DRI12544 and QUEST, the pre-specified subgroup analyses included blood eosinophils ≥ 150 and ≥ 300 cells/mcL, FeNO ≥ 25 and ≥ 50 ppb.

DRI12544 was a 24-week dose-ranging study which included 776 patients (18 years of age and older). Dupilumab compared with placebo was evaluated in adult patients with moderate to severe asthma on a medium-to-high dose inhaled corticosteroid and a long acting beta agonist. The primary endpoint was change from baseline to week 12 in FEV_1 (L). Annualised rate of severe asthma exacerbation events during the 24-week placebo controlled treatment period was also determined. Results were evaluated in the overall population (unrestricted by minimum baseline eosinophils or other type 2 inflammatory biomarkers) and subgroups based on baseline blood eosinophil count.

QUEST was a 52-week confirmatory study which included 1,902 patients (12 years of age and older). Dupilumab compared with placebo was evaluated in 107 adolescent and 1,795 adult patients with persistent asthma on a medium-to-high dose inhaled corticosteroid (ICS) and a second controller medication. Patients requiring a third controller were allowed to participate in this trial. The primary endpoints were the annualised rate of severe exacerbation events during the 52-week placebo controlled period and change from baseline in pre-bronchodilator FEV_1 at week 12 in the overall population (unrestricted by minimum baseline eosinophils or other type 2 inflammatory biomarkers) and subgroups based on baseline blood eosinophil count and FeNO.

VENTURE was a 24-week oral corticosteroid-reduction study in 210 patients with asthma unrestricted by baseline type 2 biomarker levels who required daily oral corticosteroids in addition to regular use of high dose inhaled corticosteroids plus an additional controller. The OCS dose was optimized during the screening period. Patients continued to receive their existing asthma medicine during the study; however their OCS dose was reduced every 4 weeks during the OCS reduction phase (week 4-20), as long as asthma control was maintained. The primary endpoint was the percent reduction in oral corticosteroid dose assessed in the overall population, based on a comparison of the oral corticosteroid dose at weeks 20 to 24 that maintained asthma control with the previously optimized (at baseline) oral corticosteroid dose.

The demographics and baseline characteristics of these 3 studies are provided in Table 13 below.

Table 13: Demographics and baseline characteristics of asthma trials

Parameter	**DRI12544 (n = 776)**	**QUEST (n = 1902)**	**VENTURE (n=210)**
Mean age (years) (SD)	48.6 (13.0)	47.9 (15.3)	51.3 (12.6)
% Female	63.1	62.9	60.5
% White	78.2	82.9	93.8
Duration of Asthma (years), mean ± SD	22.03 (15.42)	20.94 (15.36)	19.95 (13.90)

Never smoked, (%)	77.4	80.7	80.5
Mean exacerbations in previous year ± SD	2.17 (2.14)	2.09 (2.15)	2.09 (2.16)
High dose ICS use (%)[a]	49.5	51.5	88.6
Pre-dose FEV_1 (L) at baseline ± SD	1.84 (0.54)	1.78 (0.60)	1.58 (0.57)
Mean percent predicted FEV_1 at baseline (%)(± SD)	60.77 (10.72)	58.43 (13.52)	52.18 (15.18)
% Reversibility (± SD)	26.85 (15.43)	26.29 (21.73)	19.47 (23.25)
Mean ACQ-5 score (± SD)	2.74 (0.81)	2.76 (0.77)	2.50 (1.16)
Mean AQLQ score (± SD)	4.02 (1.09)	4.29 (1.05)	4.35 (1.17)
Atopic Medical History % Overall (AD %, NP %, AR %)	72.9 (8.0, 10.6, 61.7)	77.7 (10.3, 12.7, 68.6)	72.4 (7.6, 21.0, 55.7)
Mean FeNO ppb (± SD)	39.10 (35.09)	34.97 (32.85)	37.61 (31.38)
% patients with FeNO ppb ≥ 25 ≥ 50	 49.9 21.6	 49.6 20.5	 54.3 25.2
Mean total IgE IU/mL **(±** SD)	435.05 (753.88)	432.40 (746.66)	430.58 (775.96)
Mean baseline Eosinophil count (± SD) cells/mcL	350 (430)	360 (370)	350 (310)
% patients with EOS ≥ 150 cells/mcL ≥ 300 cells/mcL	 77.8 41.9	 71.4 43.7	 71.4 42.4

ICS = inhaled corticosteroid; FEV_1 = Forced expiratory volume in 1 second; ACQ-5 = Asthma Control Questionnaire-5; AQLQ = Asthma Quality of Life Questionnaire; AD = atopic dermatitis; NP = nasal polyposis; AR = allergic rhinitis; FeNO = fraction of exhaled nitric oxide; EOS = blood eosinophil

[a]the population in dupilumab asthma trials included patients on medium and high dose ICS. The medium ICS dose was defined as equal to 500 mcg fluticasone or equivalent per day.

Exacerbations

In the overall population in DRI12544 and QUEST subjects receiving either dupilumab 200 mg or 300 mg every other week had significant reductions in the rate of severe asthma exacerbations compared to placebo. There were greater reductions in exacerbations in subjects with higher baseline levels of type 2 inflammatory biomarkers such as blood eosinophils or FeNO (Table 14 and Table 15).

Table 14: Rate of severe exacerbations in DRI12544 and QUEST (baseline blood eosinophil levels ≥ 150 and ≥ 300 cells/mcL)

Treatment	**Baseline blood EOS**							
	≥150 cells/mcL				**≥300 cells/mcL**			
	Exacerbations per Year			**% reduction**	**Exacerbations per Year**			**% reduction**
	N	**Rate (95% CI)**	**Rate ratio (95%CI)**		**N**	**Rate (95% CI)**	**Rate ratio (95%CI)**	
All Severe Exacerbations								
DRI12544 study								
Dupilumab 200 mg Q2W	120	0.29 (0.16, 0.53)	0.28[a] (0.14, 0.55)	72 %	65	0.30 (0.13, 0.68)	0.29[c] (0.11, 0.76)	71 %
Dupilumab 300 mg Q2W	129	0.28 (0.16, 0.50)	0.27[b] (0.14, 0.52)	73 %	64	0.20 (0.08, 0.52)	0.19[d] (0.07, 0.56)	81 %
Placebo	127	1.05 (0.69, 1.60)			68	1.04 (0.57, 1.90)		
QUEST study								

Dupilumab 200 mg Q2W	437	0.45 (0.37, 0.54)	0.44[f] (0.34,0.58)	56 %	264	0.37 (0.29, 0.48)	0.34[f] (0.24,0.48)	66 %
Placebo	232	1.01 (0.81, 1.25)			148	1.08 (0.85, 1.38)		
Dupilumab 300 mg Q2W	452	0.43 (0.36, 0.53)	0.40 [e] (0.31,0.53)	60 %	277	0.40 (0.32, 0.51)	0.33[e] (0.23,0.45)	67 %
Placebo	237	1.08 (0.88, 1.33)			142	1.24 (0.97, 1.57)		

[a]p-value = 0.0003, [b]p-value = 0.0001, [c]p-value = 0.0116, [d]p-value = 0.0024, [e]p-value < 0.0001 (all statistically significant vs placebo with adjustment for multiplicity); [f]nominal p-value < 0.0001

Table 15. Rate of severe exacerbations in QUEST defined by baseline FeNO subgroups

Treatment	Exacerbations per Year			% reduction
	N	Rate (95% CI)	Rate ratio (95%CI)	
FeNO ≥ 25 ppb				
Dupilumab 200 mg Q2W	299	0.35 (0.27, 0.45)	0.35 (0.25, 0.50)[a]	65 %
Placebo	162	1.00 (0.78, 1.30)		
Dupilumab 300 mg Q2W	310	0.43 (0.35, 0.54)	0.39 (0.28, 0.54) [a]	61 %
Placebo	172	1.12 (0.88, 1.43)		
FeNO ≥ 50 ppb				
Dupilumab 200 mg Q2W	119	0.33 (0.22, 0.48)	0.31 (0.18, 0.52) [a]	69 %
Placebo	71	1.057 (0.72, 1.55)		
Dupilumab 300 mg Q2W	124	0.39 (0.27, 0.558)	0.31 (0.19, 0.49) [a]	69 %
Placebo	75	1.27 (0.90, 1.80)		

[a]nominal p-value < 0.0001

In the pooled analysis of DRI12544 and QUEST, hospitalisations and/or emergency room visits due to severe exacerbations were reduced by 25.5 % and 46.9 % with dupilumab 200 mg or 300 mg every other week, respectively.

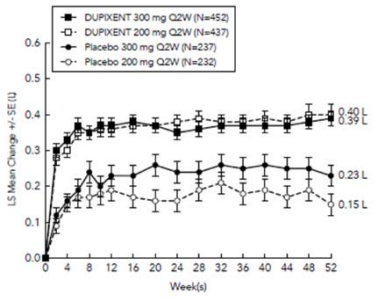
Lung function

Clinically significant increases in pre-bronchodilator FEV_1 were observed at week 12 for DRI12544 and QUEST. There were greater improvements in FEV_1 in the subjects with higher baseline levels of type 2 inflammatory biomarkers such as blood eosinophils or FeNO (Table 16 and Table 17).

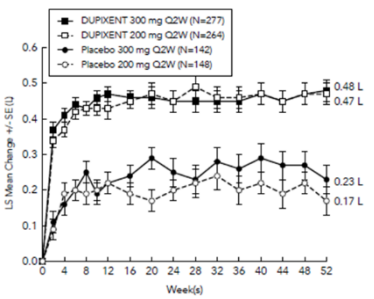
Significant improvements in FEV_1 were observed as early as week 2 following the first dose of dupilumab for both the 200 mg and 300 mg dose strengths and were maintained through week 24 (DRI12544) and week 52 in QUEST (see Figure 3).

Figure 3: Mean change from baseline in pre-bronchodilator FEV_1 (L) over time (baseline eosinophils ≥ 150 and ≥ 300 cells/mcL and FeNO ≥ 25 ppb) in QUEST

QUEST: blood eosinophils ≥ 150 cells/mcL



QUEST: blood eosinophils ≥ 300 cells/mcL



QUEST: FeNO ≥ 25 ppb

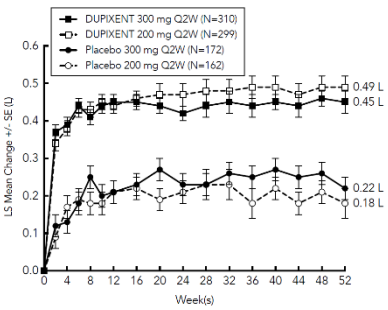


Table 16: Mean change from baseline in pre-bronchodilator FEV_1 at week 12 in DRI12544 and QUEST (baseline blood eosinophil Levels ≥ 150 and ≥ 300 cells/mcL)

Treatment	Baseline blood EOS					
	≥ 150 cells/mcL			≥ 300 cells/mcL		
	N	LS mean Δ from baseline L (%)	LS mean difference vs. placebo (95% CI)	N	LS mean Δ from baseline L (%)	LS mean difference vs. placebo (95% CI)
DRI12544 study						
Dupilumab 200 mg Q2W	120	0.32 (18.25)	0.23[a] (0.13, 0.33)	65	0.43 (25.9)	0.26[c] (0.11, 0.40)
Dupilumab 300 mg Q2W	129	0.26 (17.1)	0.18[b] (0.08, 0.27)	64	0.39 (25.8)	0.21[d] (0.06, 0.36)
Placebo	127	0.09 (4.36)		68	0.18 (10.2)	
QUEST study						
Dupilumab 200 mg Q2W	437	0.36 (23.6)	0.17[f] (0.11, 0.23)	264	0.43 (29.0)	0.21[f] (0.13, 0.29)
Placebo	232	0.18 (12.4)		148	0.21 (15.6)	
Dupilumab 300 mg Q2W	452	0.37 (25.3)	0.15[e] (0.09, 0.21)	277	0.47 (32.5)	0.24[e] (0.16, 0.32)
Placebo	237	0.22 (14.2)		142	0.22 (14.4)	

[a]p-value < 0.0001, [b]p-value = 0.0004, [c]p-value = 0.0008, [d]p-value = 0.0063, [e]p-value < 0.0001 (all statistically significant vs placebo with adjustment for multiplicity); [f]nominal p-value < 0.0001

Table 17: Mean change from baseline in pre-bronchodilator FEV_1 at week 12 and week 52 in QUEST by baseline FeNO subgroups

Treatment		At week 12		At week 52	
	N	LS mean Δ from baseline L (%)	LS mean difference vs. placebo (95% CI)	LS mean Δ from baseline L (%)	LS mean difference vs. placebo (95% CI)
FeNO ≥ 25 ppb					
Dupilumab 200 mg Q2W	288	0.44 (29.0 %)	0.23 (0.15, 0.31)[a]	0.49 (31.6 %)	0.30 (0.22, 0.39)[a]
Placebo	157	0.21 (14.1 %)		0.18 (13.2 %)	
Dupilumab 300 mg Q2W	295	0.45 (29.8 %)	0.24 (0.16, 0.31)[a]	0.45 (30.5 %)	0.23 (0.15, 0.31)[a]
Placebo	167	0.21 (13.7 %)		0.22 (13.6 %)	
FeNO ≥ 50 ppb					
Dupilumab 200 mg Q2W	114	0.53 (33.5 %)	0.30 (0.17, 0.44)[a]	0.59 (36.4 %)	0.38 (0.24, 0.53)[a]
Placebo	69	0.23 (14.9 %)		0.21 (14.6 %)	
Dupilumab 300 mg Q2W	113	0.59 (37.6 %)	0.39 (0.26, 0.52)[a]	0.55 (35.8 %)	0.30 (0.16, 0.44)[a]
Placebo	73	0.19 (13.0 %)		0.25 (13.6 %)	

[a]nominal p-value < 0.0001

Quality of life/patient-reported outcomes in asthma

Pre-specified secondary endpoint of ACQ-5 and AQLQ(S) responder rates were analysed at 24 weeks (DRI12544 and VENTURE) and at 52 weeks (QUEST, Table 18). The responder rate was defined as an improvement in score of 0.5 or more (scale range 0-6 for ACQ-5 and 1-7 for AQLQ(S)). Improvements in ACQ-5 and AQLQ(S) were observed as early as week 2 and maintained for 24 weeks in DRI12544 study and 52 weeks in QUEST study. Similar results were observed in VENTURE.

Table 18: ACQ-5 and AQLQ(S) responder rates at week 52 in QUEST

PRO	Treatment	EOS ≥ 150 cells/mcL		EOS ≥ 300 cells/mcL		FeNO ≥ 25 ppb	
		N	Responder rate %	N	Responder rate (%)	N	Responder rate (%)
ACQ-5	Dupilumab 200 mg Q2W	395	72.9	239	74.5	262	74.4
	Placebo	201	64.2	124	66.9	141	65.2
	Dupilumab 300 mg Q2W	408	70.1	248	71.0	277	75.8
	Placebo	217	64.5	129	64.3	159	64.2
AQLQ(S)	Dupilumab 200 mg Q2W	395	66.6	239	71.1	262	67.6
	Placebo	201	53.2	124	54.8	141	54.6
	Dupilumab 300 mg Q2W	408	62.0	248	64.5	277	65.3
	Placebo	217	53.9	129	55.0	159	58.5

Oral corticosteroid reduction study (VENTURE)

VENTURE evaluated the effect of dupilumab on reducing the use of maintenance oral corticosteroids. Baseline characteristics are presented in Table 13. All patients were on oral corticosteroids for at least 6 months prior to the study initiation. The baseline mean oral corticosteroid use was 11.75 mg in the placebo group and 10.75 mg in the group receiving dupilumab.

In this 24-week trial, asthma exacerbations (defined as a temporary increase in oral corticosteroid dose for at least 3 days) were reduced by 59 % in subjects receiving dupilumab compared with those receiving placebo (annualised rate 0.65 and 1.60 for the dupilumab and placebo group, respectively; rate ratio 0.41 [95% CI 0.26, 0.63]) and improvement in pre-bronchodilator FEV_1 from baseline to week 24 was greater in subjects receiving dupilumab compared with those receiving placebo (LS mean difference for dupilumab versus placebo of 0.22 L [95% CI: 0.09 to 0.34 L]). Effects on lung function, on oral steroid and exacerbation reduction were similar irrespective of baseline levels of type 2 inflammatory biomarkers (e.g. blood eosinophils, FeNO). The ACQ-5 and AQLQ(S) were also assessed in VENTURE and showed improvements similar to those in QUEST.

The results for VENTURE by baseline biomarkers are presented in the Table 19.

Table 19: Effect of dupilumab on OCS dose reduction, VENTURE (baseline blood eosinophil levels ≥ 150 and ≥ 300 cells/mcL and FeNO ≥ 25 ppb)

	Baseline blood EOS ≥ 150 cells/mcL		Baseline blood EOS ≥ 300 cells/mcL		FeNO ≥ 25 ppb	
	Dupilumab 300 mg Q2W N=81	Placebo N=69	Dupilumab 300 mg Q2W N=48	Placebo N=41	Dupilumab 300 mg Q2W N=57	Placebo N=57
Primary endpoint (week 24)						
Percent reduction in OCS from baseline						
Mean overall percent reduction from baseline (%)	75.91	46.51	79.54	42.71	77.46	42.93
Difference (% [95% CI]) (Dupilumab vs. placebo)	29.39[b] (15.67, 43.12)		36.83[b] (18.94, 54.71)		34.53[b] (19.08, 49.97)	
Median % reduction in daily OCS dose from baseline	100	50	100	50	100	50
Percent reduction from baseline						
100% %	54.3	33.3	60.4	31.7	52.6	28.1
≥ 90 %	58.0	34.8	66.7	34.1	54.4	29.8
≥ 75 %	72.8	44.9	77.1	41.5	73.7	36.8
≥ 50 %	82.7	55.1	85.4	53.7	86.0	50.9
> 0 %	87.7	66.7	85.4	63.4	89.5	66.7
	12.3	33.3	14.6	36.6	10.5	33.3

No reduction or any increase in OCS dose, or dropped out of study						
Secondary endpoint (week 24)[a]						
Proportion of patients achieving a reduction of OCS dose to < 5 mg/day	77	44	84	40	79	34
Odds ratio (95% CI)	4.29[c] (2.04, 9.04)		8.04[d] (2.71, 23.82)		7.21[b] (2.69, 19.28)	

[a]model estimates by logistic regression, [b]nominal p-value < 0.0001, [c]nominal p-value = 0.0001, [d]nominal p-value = 0.0002

Long-term extension study (TRAVERSE)

The long-term safety of dupilumab in 2,193 adults and 89 adolescents with moderate-to-severe asthma, including 185 adults with oral corticosteroid-dependent asthma, who had participated in previous clinical trials of dupilumab (DRI12544, QUEST, and VENTURE), was assessed in the open-label extension study (TRAVERSE) (see section 4.8). Efficacy was measured as a secondary endpoint, was similar to results observed in the pivotal studies and was sustained up to 96 weeks. In the adults with oral-corticosteroid-dependent asthma, there was sustained reduction in exacerbations and improvement in lung function up to 96 weeks, despite decrease or discontinuation of oral corticosteroid dose.

Paediatric study (6 to 11 years of age; VOYAGE)

The efficacy and safety of dupilumab in paediatric patients was evaluated in a 52-week multicentre, randomised, double-blind, placebo-controlled study (VOYAGE) in 408 patients 6 to 11 years of age, with moderate-to-severe asthma on a medium- or high- dose ICS and one controller medication or high dose ICS alone. Patients were randomised to dupilumab (N=273) or matching placebo (N=135) every other week based on body weight ≤ 30 kg or > 30 kg, respectively. The efficacy was evaluated in populations with type 2 inflammation defined as blood eosinophil levels of ≥ 150 cells/mcL or FeNO ≥ 20 ppb.

The primary endpoint was the annualised rate of severe exacerbation events during the 52-week placebo-controlled period and the key secondary endpoint was the change from baseline in pre-bronchodilator FEV_1 percent predicted at week 12. Additional secondary endpoints included mean change from baseline and responder rates in the ACQ-7-IA and PAQLQ(S)-IA scores.

The demographics and baseline characteristics for VOYAGE are provided in Table 20 below.

Table 20. Demographics and baseline characteristics for VOYAGE

Parameter	**EOS ≥ 150 cells/mcL or FeNO ≥ 20 ppb (N = 350)**	**EOS ≥ 300 cells/mcL (N = 259)**
Mean age (years) (SD)	8.9 (1.6)	9.0 (1.6)
% Female	34.3	32.8
% White	88.6	87.3
Mean body weight (kg)	36.09	35.94
Mean exacerbations in previous year (± SD)	2.47 (2.30)	2.64 (2.58)
ICS dose (%) Medium High	 55.7 43.4	 54.4 44.4
Pre-dose FEV_1 (L) at baseline (± SD)	1.49 (0.41)	1.47 (0.42)

Mean percent predicted FEV_1 (%) (±SD)	77.89 (14.40)	76.85 (14.78)
Mean % Reversibility *(*± SD)	27.79 (19.34)	22.59 (20.78)
Mean ACQ-7-IA score (± SD)	2.14 (0.72)	2.16 (0.75)
Mean PAQLQ(S)-IA score (± SD)	4.94 (1.10)	4.93 (1.12)
Atopic Medical History % Overall (AD %, AR %)	94 (38.9, 82.6)	96.5 (44.4, 85.7)
Median total IgE IU/mL (± SD)	905.52 (1140.41)	1077.00 (1230.83)
Mean FeNO ppb (± SD)	30.71 (24.42)	33.50 (25.11)
% patients with FeNO ≥ 20 ppb	58	64.1
Mean baseline Eosinophil count (± SD) cells/mcL	570 (380)	710 (360)
% patients with EOS ≥ 150 cells/mcL ≥ 300 cells/mcL	 94.6 74	 0 100

ICS = inhaled corticosteroid; FEV_1 = Forced expiratory volume in 1 second; ACQ-7-IA = Asthma Control Questionnaire-7 Interviewer Administered; PAQLQ(S)-IA = Paediatric Asthma Quality of Life Questionnaire with Standardised Activities–Interviewer Administered; AD = atopic dermatitis; AR = allergic rhinitis; EOS = blood eosinophil; FeNO = fraction of exhaled nitric oxide

Dupilumab significantly reduced the annualised rate of severe asthma exacerbation events during the 52-week treatment period compared to placebo in the population with the type 2 inflammation and in population defined by baseline blood eosinophils ≥ 300 cells/mcL or by baseline FeNO ≥ 20 ppb. Clinically significant improvements in percent predicted pre-bronchodilator FEV_1 were observed at week 12. Improvements were also observed for ACQ-7-IA and PAQLQ(S)-IA at week 24 and were sustained at week 52. Greater responder rates were observed for ACQ-7-IA and PAQLQ(S)-IA compared to placebo at week 24. The efficacy results for VOYAGE are presented in Table 21.

In the population with the type 2 inflammation, the LS mean change from baseline in pre-bronchodilator FEV_1 at week 12 was 0.22 L in the dupilumab group and 0.12 L in the placebo group, with an LS mean difference versus placebo of 0.10 L (95% CI: 0.04, 0.16). The treatment effect was sustained over the 52-week treatment period, with an LS mean difference versus placebo at week 52 of 0.17 L (95% CI: 0.09, 0.24).

In the population defined by baseline blood eosinophils ≥ 300 cells/mcL, the LS mean change from baseline in pre-bronchodilator FEV_1 at week 12 was 0.22 L in the dupilumab group and 0.12 L in the placebo group, with an LS mean difference versus placebo of 0.10 L (95% CI: 0.03, 0.17). The treatment effect was sustained over the 52-week treatment period, with an LS mean difference versus placebo at week 52 of 0.17 L (95% CI: 0.09, 0.26).

In both primary efficacy populations, there was a rapid improvement in FEF25-75% and FEV_1/FVC (onset of a difference was observed as early as week 2) and sustained over the 52-week treatment period, see Table 21.

Table 21: Rate of severe exacerbations, mean change from baseline in FEV_1, ACQ-7-IA and PAQLQ(S)-IA responder rates in VOYAGE

Treatment	EOS ≥ 150 cells/mcL or FeNO ≥ 20 ppb			EOS ≥ 300 cells/mcL			FeNO ≥20 ppb		
Annualised severe exacerbations rate over 52 weeks									
	N	**Rate (95% CI)**	**Rate ratio (95% CI)**	**N**	**Rate (95% CI)**	**Rate ratio (95% CI)**	**N**	**Rate (95% CI)**	**Rate ratio (95% CI)**
Dupilumab 100 mg Q2W (<30 kg)/ 200 mg Q2W (≥30 kg)	236	0.305 (0.223, 0.416)	0.407[b] (0.274, 0.605)	175	0.235 (0.160, 0.345)	0.353[b] (0.222, 0.562)	141	0.271 (0.170, 0.432)	0.384[c] (0.227, 0.649)
Placebo	114	0.748 (0.542, 1.034)		84	0.665 (0.467, 0.949)		62	0.705 (0.421, 1.180)	
Mean change from baseline in percent predicted FEV1 at week 12									
	N	**LS mean Δ from baseline**	**LS mean difference vs. placebo (95% CI)**	**N**	**LS mean Δ from baseline**	**LS mean difference vs. placebo (95% CI)**	**N**	**LS mean Δ from baseline i**	**LS mean difference vs. placebo (95% CI)**
Dupilumab 100 mg Q2W (<30 kg)/ 200 mg Q2W (≥30 kg)	229	10.53	5.21[c] (2.14, 8.27)	168	10.15	5.32[d] (1.76, 8.88)	141	11.36	6.74[d] (2.54, 10.93)
Placebo	110	5.32		80	4.83		62	4.62	
Mean change from baseline in percent predicted FEF 25-75% at week 12									
	N	**LS mean Δ from baseline**	**LS mean difference vs. placebo (95% CI)**	**N**	**LS mean Δ from baseline**	**LS mean difference vs. placebo (95% CI)**	**N**	**LS mean Δ from baseline**	**LS mean difference vs. placebo (95% CI)**
Dupilumab 100 mg Q2W (<30 kg)/ 200 mg Q2W (≥30 kg)	229	16.70	11.93[e] (7.44, 16.43)	168	16.91	13.92[e] (8.89, 18.95)	141	17.96	13.97[e] (8.30, 19.65)
Placebo	110	4.76		80	2.99		62	3.98	
Mean change from baseline in FEV_1/FVC % at week 12									
	N	**LS mean Δ from baseline**	**LS mean difference vs. placebo (95% CI)**	**N**	**LS mean Δ from baseline**	**LS mean difference vs. placebo (95% CI)**	**N**	**LS mean Δ from baseline**	**LS mean difference vs. placebo (95% CI)**
Dupilumab 100 mg Q2W (<30 kg)/ 200 mg Q2W (≥30 kg)	229	5.67	3.73[e] (2.25, 5.21)	168	6.10	4.63[e] (2.97, 6.29)	141	6.84	4.95[e] (3.08, 6.81)
Placebo	110	1.94		80	1.47		62	1.89	
ACQ-7-IA at week 24[a]									
	N	**Responder rate %**	**OR vs. placebo (95% CI)**	**N**	**Responder rate %**	**OR vs. placebo (95% CI)**	**N**	**Responder rate %**	**OR vs. placebo (95% CI)**
Dupilumab 100 mg Q2W (<30 kg)/ 200 mg Q2W	236	79.2	1.82[g] (1.02, 3.24)	175	80.6	2.79[f] (1.43, 5.44)	141	80.9	2.60[g] (1.21, 5.59)

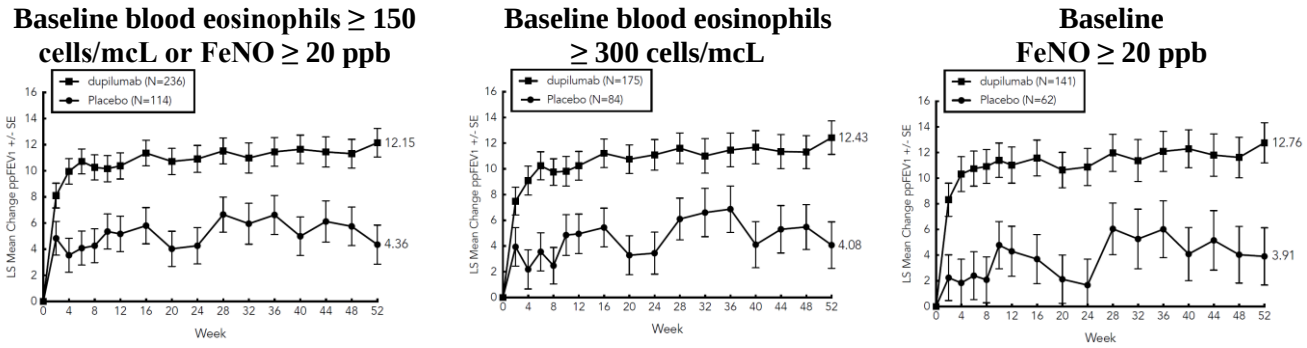
(≥30 kg)									
Placebo	114	69.3		84	64.3		62	66.1	
PAQLQ(S)-IA at week 24[a]									
	N	**Responder rate %**	**OR vs. placebo (95% CI)**	**N**	**Responder rate %**	**OR vs. placebo (95% CI)**	**N**	**Responder rate %**	**OR vs. placebo (95% CI)**
Dupilumab 100 mg Q2W (<30 kg)/ 200 mg Q2W (≥30 kg)	211	73.0	1.57 (0.87, 2.84)	158	72.8	1.84 (0.92, 3.65)	131	75.6	2.09 (0.95, 4.61)
Placebo	107	65.4		81	63.0		61	67.2	

[a]the responder rate was defined as an improvement in score of 0.5 or more (scale range 0-6 for ACQ-7-IA and 1-7 for PAQLQ(S))
[b]p-value < 0.0001; [c]p-value < 0.001, [d]p-value < 0.01 (all statistically significant vs placebo with adjustment for multiplicity);
[e]nominal p-value < 0.0001, [f]nominal p-value < 0.01, [g]nominal p-value < 0.05

Significant improvements in percent predicted FEV1 were observed as early as week 2 and were maintained through week 52 in VOYAGE study.

Improvements in percent predicted FEV_1 over time in VOYAGE are shown in Figure 4.

Figure 4: Mean change from baseline in percent predicted pre-bronchodilator FEV_1 (L) over time in VOYAGE (baseline blood eosinophils ≥ 150 cells/mcL or FeNO ≥ 20 ppb, baseline eosinophils ≥ 300 cells/mcL, and baseline FeNO ≥ 20 ppb)



In VOYAGE, in the population with the type 2 inflammation, the mean annualised total number of systemic corticosteroid courses due to asthma was reduced by 59.3% versus placebo (0.350 [95% CI: 0.256, 0.477] versus 0.860 [95% CI: 0.616, 1.200]). In the population defined by baseline blood eosinophils ≥ 300 cells/mcL, the mean annualised total number of systemic corticosteroid courses due to asthma was reduced by 66.0% versus placebo (0.274 [95% CI: 0.188, 0.399] versus 0.806 [95% CI: 0.563, 1.154]).

Dupilumab improved the overall health status as measured by the European Quality of Life 5-Dimension Youth Visual Analog Scale (EQ-VAS) in both the type 2 inflammation and the baseline blood eosinophil count of ≥ 300 cells/mcL populations at week 52; the LS mean difference versus placebo was 4.73 (95% CI: 1.18, 8.28), and 3.38 (95% CI: -0.66, 7.43), respectively.

Dupilumab reduced the impact of paediatric patient's asthma on the caregiver quality of life as measured by the Paediatric Asthma Quality of Life Questionnaire (PACQLQ) in both the type 2 inflammation and the baseline blood eosinophil count of ≥ 300 cells/mcL population at week 52; the LS mean difference versus placebo was 0.47 (95% CI: 0.22, 0.72), and 0.50 (95% CI: 0.21, 0.79), respectively.

Long-term extension study (EXCURSION)

The efficacy of dupilumab, measured as a secondary endpoint, was assessed in 365 paediatric asthma patients (6 to 11 years of age) in the long-term extension study (EXCURSION). There were sustained reductions in exacerbations requiring hospitalization and/or emergency room visits and a reduction in exposure to systemic oral corticosteroids. Sustained improvements in lung function were observed across multiple parameters including percent predicted FEV_1, percent predicted FVC, FEV_1/FVC ratio and percent predicted FEF 25-75%. Furthermore, 75% of patients achieved and/or maintained normal lung function with pre-bronchodilator percent predicted $FEV_1 > 80\%$ by the end of EXCURSION. Efficacy was sustained for a cumulative treatment duration of up to 104 weeks (VOYAGE and EXCURSION).

Clinical efficacy in chronic rhinosinusitis with nasal polyposis (CRSwNP)

The chronic rhinosinusitis with nasal polyposis (CRSwNP) development program included two randomised, double-blind, parallel-group, multicentre, placebo-controlled studies (SINUS-24 and SINUS-52) in 724 patients aged 18 years and older on background intranasal corticosteroids (INCS). These studies included patients with severe CRSwNP despite prior sino-nasal surgery or treatment with, or who were ineligible to receive, systemic corticosteroids in the past 2 years. Rescue with systemic corticosteroids or surgery was allowed during the studies at the investigator's discretion All patients had evidence of sinus opacification on the Lund MacKay (LMK) sinus CT scan and 73 % to 90 % of patients had opacification of all sinuses. Patients were stratified based on their histories of prior surgery and co-morbid asthma/nonsteroidal anti-inflammatory drug exacerbated respiratory disease (NSAID-ERD).

The co-primary efficacy endpoints were change from baseline to week 24 in bilateral endoscopic nasal polyps score (NPS) as graded by central blinded readers, and change from baseline to week 24 in nasal congestion/obstruction score averaged over 28 days (NC), as determined by patients using a daily diary. For NPS, polyps on each side of the nose were graded on a categorical scale (0=no polyps; 1=small polyps in the middle meatus not reaching below the inferior border of the middle turbinate; 2=polyps reaching below the lower border of the middle turbinate; 3=large polyps reaching the lower border of the inferior turbinate or polyps medial to the middle turbinate; 4=large polyps causing complete obstruction of the inferior nasal cavity). The total score was the sum of the right and left scores. Nasal congestion was rated daily by the subjects on a 0 to 3 categorical severity scale (0=no symptoms; 1=mild symptoms; 2=moderate symptoms; 3=severe symptoms).

The demographics and baseline characteristics of these 2 studies are provided in Table 22 below.

Table 22: Demographics and baseline characteristics of CRSwNP studies

Parameter	**SINUS-24 (N=276)**	**SINUS-52 (N=448)**
Mean age (years) (SD)	50.49 (13.39)	51.95 (12.45)
% Male	57.2	62.3
Mean CRSwNP duration (years)(SD)	11.11 (9.16)	10.94 (9.63)
Patients with ≥ 1 prior surgery (%)	71.7	58.3
Patients with systemic corticosteroid use in the previous 2 years (%)	64.9	80.1
Mean Bilateral endoscopic NPS[a] (SD), range 0–8	5.75 (1.28)	6.10 (1.21)
Mean Nasal congestion (NC) score[a] (SD) range 0–3	2.35 (0.57)	2.43 (0.59)
Mean LMK sinus CT total score[a](SD), range 0–24	19.03 (4.44)	17.96 (3.76)
Mean Smell test (UPSIT) score[a] (SD), range 0–40	14.56 (8.48)	13.61 (8.02)
Mean loss of smell score[a] (AM), (SD) range 0–3	2.71 (0.54)	2.75 (0.52)
Mean SNOT-22 total score[a] (SD), range 0–110	49.40 (20.20)	51.86 (20.90)
Mean Rhinosinusitis severity scale[a] (VAS), (SD) 0–10 cm	7.68 (2.05)	8.00 (2.08)
Mean blood eosinophils (cells/mcL)(SD)	437 (333)	431 (353)

Mean total IgE IU/mL (SD)	211.97 (275.73)	239.84 (341.53)
Atopic (type 2 inflammatory disease) Medical History % Overall	75.4 %	82.4 %
Asthma (%)	58.3	59.6
Mean FEV_1 (L)(SD)	2.69 (0.96)	2.57 (0.83)
Mean FEV_1 percent predicted (%)(SD)	85.30 (20.23)	83.39 (17.72)
Mean ACQ-6 score[a] (SD)	1.62 (1.14)	1.58 (1.09)
NSAID-ERD (%)	30.4	26.8

[a]higher scores indicate greater disease severity except UPSIT where higher scores indicate lower disease severity; SD=standard deviation; AM = morning; NPS = nasal polyps score; UPSIT = University of Pennsylvania smell identification test; SNOT-22 = 22-item Sino-Nasal Outcome Test; VAS = visual analogue scale; FEV_1 = Forced expiratory volume in 1 second; ACQ-6 = Asthma Control Questionnaire-6; NSAID-ERD= aspirin/nonsteroidal anti-inflammatory drug exacerbated respiratory disease

Clinical Response (SINUS-24 and SINUS-52)

The results for primary and secondary endpoints in CRSwNP studies are presented in the Table 23.

Table 23: Results of the primary and secondary endpoints in CRSwNP trials

	SINUS -24					SINUS -52				
	Placebo (n=133)		**Dupilumab 300mg Q2W (n=143)**		**LS mean difference vs. placebo (95%CI)**	**Placebo (n=153)**		**Dupilumab 300mg Q2W (n=295)**		**LS mean difference vs. placebo (95%CI)**
Primary endpoints at week 24										
Scores	Baseline mean	LS mean change	Baseline mean	LS mean change		Baseline mean	LS mean change	Baseline mean	LS mean change	
NPS	5.86	0.17	5.64	-1.89	-2.06 (-2.43, -1.69)	5.96	0.10	6.18	-1.71	-1.80 (-2.10, -1.51)
NC	2.45	-0.45	2.26	-1.34	-0.89 (-1.07, -0.71)	2.38	-0.38	2.46	-1.25	-0.87 (-1.03, -0.71)
Key secondary endpoints at week 24										
Scores	Baseline mean	LS mean change	Baseline mean	LS mean change		Baseline mean	LS mean change	Baseline mean	LS mean change	
LMK sinus CT scan score	19.55	-0.74	18.55	-8.18	-7.44 (-8.35, -6.53)	17.65	-0.09	18.12	-5.21	-5.13 (-5.80, -4.46)
Total symptom score	7.28	-1.17	6.82	-3.77	-2.61 (-3.04, -2.17)	7.08	-1.00	7.30	-3.45	-2.44 (-2.87, -2.02)
UPSIT	14.44	0.70	14.68	11.26	10.56 (8.79, 12.34)	13.78	-0.81	13.53	9.71	10.52 (8.98, 12.07)
Loss of smell	2.73	-0.29	2.70	-1.41	-1.12 (-1.31, -0.93)	2.72	-0.23	2.77	-1.21	-0.98 (-1.15, -0.81)
SNOT-22	50.87	-9.31	48.0	-30.43	-21.12 (-25.17, -17.06)	53.48	-10.40	51.02	-27.77	-17.36 (-20.87, -13.85)
VAS	7.96	-1.34	7.42	-4.54	-3.20 (-3.79, -2.60)	7.98	-1.39	8.01	-4.32	-2.93 (-3.45, -2.40)

A reduction in score indicates improvement, except UPSIT where an increase indicates improvement.
Total symptom score is a composite severity score consisting of the sum of daily symptoms of NC, loss of smell, and anterior/posterior rhinorrhoea. NC = nasal congestion, NPS = nasal polyposis score; LMK = Lund-MacKay total CT score; UPSIT = University of Pennsylvania smell identification test; SNOT-22 = 22-item Sino-Nasal Outcome Test; TSS = total symptom score; VAS = visual analogue scale for rhinosinusitis
(all p-values < 0.0001 (all statistically significant vs placebo with adjustment for multiplicity); nominal for VAS)

The results of SINUS-52 study at week 52 are presented in Table 24.

Table 24: Results of the efficacy at week 52 in SINUS-52 study

	Placebo (n=153)		**Dupilumab 300mg Q2W (n=150)**		**LS mean difference vs. placebo (95%CI)**	**Dupilumab 300mg Q2W-Q4W (n=145)**		**LS mean difference vs. placebo (95%CI)**
	Baseline mean	LS mean change	Baseline mean	LS mean change		Baseline mean	LS mean change	
NPS	5.96	0.15	6.07	-2.24	-2.40[a] (-2.77, -2.02)	6.29	-2.06	-2.21[b] (-2.59, -1.83)
NC	2.38	-0.37	2.48	-1.35	-0.98[a] (-1.17, -0.79)	2.44	-1.48	-1.10[b] (-1.29, -0.91)
LMK sinus CT scan score	17.65	0.11	18.42	-6.83	-6.94[b] (-7.87, -6.01)	17.81	-5.60	-5.71[b] (-6.64, -4.77)
Total symptom score	7.08	-0.94	7.31	-3.79	-2.85[b] (-3.35, -2.35)	7.28	-4.16	-3.22[b] (-3.73, -2.72)
UPSIT	13.78	-0.77	13.46	9.53	10.30[b] (8.50, 12.10)	13.60	9.99	10.76[b] (8.95, 12.57)
Loss of Smell	2.72	-0.19	2.81	-1.29	-1.10[b] (-1.31, -0.89)	2.73	-1.49	-1.30[b] (-1.51, -1.09)
SNOT-22	53.48	-8.88	50.16	-29.84	-20.96[a] (-25.03, -16.89)	51.89	-30.52	-21.65[b] (-25.71, -17.58)
VAS	7.98	-0.93	8.24	-4.74	-3.81[b] (-4.46, -3.17)	7.78	-4.39	-3.46[b] (-4.10, -2.81)

A reduction in score indicates improvement, except UPSIT where an increase indicates improvement.
Total symptom score is a composite severity score consisting of the sum of daily symptoms of NC, loss of smell, and anterior/posterior rhinorrhoea. NC = nasal congestion, NPS = nasal polyposis score; LMK = Lund-MacKay total CT score; UPSIT = University of Pennsylvania smell identification test; SNOT-22 = 22-item Sino-Nasal Outcome Test; TSS = total symptom score; VAS = visual analogue scale for rhinosinusitis
([a]p-value < 0.0001 (all statistically significant vs placebo with adjustment for multiplicity); [b]nominal p-value <0.0001

Statistically significant and clinically meaningful efficacy was observed in SINUS-24 with regard to improvement in bilateral endoscopic NPS score at week 24. In the post-treatment period when patients were off dupilumab, the treatment effect diminished over time (see Figure 5a). Similar results were also seen in SINUS-52 at both week 24 and week 52 with a progressive improvement over time (see Figure 5b).

Figure 5. LS mean change from baseline in bilateral nasal polyps score (NPS) in SINUS-24 and SINUS-52 - ITT population.

Figure 5a. SINUS-24

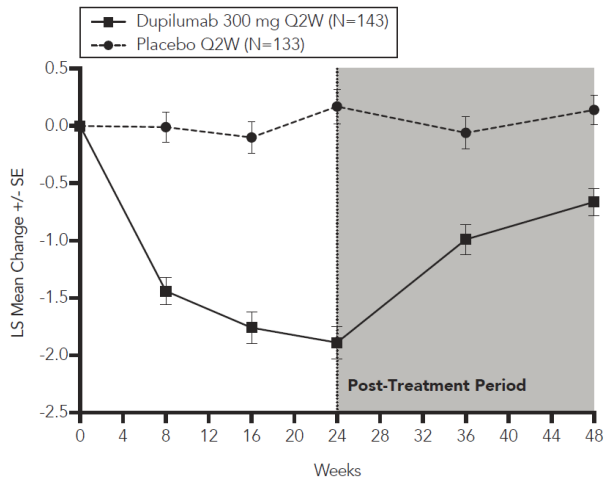
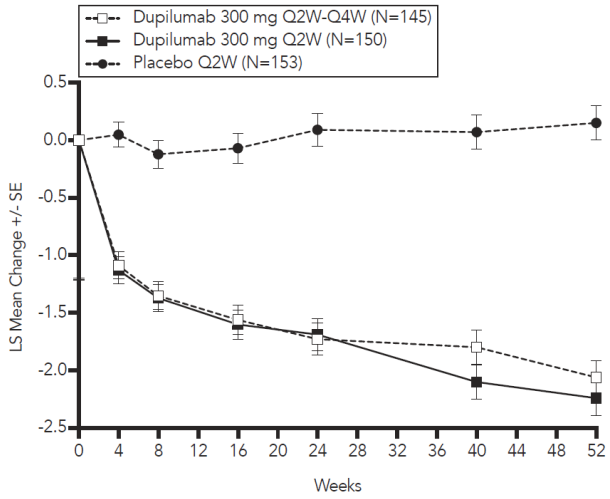


Figure 5b. SINUS-52

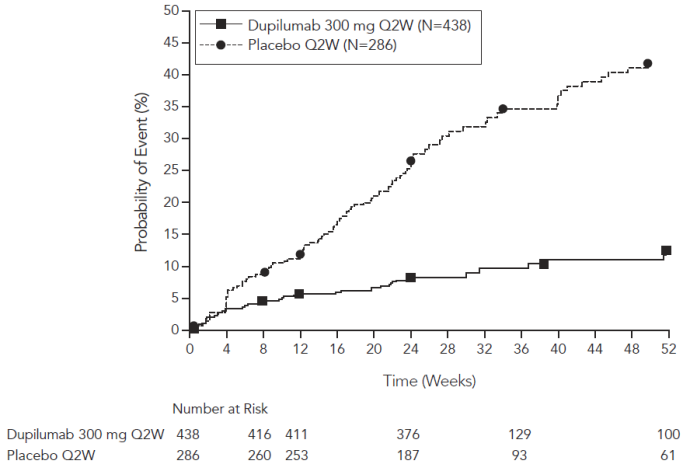


In both studies, significant improvements in NC and daily loss of smell severity were observed as early as the first assessment at week 4. The LS mean difference for NC at week 4 in the dupilumab group versus placebo was -0.41 (95% CI: -0.52, -0.30) in SINUS-24 and -0.37 (95% CI: -0.46, -0.27) in SINUS-52. The LS mean difference for loss of smell at week 4 in the dupilumab group versus placebo was -0.34 (95% CI: -0.44, -0.25) in SINUS-24 and -0.31 (95% CI: -0.41, -0.22) in SINUS-52. A reduction in the proportion of patients with anosmia was observed in SINUS-24 and SINUS-52. At baseline, 74 % to 79 % of patients had anosmia, which was reduced to 24 % in SINUS-24 and 30 % in SINUS-52 at week 24, compared to no change in placebo. Improvement in nasal peak inspiratory flow (NPIF) was observed in SINUS-24 and SINUS-52 at week 24. The LS mean difference in the dupilumab group versus placebo was 40.4 L/min (95% CI: 30.4, 50.4) and 36.6 L/min (95% CI: 28.0, 45.3), respectively.

Among the patients with rhinosinusitis VAS score > 7 at baseline, a higher percentage of patients achieved VAS ≤ 7 in the dupilumab group compared with the placebo group (83.3 % versus 39.4 % in SINUS-24 and 75.0 % versus 39.3 % in SINUS-52) at week 24.

In the pre-specified multiplicity-adjusted pooled analysis of two studies, treatment with dupilumab resulted in significant reduction of systemic corticosteroid use and need for sino-nasal surgery versus placebo (HR of 0.24; 95% CI: 0.17, 0.35) (see Figure 6). The proportion of patients who required systemic corticosteroids was reduced by 74 % (HR of 0.26; 95% CI: 0.18, 0.38). The total number of systemic corticosteroid courses per year was reduced by 75 % (RR of 0.25; 95% CI: 0.17, 0.37). The mean individual annualised prescribed total dose of systemic corticosteroids (in mg) during the treatment period was 71 % lower in the pooled dupilumab group compared with the pooled placebo group (60.5 [531.3] mg versus 209.5 [497.2] mg, respectively). The proportion of patients who required surgery was reduced by 83 % (HR of 0.17; 95% CI: 0.07, 0.46).

Figure 6. Kaplan Meier Curve for time to first systemic corticosteroid use and/or sino-nasal surgery during treatment period - ITT population [SINUS-24 and SINUS-52 pooled]



The effects of dupilumab on the primary endpoints of NPS and nasal congestion and the key secondary endpoint of LMK sinus CT scan score were consistent in patients with prior surgery and without prior surgery.

In patients with co-morbid asthma, significant improvements in FEV_1 and ACQ-6 were observed at week 24 irrespective of baseline blood eosinophil levels. The pooled LS Mean change from baseline in FEV_1 at week 24 for dupilumab 300 mg Q2W was 0.14 vs -0.07 L for placebo, for a difference of 0.21 L (95% CI: 0.13, 0.29). In addition, improvements in FEV_1 were noted from the first post-baseline assessment, at week 8 in SINUS-24 and week 4 in SINUS-52. Improvements in ACQ-6 in patients with co-morbid asthma were observed in both studies. A response was defined as an improvement in score of 0.5 or more. The LS mean difference in the dupilumab group versus placebo at week 24 was -0.76 (95% CI: -1.00 to -0.51) in SINUS-24 and -0.94 (95% CI: -1.19, -0.69) in SINUS-52.

The ACQ-6 responder rate for dupilumab 300 mg Q2W for SINUS-24 at week 24 was 56 % versus 28 % in placebo (odds ratio 3.17; 95% CI: 1.65, 6.09). The ACQ-6 responder rate for dupilumab 300 mg Q2W for SINUS-52 was 46 % versus 14 % placebo at week 52 (odds ratio 7.02; 95% CI: 3.10, 15.90).

In patients with NSAID-ERD, the effects of dupilumab on the primary endpoints of NPS and NC and the key secondary endpoint of LMK sinus CT scan score were consistent with that observed in the overall CRSwNP population.

Clinical efficacy in prurigo nodularis (PN)

The prurigo nodularis (PN) development program included two 24-week randomised, double-blind, placebo-controlled, multicenter, parallel-group studies (PRIME and PRIME2) in 311 patients 18 years of age and older with moderate to severe PN, defined as severe pruritus (WI-NRS ≥ 7 on a scale of 0 to 10) and greater than or equal to 20 nodular lesions, whose disease was not adequately controlled with topical prescription therapies or when those therapies were not advisable. PRIME and PRIME2 assessed the effect of dupilumab on itch improvement as well as its effect on PN lesions, Dermatology Life Quality Index (DLQI), Hospital Anxiety and Depression Scale (HADS) and skin pain.

In these two studies, patients received either subcutaneous dupilumab 600 mg (two 300 mg injections) on day 1, followed by 300 mg once every other week (Q2W) for 24 weeks, or matching placebo.

In these studies, the mean age was 49.5 years, the median weight was 71.3 kg, 65.3% of patients were female, 56.6% were White, 6.1% were Black, and 34.1% were Asian. At baseline, the mean WI-NRS was 8.5, 66.3% had 20 to 100 nodules (moderate), 33.7% had greater than 100 nodules (severe), 99.7% received prior topical therapies, 12.5% received prior systemic corticosteroids, 20.6% received prior systemic non-steroidal immunosuppressants, and 4.5% prior gabapentinoids. Eleven percent of patients were taking stable doses of antidepressants at baseline and were instructed to continue taking these medications during the study. 43.4 % had history of atopy (defined as having a medical history of AD, allergic rhinitis/rhinoconjunctivitis, asthma, or food allergy).

The WI-NRS is comprised of a single item, rated on a scale from 0 (“no itch”) to 10 (“worst imaginable itch”). Participants were asked to rate the intensity of their worst pruritus (itch) over the past 24 hours using this scale. The IGA PN-S is a scale that measures the approximate number of nodules using a 5-point scale from 0 (clear) to 4 (severe).

The primary efficacy endpoint was the proportion of patients with improvement (reduction) in WI-NRS by ≥4. Key secondary endpoints included the proportion of participants with IGA PN-S 0 or 1 (the equivalent of 0-5 nodules).

The efficacy results for PRIME and PRIME2 are presented in Table 25 and Figures 7 and 8.

Table 25: Results of the Primary and Secondary Endpoints in PRIME and PRIME2

	PRIME			PRIME2		
	Placebo (N=76)	**Dupilumab 300 mg Q2W (N=75)**	**Difference (95% CI) for Dupilumab vs. Placebo**	**Placebo (N=82)**	**Dupilumab 300 mg Q2W (N=78)**	**Difference (95% CI) for Dupilumab vs. Placebo**
Proportion of patients with improvement (reduction) in WI-NRS by ≥4 points from baseline at week 24 (Primary endpoint in PRIME) [b]	18.4%	60.0%	42.7% (27.76, 57.72)	19.5%	57.7%	42.6% (29.06, 56.08)
Proportion of patients with improvement (reduction) in WI-NRS by ≥4 points from baseline at week 12. (Primary endpoint in PRIME2) [b]	15.8% [a]	44.0% [a]	29.2% (14.49, 43.81) [a]	22.0%	37.2%	16.8% (2.34, 31.16)
Proportion of patients with IGA PN-S 0 or 1 at week 24. [b]	18.4%	48.0%	28.3% (13.41, 43.16)	15.9%	44.9%	30.8% (16.37, 45.22)
Proportion of patients with both an improvement (reduction) in WI-NRS by ≥4 points from baseline to Week 24 and an IGA PN-S 0 or 1 at Week 24 [b]	9.2%	38.7%	29.6% (16.42, 42.81)	8.5%	32.1%	25.5% (13.09, 37.86)
% change from baseline in WI-NRS at week 24 (SE)	-22.22 (5.74)	-48.89 (5.61)	-26.67 (-38.44, -14.90)	-36.18 (6.21)	-59.34 (6.39)	-23.16 (-33.81, -12.51_
Change from baseline in DLQI at week 24 (SE)	-5.77 (1.05)	-11.97 (1.02)	-6.19 (-8.34, -4.05)	-6.77 (1.18)	-13.16 (1.21)	-6.39 (-8.42, -4.36)
Change from baseline in skin pain-NRS at week 24 (SE)[c]	-2.16 (0.44)	-4.33 (0.43)	-2.17 (-3.07, -1.28)	-2.74 (0.51)	-4.35 (0.53)	-1.61 (-2.49, -0.73)
Change from baseline in HADS at week 24 (SE)[c]	-2.02 (0.94)	-4.62 (0.93)	-2.60 (-4.52, -0.67)	-2.59 (1.03)	-5.55 (1.06)	-2.96 (-4.73, -1.19)

[a] Not adjusted for multiplicity in PRIME.
[b] Subjects who received rescue treatment earlier or had missing data were considered as non-responders.
[c] Subjects who received rescue treatment earlier or discontinued due to lack of efficacy were imputed using worst observation carried forward; other missing data were imputed using multiple imputation.
SE = secondary endpoint

The onset of action in change from baseline in WI-NRS, defined as the first timepoint at which difference from placebo was and remained significant (nominal $p<0.05$) in the weekly average of daily WI-NRS, was observed as early as Week 3 in PRIME (Figure 7a) and Week 4 in PRIME2 (Figure7b).

Figure 7. LS mean percent change from baseline in WI-NRS in PRIME and PRIME2 up to Week 24

Fig 7a. PRIME

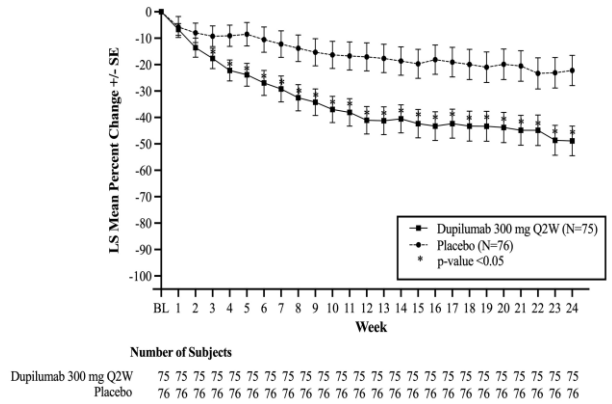
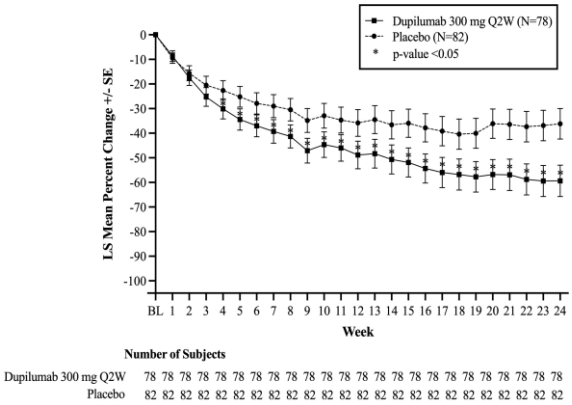


Fig 7b. PRIME2



A greater proportion of patients experienced WI-NRS improvements of ≥4 points from baseline by Weeks 4 and 11 in the dupilumab group as compared to the placebo group in PRIME (Figure 8a nominal p<0.007) and PRIME2 (Figure 8b nominal p<0.013), respectively, and this difference remained significant throughout the treatment period.

Figure 8. Proportion of patients with WI-NRS ≥4 improvement over time in PRIME and PRIME2

Fig 8a. PRIME

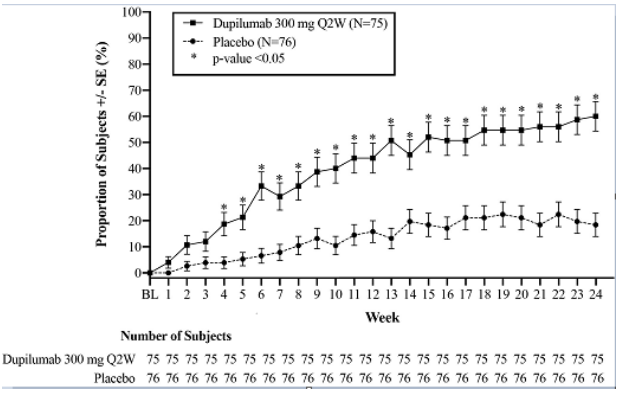
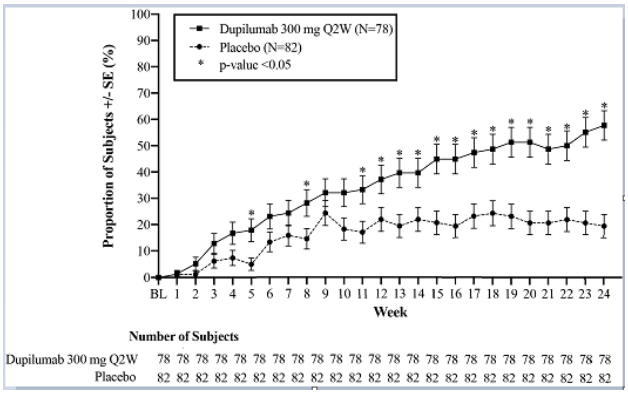


Fig 8b. PRIME2



Treatment effects in subgroups (age, gender, with or without medical history of atopy, and background treatment, including immunosuppressants) in PRIME and PRIME2 were consistent with the results in the overall study population.

Once treatment was discontinued after 24 weeks, there was an indication towards recurrence of signs and symptoms within the 12-week follow-up period.

Clinical efficacy in eosinophilic esophagitis (EoE)

The eosinophilic esophagitis (EoE) development program included a three-part protocol (TREET) consisting of two separately randomised, double-blind, parallel-group, multicentre, placebo-controlled, 24-week treatment studies (TREET Part A and TREET Part B) in adult and paediatric patients 12 to 17 years of age, excluding patients <40 kg. In TREET Parts A and B, all enrolled patients had to have failed conventional medicinal therapy (proton pump inhibitors), 74% were treated with another conventional medicinal therapy (swallowed topical corticosteroids) prior to inclusion. In TREET Part B, 49% of patients were inadequately controlled, intolerant or contraindicated to swallowed topical

corticosteroid treatment. In both parts, patients were required to have ≥15 intraepithelial eosinophils per high-power field (eos/hpf) following an at least 8-week course of a high-dose proton pump inhibitor (PPI) either prior to or during the screening period and a Dysphagia Symptom Questionnaire (DSQ) score ≥10 on a scale of 0 to 84. Patients were stratified based on age at the time of the screening visit (12 to 17 years of age vs. 18 years and older) and use of PPI at randomisation. TREET Part A was conducted first. TREET Part B opened after enrollment into TREET Part A was complete. Patients completing the 24 weeks of the double-blind treatment period in Parts A or B were provided an option to enroll in a 28-week active treatment extension study (TREET Part C).

In Part A, a total of 81 patients, of which 61 were adults and 20 were paediatric patients 12 to 17 years of age, were randomised to receive either 300 mg dupilumab every week (N=42) or placebo (N=39). In Part B, a total of 240 patients, of which 161 were adults and 79 were paediatric patients 12 to 17 years of age, were randomised to receive either 300 mg dupilumab every week (N=80), 300 mg dupilumab every other week (N=81; the 300 mg every other week dosage regimen is not approved for EoE) or placebo (N=79). In Part C, all patients who previously participated in Part A received 300 mg dupilumab (N=77) every week. Of the patients who previously participated in Part B, 111 received dupilumab 300 mg every week in Part C. Rescue with systemic and/or swallowed topical corticosteroids or emergency esophageal dilation was allowed during the study at the investigator's discretion.

In Part A, a total of 74.1% of patients enrolled had a history of prior use of swallowed topical corticosteroids for the treatment of EoE and 43.2% had a history of prior esophageal dilation. In Part B, a total of 73.3% of patients enrolled had a history of prior use of swallowed topical corticosteroids for the treatment of EoE and 35.4% had a history of prior esophageal dilation.

The co-primary efficacy endpoints in both trials were the proportion of patients achieving histological remission defined as peak esophageal intraepithelial eosinophil count of ≤6 eos/hpf at week 24 and the absolute change in the patient-reported DSQ score from baseline to week 24. Secondary endpoints included change from baseline in the following: percent change in peak esophageal intraepithelial eosinophil count (eos/hpf), absolute change in Mean Grade Score from the Histology Scoring System (EoEHSS), absolute change in Mean Stage Score from the EoEHSS, absolute change in EoE-Endoscopic Reference Score (EoE-EREFS), and proportion of patients achieving peak esophageal intraepithelial eosinophil count of <15 eos/hpf.

The demographics and baseline characteristics of TREET Parts A and B are provided in Table 26.

Table 26: Demographics and baseline characteristics (TREET Parts A and B)

Parameter	TREET Part A (N=81)	TREET Part B (N=240)
Age (years), mean (SD)	31.5 (14.3)	28.1 (13.1)
% Male	60.5	63.8
% White	96.3	90.4
Weight (kg), mean (SD)	77.8 (21.0)	76.2 (20.6)
BMI (kg/m^2), mean (SD)	26.1 (6.3)	25.7 (6.2)
Duration of EoE (yr), mean (SD)	5.01 (4.3)	5.57 (4.8)
Prior swallowed topical steroid use (%)	74.1	73.3
Prior esophageal dilations (%)	43.2	35.4
PPI use at randomisation (%)	67.9	72.5
Food elimination diet at screening (%)	40.7	37.1
DSQ (0-84[a]), mean (SD)	33.6 (12.4)	36.7 (11.2)
Peak esophageal intraepithelial EOS count of 3 regions, mean (SD)	89.3 (48.3)	87.1 (45.8)
Mean esophageal intraepithelial EOS count of 3 regions, mean (SD)	64.3 (37.6)	60.5 (32.9)
EoEHSS grade Score [0-3[a]], mean (SD)	1.3 (0.4)	1.3 (0.4)

EoEHSS stage Score [0-3[a]], mean (SD)	1.3 (0.4)	1.3 (0.3)
EREFS total Score [0-18[a]], mean (SD)	6.3 (2.8)	7.2 (3.2)

[a]Higher scores indicate greater disease severity
SD = standard deviation

The results for TREET Parts A and B are presented in Table 27.

Table 27: Efficacy results of dupilumab at week 24 in patients 12 years of age and older with EoE (TREET Parts A and B)

	TREET Part A			TREET Part B		
	Dupilumab 300 mg QW N=42	**Placebo N=39**	**Difference vs. placebo (95% CI)[d]**	**Dupilumab 300 mg QW N=80**	**Placebo N=79**	**Difference vs. placebo (95% CI)[d]**
Co-primary endpoints						
Proportion of patients achieving histological remission (peak esophageal intraepithelial eosinophil count ≤6 eos/hpf), n (%)	25 (59.5)	2 (5.1)	55.3 (39.58, 71.04)	47 (58.8)	5 (6.3)	53.5 (41.20, 65.79)
Absolute change from baseline in DSQ score (0-84[a]), LS mean (SE)	-21.92 (2.53)	-9.60 (2.79)	-12.32 (-19.11, -5.54)	-23.78 (1.86)	-13.86 (1.91)	-9.92 (-14.81, -5.02)
Secondary endpoints						
Percent change from baseline in peak esophageal intraepithelial eosinophil count, LS mean (SE)	-71.24 (6.95)	-2.98 (7.60)	-68.26 (-86.90, -49.62)	-80.24 (8.34)	8.38 (10.09)	-88.62 (-112.19, 65.05)
Absolute change from baseline in EoEHSS mean grade score (0-3[b]), LS mean (SE)	-0.76 (0.06)	-0.00 (0.06)	-0.76 (-0.91, -0.61)	-0.83 (0.04)	-0.15 (0.05)	-0.682 (-0.79, -0.57)
Absolute change from baseline in EoEHSS mean stage score (0-3[b]), LS mean (SE)	-0.75 (0.06)	-0.01 (0.06)	-0.74 (-0.88, -0.60)	-0.80 (0.04)	-0.13 (0.04)	-0.672 (-0.78, -0.57)
Absolute change from baseline in EoE-EREFS (0-18[c]), LS mean (SE)	-3.2 (0.41)	-0.3 (0.41)	-2.9 (-3.91, -1.84)	-4.5 (0.36)	-0.6 (0.38)	-3.8 (-4.77, -2.93)
Proportion of patients achieving peak esophageal intraepithelial eosinophil count of <15 eos/hpf, n (%)	27 (64.3)	3 (7.7)	57 (41.69, 73.33)	66 (82.5)	6 (7.6)	74.9 (64.25, 85.5)

[a]Total biweekly DSQ scores range from 0 to 84; higher scores indicate greater frequency and severity of dysphagia
[b]EoEHSS scores range from 0 to 3; higher scores indicate greater severity and extent of histological abnormalities
[c]EoE-EREFS overall scores range from 0 to 18; higher scores indicate worse endoscopic inflammatory and remodeling findings
[d]LS mean difference for continuous endpoints and absolute difference in proportions for categorical endpoints

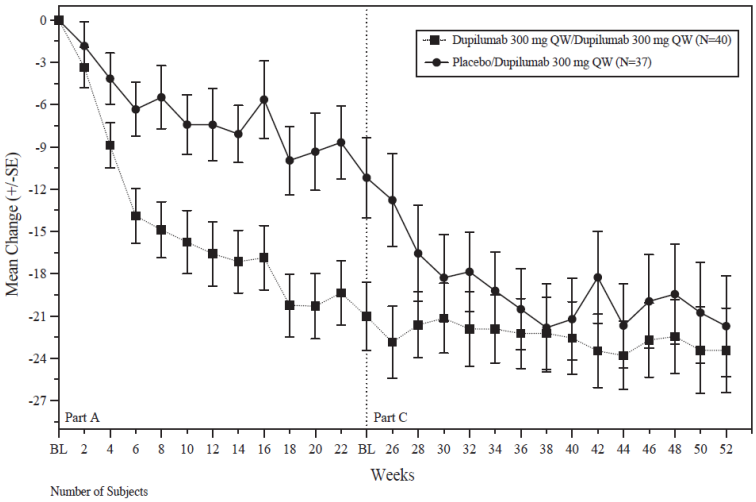
The efficacy results for co-primary and key secondary endpoints in prior swallowed topical corticosteroids subgroup and in patients who were inadequately controlled, intolerant or contraindicated to swallowed topical corticosteroids were consistent with the overall population.

In Parts A and B, a greater proportion of patients randomised to dupilumab achieved histological remission (peak esophageal intraepithelial eosinophil count ≤6 eos/hpf) compared to placebo. The proportion of patients with histological remission observed after 24 weeks of treatment in Part A and B

was maintained for 52 weeks in Part C. Similarly, other histological and endoscopic improvement were maintained through 52 weeks.

Treatment with dupilumab also resulted in a significant improvement in LS mean change in DSQ score compared to placebo as early as week 4 and were maintained through week 24. Efficacy in part C was similar to results observed in Parts A and B, with a continuous improvement for DSQ up to 52 weeks (TREET Part A and C Figure 9 and TREET Parts B and C Figure 10).

Figure 9: LS mean change from baseline in DSQ score over time in patients 12 years of age and older with EoE (TREET Part A and C)

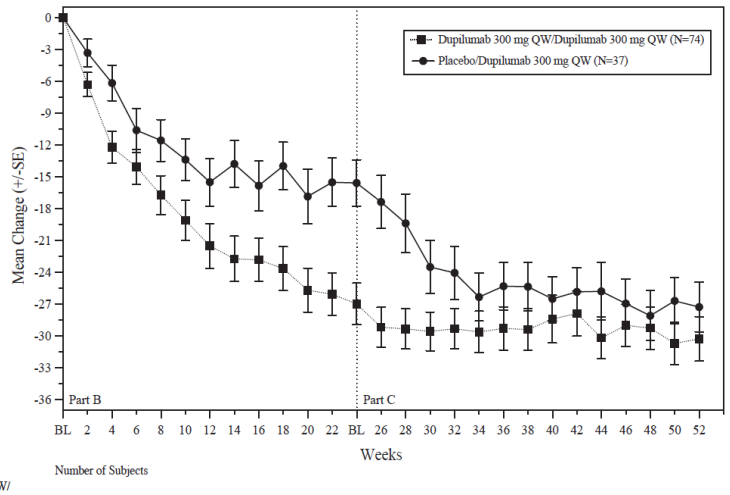


Number of Subjects

Dupilumab 300 mg QW/ Dupilumab 300 mg QW (N=40)	40	40	39	38	36	38	40	32	34	36	33	35	32	29
Placebo/Dupilumab 300 mg QW (N=37)	37	34	34	33	28	30	37	26	32	29	25	25	26	23

All observed values were used regardless of rescue treatment use

Figure 10: Mean change from baseline in DSQ score over time in patients 12 years of age and older with EoE (TREET Parts B and C)



Number of Subjects

Dupilumab 300 mg QW/ Dupilumab 300 mg QW (N=74)	74	71	69	69	68	60	74	58	61	57	54	55	51	54
Placebo/Dupilumab 300 mg QW (N=37)	37	35	35	32	33	31	37	26	29	29	28	26	26	24

All observed values were used regardless of rescue treatment use

Consistent with improvement in DSQ total score in TREET Parts A and B, nominally significant improvements were observed at week 24 compared to placebo in pain related to dysphagia (DSQ pain score), health-related QoL (EoE-IQ), and the frequency of other non-dysphagia symptoms (EoE-SQ).

Paediatric population

Atopic dermatitis
The safety and efficacy of dupilumab have been established in paediatric patients 6 months of age and older with atopic dermatitis. Use of dupilumab in this age group is supported by study AD-1526 which included 251 adolescents aged 12 to 17 years old with moderate-to-severe atopic dermatitis, in study AD-1652 which included 367 paediatric patients aged 6 to 11 years old with severe atopic dermatitis, and study AD-1539 which included 162 children ages 6 months to 5 years old with moderate-to-severe atopic dermatitis (125 of whom had severe atopic dermatitis). Long term use is supported by study AD-1434 which enrolled 823 paediatric patients aged 6 months to 17 years of age, this included 275 adolescents, 368 children 6 to 11 years of age, and 180 children 6 months to 5 years of age. The safety and efficacy were generally consistent between children 6 months to 5 years old, 6 to 11 years old, adolescent (12 to 17 years old), and adult patients with atopic dermatitis (see section 4.8). Safety and efficacy in paediatric patients < 6 months of age with atopic dermatitis have not been established.

Asthma
A total of 107 adolescents aged 12 to 17 years with moderate to severe asthma were enrolled in QUEST study and received either 200 mg (N=21) or 300 mg (N=18) dupilumab (or matching placebo either 200 mg [N=34] or 300 mg [N=34]) every other week. Efficacy with respect to severe asthma exacerbations and lung function was observed in both adolescents and adults. For both the 200 mg and 300 mg every other week doses, significant improvements in FEV_1 (LS mean change from baseline at week 12) were observed (0.36 L and 0.27 L, respectively). For the 200 mg every other week dose, patients had a reduction in the rate of severe exacerbations that was consistent with adults. The safety profile in adolescents was generally similar to the adults.

A total of 89 adolescents aged 12 to 17 years with moderate-to-severe asthma were enrolled in the open label long-term study (TRAVERSE). In this study, efficacy was measured as a secondary endpoint, was similar to results observed in the pivotal studies and was sustained up to 96 weeks.

A total of 408 children aged 6 to 11 years with moderate-to-severe asthma was enrolled in the VOYAGE study, which evaluated doses of 100 mg Q2W and 200 mg Q2W. The efficacy of dupilumab 300 mg Q4W in children aged 6 to 11 years is extrapolated from the efficacy of 100 mg and 200 mg Q2W in VOYAGE and 200 mg and 300 mg Q2W in adults and adolescents (QUEST). Patients who completed the treatment period of the VOYAGE study could participate in the open label extension study (EXCURSION). Eighteen patients (≥ 15 kg to < 30 kg) out of 365 patients were exposed to 300 mg Q4W in this study, and the safety profile was similar to that seen in VOYAGE. Safety and efficacy in paediatric patients < 6 years of age with asthma have not been established.

The European Medicines Agency has deferred the obligation to submit the results of studies with dupilumab in one or more subset of the paediatric population in asthma and EoE (see section 4.2 for information on paediatric use). The European Medicines Agency has waived the obligation to submit the results of studies with dupilumab in all subsets of the paediatric population in the treatment of nasal polyposis and prurigo nodularis (see section 4.2 for information on paediatric use). Obligations related to the paediatric investigation plans for atopic dermatitis have been fulfilled.

5.2 Pharmacokinetic properties

The pharmacokinetics of dupilumab is similar in patients with atopic dermatitis, asthma, CRSwNP, PN and EoE.

Absorption

After a single subcutaneous (SC) dose of 75-600 mg dupilumab to adults, median times to maximum concentration in serum (t_{max}) were 3-7 days. The absolute bioavailability of dupilumab following a SC dose is similar between AD, asthma, CRSwNP, and EoE patients, 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 or 300 mg dose every other week without a loading dose. Across clinical trials, the mean ±SD steady-state trough concentrations ranged from 60.3±35.1 mcg/mL to 81.5±43.9 mcg/mL for 300 mg administered Q2W, from 172±76.6 mcg/ml to 195±71.7 mcg/ml for 300 mg administered weekly, and from 29.2±18.7 to 36.5±22.2 mcg/mL for 200 mg administered Q2W.

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 of 300 mg QW, 300 mg Q2W, 200 mg Q2W, 300 mg Q4W, or 200 mg Q4W dupilumab, the median times to decrease below the lower limit of detection, estimated by population PK analysis, ranged from 9-13 weeks in adults and adolescents and are approximately 1.5 times and 2.5 times longer in paediatric patients 6 to 11 years of age and paediatric patients less than 6 years of age, respectively .

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
Of the 1,539 patients with atopic dermatitis, including patients with atopic hand and foot dermatitis exposed to dupilumab in a phase 2 dose-ranging study or phase 3 placebo-controlled studies, a total of 71 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.

Of the 1,977 patients with asthma exposed to dupilumab, a total of 240 patients were 65 years or older and 39 patients were 75 years or older. Efficacy and safety in this age group were similar to the overall study population.

There were only 79 patients older than 65 years with CRSwNP exposed to dupilumab among them 11 patients were 75 years and older.

Of the 152 patients with PN exposed to dupilumab, a total of 37 were 65 years of age or older. A total of 8 patients were 75 years of age or older. Efficacy and safety in these age groups were similar to the overall study population.

There were only 2 patients older than 65 years with EoE exposed to dupilumab.

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. There were only 6 patients exposed to dupilumab with body weight ≥130 kg in CRSwNP clinical studies.

Paediatric population

Atopic dermatitis
Based on population pharmacokinetic analysis, age did not affect dupilumab clearance in adults and in paediatric patients 6 to 17 years of age. In paediatric patients from 6 months to 5 years of age, clearance increased with age but is accommodated in the recommended dose regimen.

The pharmacokinetics of dupilumab in paediatric patients (< 6 months of age) or body weight < 5 kg with atopic dermatitis has not been studied.

For adolescents 12 to 17 years of age with atopic dermatitis receiving every other week dosing (Q2W) with either 200 mg (< 60 kg) or 300 mg (≥ 60 kg), the mean ±SD steady state trough concentration of dupilumab was 54.5±27.0 mcg/mL.

For children 6 to 11 years of age with atopic dermatitis receiving every four week dosing (Q4W) with 300 mg (≥ 15 kg) in AD-1652, the mean ± SD steady-state trough concentration was 76.3±37.2 mcg/mL. At week 16 in AD-1434 in children 6 to 11 years of age who initiated every four week dosing (Q4W) with 300 mg (≥ 15 kg), and whose dose was increased to every other week dosing (Q2W) with 200 mg (≥ 15 to < 60 kg) or 300 mg (≥ 60 kg), the mean±SD steady-state trough concentration was 108±53.8 mcg/mL. For children 6 to 11 years of age 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.

For children 6 months to 5 years of age with atopic dermatitis receiving every four week dosing (Q4W) with 300 mg (≥ 15 to < 30 kg) or 200 mg (≥ 5 to < 15 kg) mean ± SD steady-state trough concentration was 110±42.8 mcg/mL and 109±50.8 mcg/mL, respectively.

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

A total of 107 adolescents aged 12 to 17 years with asthma were enrolled in QUEST study. The mean ±SD steady-state trough concentrations of dupilumab were 107±51.6 mcg/mL and 46.7±26.9 mcg/mL, respectively, for 300 mg or 200 mg administered every other week. No age-related pharmacokinetic difference was observed in adolescent patients after correction for body weight.

In the VOYAGE study, dupilumab pharmacokinetics was investigated in 270 patients with moderate-to-severe asthma following subcutaneous administration of either 100 mg Q2W (for 91 children weighing < 30 kg) or 200 mg Q2W (for 179 children weighing ≥ 30 kg). The volume of distribution for dupilumab of approximately 3.7 L was estimated by population PK analysis. Steady-state concentrations were achieved by week 12. The mean ± SD steady-state trough concentration was 58.4±28.0 mcg/mL and 85.1±44.9 mcg/mL, respectively. Simulation of a 300 mg Q4W subcutaneous dose in children aged 6 to 11 years with body weight of ≥ 15 kg to < 30 kg and ≥ 30 kg to < 60 kg resulted in predicted steady-state trough concentrations similar to the observed trough concentrations of 200 mg Q2W (≥ 30 kg) and 100 mg Q2W (< 30 kg), respectively. In addition, simulation of a 300 mg Q4W subcutaneous dose in children aged 6 to 11 years with body weight of ≥ 15 kg to < 60 kg resulted in predicted steady-state trough concentrations similar to those demonstrated to be efficacious in adults and adolescents. 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 14 to 18 weeks for 100 mg Q2W, 200 mg Q2W or 300 mg Q4W.

CRSwNP
CRSwNP does not normally occur in children. The pharmacokinetics of dupilumab in paediatric patients (< 18 years of age) with CRSwNP has not been studied.

PN
The pharmacokinetics of dupilumab in paediatric patients (< 18 years of age) with PN has not been studied.

Eosinophilic esophagitis
A total of 35 adolescents aged 12 to 17 years with eosinophilic esophagitis weighing ≥40 kg were enrolled in TREET Parts A and B, receiving 300 mg every week dosing (QW). The mean ± SD steady-state trough concentration of dupilumab was 227 ± 95.3 mcg/mL.

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 doses 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

L-Arginine monohydrochloride
L-Histidine
L-Histidine monohydrochloride monohydrate
Polysorbate 80 (E 433)
Sodium acetate trihydrate
Acetic acid, glacial (E 260)
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

3 years.

If necessary, the pre-filled syringe or pre-filled pen can be removed from the refrigerator and kept in the pack for up to 14 days at room temperature up to 25°C, while protected from light. The date of removal from the refrigerator shall be recorded in the space provided on the outer carton. The pack must be discarded if left out of the refrigerator for more than 14 days or if the expiry date has passed.

6.4 Special precautions for storage

Store in a refrigerator (2°C - 8°C).

Do not freeze.

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

6.5 Nature and contents of container

<u>Dupixent 300 mg solution for injection in pre-filled syringe</u>

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

Pack size:
- 1 pre-filled syringe
- 2 pre-filled syringes
- Multipack containing 6 (3 packs of 2) pre-filled syringes

Dupixent 300 mg solution for injection in pre-filled pen

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

The pre-filled pen is available either with a round cap and oval viewing window encircled with an arrow or with a square cap with ridges and an oval viewing window without an arrow.

Pack size:
- 1 pre-filled pen
- 2 pre-filled pens
- 6 pre-filled pens
- Multipack containing 6 (2 packs of 3) pre-filled pens

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Comprehensive instructions for the administration of Dupixent in a pre-filled syringe or in a pre-filled pen are given at the end of 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 or pre-filled pen from the refrigerator, it should be allowed to reach room temperature up to 25°C by waiting for 45 min before injecting Dupixent.

The pre-filled syringe or the pre-filled pen 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 or the pre-filled pen into a puncture-resistant container and discard as required by local regulations. Do not recycle the container.

7. MARKETING AUTHORISATION HOLDER

Sanofi Winthrop Industrie
82 avenue Raspail
94250 Gentilly
France

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/17/1229/005
EU/1/17/1229/006
EU/1/17/1229/008
EU/1/17/1229/017
EU/1/17/1229/018
EU/1/17/1229/020
EU/1/17/1229/026
EU/1/17/1229/027
EU/1/17/1229/028

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 26 September 2017
Date of latest renewal: 02 September 2022

10. DATE OF REVISION OF THE TEXT

03/2024

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu