SUMMARY OF PRODUCT CHARACTERISTICS

▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1 NAME OF THE MEDICINAL PRODUCT

Dupixent 200 mg solution for injection in pre-filled syringe

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

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

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

Excipients with known effect

This medicine contains 2.28 mg of polysorbate 80 in each 200 mg dose (1.14mL). Polysorbates may cause allergic reactions.

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.

4.1 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.
Eosinophilic esophagitis (EoE)

Dupixent is indicated for the treatment of eosinophilic esophagitis in adults, adolescents and children aged 1 year and older, weighing at least 15 kg, who are inadequately controlled by, are intolerant to, or who are not candidates for conventional medicinal therapy (see section 5.1).

Chronic Spontaneous Urticaria (CSU)

Dupixent is indicated for the treatment of chronic spontaneous urticaria (CSU) in patients aged 12 years and older whose disease is not adequately controlled with H1 antihistamine treatment.

44.2 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 is provided in Table 2.

Patients receiving concomitant oral corticosteroids may reduce their steroid dose once clinical improvement with dupilumab has occurred (see section 5.1). It is recommended that steroid reductions 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.

Eosinophilic esophagitis (EoE)

The recommended dose of dupilumab for adults, adolescents and children 1 year of age and older, weighing at least 15 kg, is specified in Table 5.

Table 5: Dose of dupilumab for subcutaneous administration in adults, adolescents and children 1 year of age and older with EoE

Body Weight	Dose
15 to less than 30 kg	200 mg every other week (Q2W)
30 to less than 40 kg	300 mg every other week (Q2W)
40 kg or more	300 mg every week (QW)

Dupilumab is intended for long-term treatment.

Chronic Spontaneous Urticaria (CSU)

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.

Adolescent patients (12 to 17 years of age)

The recommended dose of dupilumab for adolescent patients 12 to 17 years of age is specified in Table 6.

Table 6: Dose of dupilumab for subcutaneous administration in adolescent patients 12 to 17 years of age with CSU

Body Weight	Initial Dose	Subsequent Doses
30 to less than 60 kg	400 mg (two 200 mg injections)	200 mg every other week (Q2W)
60 kg or more	600 mg (two 300 mg injections)	300 mg every other week (Q2W)

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
No dose adjustment is recommended for elderly (≥ 65 years) 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.

The safety and efficacy of dupilumab in children with EoE below the age of 1 year, or with a body weight < 15 kg have not been established.

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

Method of administration

Subcutaneous use

The dupilumab pre-filled pen is for use in adult and paediatric patients aged 2 years and older.
The dupilumab pre-filled syringe is for use in adult and paediatric patients aged 6 months and
older. The dupilumab pre-filled pen is not intended for use in children below 2 years of age.

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 is for single use only.

For indications that require an initial dose of 400 mg (see Posology in section 4.2), administer two 200 mg injections consecutively in different injection sites.

It is recommended to rotate the injection site with each injection. Avoid injecting dupilumab 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. Provide proper training 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. In children 12 years of age and older, it is recommended that dupilumab is administered by or under supervision of an adult. In children 6 months to less than 12 years of age, it is recommended that dupilumab is administered by a caregiver.

4.3 Contraindications

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

.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 exacerbations of Asthma or COPD

Dupilumab must not be used to treat acute asthma symptoms or acute exacerbations of asthma or COPD. Dupilumab must not be used to treat acute bronchospasm or status asthmaticus.

Corticosteroids

It is recommended that 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, discontinue administration of dupilumab immediately and initiate appropriate therapy. 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 signalling. 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, dry eye and keratitis related events

Conjunctivitis, dry eye 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).

Advise patients to promptly report new onset or worsening eye symptoms to their healthcare provider. Sudden changes in vision or significant eye pain that does not settle warrant urgent review. Patients treated with dupilumab who develop conjunctivitis or dry eye 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

Advise patients on dupilumab who also have comorbid asthma to not adjust or stop their asthma treatments without consultation with their physicians. Monitor patients with comorbid asthma 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’.

Polysorbate 80 (E433)

This medicine contains 2.28 mg of polysorbate 80 in each 200 mg dose (1.14 mL). Polysorbates may cause allergic reactions.

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 and COPD. Additional adverse reactions of injection site induration, injection site rash, and injection site dermatitis were reported in COPD. 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 7 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 7 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 (≥ 1/1000 to < 1/100); rare (≥ 1/10000 to < 1/1000); very rare (< 1/10000); not known (cannot be estimated from the available data). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Table 7: 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	Conjunctivitis allergic* Keratitis*[#]

	Rare	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 and COPD patients, the 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. Among patients with EoE and CSU, the frequency of conjunctivitis was low and similar between dupilumab and placebo groups. There were no cases of keratitis in the CRSwNP, PN, EoE, and CSU 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, CRSwNP, and COPD 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 and COPD (BOREAS and NOTUS) during study treatment.

In adult and adolescent subjects with CSU (CUPID Study A, Study B, and Study C) treated with Dupilumab, an increase from baseline in blood eosinophil count was not observed compared to placebo at Week 12 and a slight increase was observed during study treatment.

Treatment-emergent eosinophilia (≥ 5,000 cells/mcL) was observed 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 studies); BOREAS and NOTUS; CUPID Study A, B and C).
Treatment-emergent eosinophilia (≥5,000 cells/mcL) was observed 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 24-week safety pool for the EoE TREET (Parts A and B) studies. The overall incidence of infections was numerically higher in placebo

(41.2%) compared to dupilumab (35.8%) in the EoE KIDS (Part A) study. In the 24-week safety pool for the EoE TREET (Parts A and B) studies serious infections were reported in 0.5% of patients treated with dupilumab and 0% of patients treated with placebo. No serious infections were reported in EoE KIDS (Part A) study. Upper respiratory tract infections composed of several terms, including, but not limited to, COVID-19, sinusitis, and upper respiratory tract infection was numerically higher with dupilumab (17.2%) compared to placebo (10.3%) in EoE TREET (Parts A and B), and with dupilumab (26.9%) compared to placebo (20.6%) in EoE KIDS (Part A) study.

No increase was observed in the overall incidence of infections with dupilumab compared to placebo in the safety pool for COPD clinical studies. Serious infections were reported in 4.9% of patients treated with dupilumab and 4.8% 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 CSU clinical studies. In the safety pool, serious infections were reported in 0% of patients treated with dupilumab and 0.8% of patients treated with placebo.

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

Antidrug 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 1 year of age and older with EoE who received dupilumab 300 mg QW (≥40 kg), 300 mg Q2W (≥30 to <60 kg), 200 mg Q2W (≥15 to <30 kg), or 100 mg

Q2W (≥5 to <15 kg) for 52 weeks developed antibodies to dupilumab; the ADA responses were neither persistent nor neutralizing.

Approximately 8% of patients with COPD who received dupilumab 300 mg Q2W for 52 weeks developed antibodies to dupilumab; approximately 3% exhibited persistent ADA responses and approximately 3% had neutralizing antibodies.

Approximately 5% of patients with CSU who received dupilumab 200 mg Q2W or 300 mg Q2W through 24 weeks developed antibodies to dupilumab; approximately 1% exhibited persistent ADA responses, and approximately 1% had neutralizing antibodies.

Regardless of age or population, up to 7 % of patients in the placebo groups were positive for antibodies to dupilumab; up to 3 % exhibited persistent ADA response and up to 2 % 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

Adolescents (12 to 17 years of age)

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.

Children 1 to 11 years of age
The safety of dupilumab was assessed in a trial of 101 children 1 to 11 years of age with EoE (EoE KIDS Part A). The safety profile of dupilumab in these patients through Week 16 was similar with the safety profile seen in adult and adolescent patients 12 to 17 years of age with EoE.

A total of 98 patients completing Part A were provided an option to enrol in a 36-week active treatment extension period (EoE-KIDS Part B). The safety profile of dupilumab through Week 52 was similar to the safety profile observed at Week 16.

Chronic Spontaneous Urticaria

Adolescents (12 to 17 years of age)
The safety of dupilumab was assessed in 12 adolescents aged 12 to 17 years with CSU enrolled in CUPID (Study A, B and C). An adverse event was reported in one adolescent treated with dupilumab.

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 in adult and adolescent patients 12 years of age and older (TREET Part C) and in children 1 to 11 years of age (EoE KIDS Part B) was generally consistent with the safety profile observed at week 24 in TREET Parts A and B and at Week 16 in EoE KIDS Part A.

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 the Yellow Card Scheme at: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

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

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, EoE, and CSU. 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 8.

Table 8: 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. Enrolment was stratified by baseline weight (< 30 kg; ≥ 30 kg).

Patients in the dupilumab Q2W + TCS group with baseline weight of < 30 kg received an initial dose of 200 mg on Day 1, followed by 100 mg Q2W from week 2 to week 14, and patients with baseline weight of ≥ 30 kg received an initial dose of 400 mg on Day 1, followed by 200 mg Q2W from week 2 to week 14. Patients in the dupilumab Q4W + TCS group received an initial dose of 600 mg on Day 1, followed by 300 mg Q4W from week 4 to week 12, regardless of weight.

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

Table 9: 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 enroled 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 10.

Table 10: 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 11 below.

Table 11: 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 12 and Table 13).

Table 12: 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 13: **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

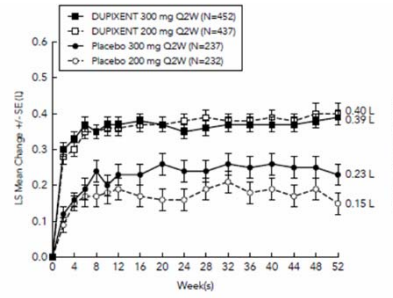
Clinically significant increases in pre-bronchodilator FEV_1 were observed at week 12 for DRI12544 and QUEST. There were greater improvements in FEV_1 in the subjects with higher

baseline levels of type 2 inflammatory biomarkers such as blood eosinophils or FeNO (Table 14 and Table 15).

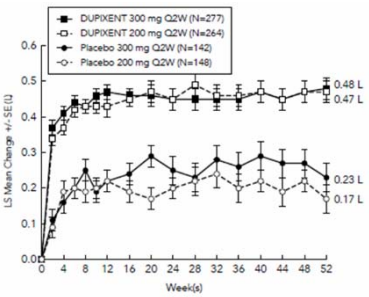
Significant improvements in FEV_1 were observed as early as week 2 following the first dose of dupilumab for both the 200 mg and 300 mg dose strengths and were maintained through week 24 (DRI12544) and week 52 in QUEST (see Figure 1).

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

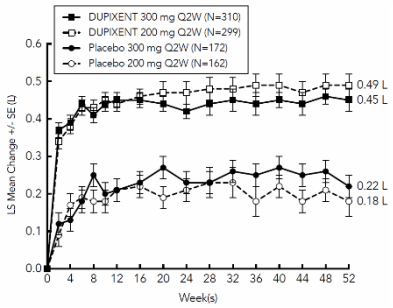


Table 14: Mean change from baseline in pre-bronchodilator FEV_1 at week 12 in DRI12544 and QUEST (baseline blood eosinophil levels ≥ 150 and ≥ 300 cells/mcL)

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%
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 15: 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 16). 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 16: 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 17.

Table 17: 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 18 below.

Table 18: 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)

Table 18: Demographics and baseline characteristics for VOYAGE

Parameter	**EOS ≥ 150 cells/mcL or FeNO ≥ 20 ppb (N = 350)**	**EOS ≥ 300 cells/mcL (N = 259)**
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 19.

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 19.

Table 19: Rate of severe exacerbations, mean change from baseline in FEV_1, ACQ-7-IA and PAQLQ(S)-I 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 r (95%**
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)	0.3 (0.227,
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 m differen place (95% C**
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	6.7 (2.54, 1
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 m differen place (95%**
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. (8.30,
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 m differen place (95%**
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	4.9 (3.08,
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 plac (95%**
Dupilumab 100 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	2.6 (1.21,

(<30 kg)/ 200 mg Q2W (≥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 plac (95%**
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	2.0 (0.95,
Placebo	107	65.4		81	63.0		61	67.2	

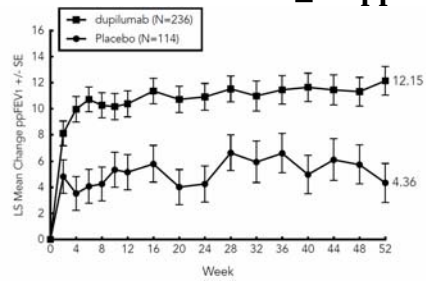
[a]the responder rate was defined as an improvement in score of 0.5 or more (scale range 0-6 for ACQ-7-IA and 1-7 for PAQL
[b]p-value < 0.0001; [c]p-value < 0.001, [d]p-value < 0.01 (all statistically significant vs placebo with adjustment for multiplicity)
[e]nominal p-value < 0.0001, [f]nominal p-value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

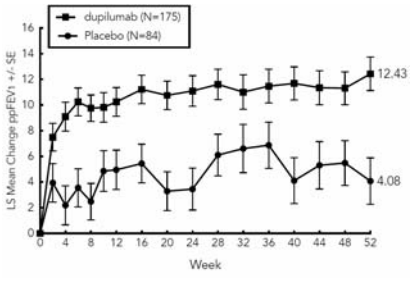
Improvements in percent predicted FEV_1 over time in VOYAGE are shown in Figure 2.

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)

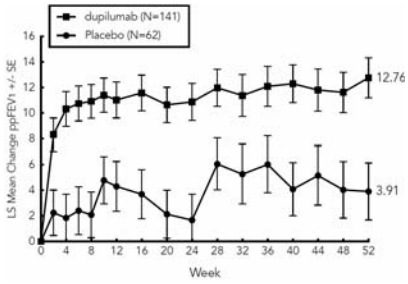
Baseline blood eosinophils ≥ 150 cells/mcL or FeNO ≥ 20 ppb



Baseline blood eosinophils ≥ 300 cells/mcL



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 and safety in eosinophilic esophagitis

Paediatric Patients 1 to 11 Years of Age with EoE

The efficacy and safety of dupilumab was evaluated in paediatric patients 1 to 11 years of age with EoE in a two-part study up to 52-weeks (EoE KIDS Part A & Part B). All enrolled patients had to have failed conventional medicinal therapy (proton pump inhibitors), 77.5% were treated with another conventional medicinal therapy (swallowed topical corticosteroids) prior to inclusion, and 53.5% of patients were inadequately controlled, intolerant or contraindicated to swallowed topical corticosteroid treatment. Eligible patients had ≥15 intraepithelial eosinophils per high-power field (eos/hpf) despite a treatment course of a proton pump inhibitor (PPI) either prior to or during the screening period and a history of EoE signs and symptoms. Part A was a 16-week randomized, double-blind, parallel-group, multicenter, placebo-controlled trial. Part B was an active treatment extension period evaluating the dupilumab regimens for an additional 36 weeks.

Part A evaluated dupilumab versus matching placebo at dosing regimens based on body weight (≥5 to <15 kg (100 mg Q2W), ≥15 to <30 kg (200 mg Q2W), and ≥30 to <60 kg (300 mg Q2W). The recommended dosing regimen of dupilumab was selected for paediatric patients 1 to 11 years of age weighing ≥40 kg (300 mg QW) based upon simulations with a population pharmacokinetic model to match exposures of adult and paediatric patients 12 to 17 years of age with EoE receiving 300mg QW for whom histologic and symptomatic efficacy were observed [see section 5.1 and section 5.2].

A total of 71 patients were enrolled in Part A. The mean age was 7 years (range 1 to 11 years), the median weight was 24.8 kg, 74.6% of patients were male, 87.3% were White, 9.9% were Black, and 1.4% were Asian. A total of 55 patients from Part A continued in Part B.

The primary efficacy endpoint in Part A was the proportion of patients achieving histological remission defined as peak esophageal intraepithelial eosinophil count of ≤6 eos/hpf at Week 16. Secondary endpoints included the proportion of patients

achieving peak esophageal intraepithelial eosinophil count of <15 eos/hpf and the change from baseline in the following: 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, and absolute change in EoE-Endoscopic Reference Score (EoE-EREFS). The impact on signs of EoE was measured using observer reported outcomes; Paediatric EoE Sign/Symptom Questionnaire-Caregiver (PESQ-C) assessed the proportion of days with one or more EoE signs and Paediatric Eosinophilic Esophagitis Symptom Score (PEESS) assessed the frequency and severity of EoE signs.

Efficacy results for Part A are presented in Table 20 and below.

Table 20: Efficacy Results of dupilumab at Week 16 in Subjects 1 to 11 Years of Age with EoE (EoE KIDS Part A)

	Dupilumab [a] N=37	**Placebo N=34**	**Difference vs Placebo (95% CI)**
Primary Endpoint			
Proportion of subjects achieving histological remission (peak esophageal intraepithelial eosinophil count ≤6 eos/hpf), n (%)[b]	25 (67.6)	1 (2.9)	64.5 (48.19, 80.85)
Secondary Endpoints			
Proportion of subjects achieving peak esophageal intraepithelial eosinophil count of <15 eos/hpf, n (%)[b]	31 (83.8)	1 (2.9)	81 (68.07, 94.10)
Percent change from baseline in peak esophageal intraepithelial eosinophil count (eos/hpf), LS mean (SE)[c]	-86.09 (11.84)	20.98 (12.23)	-107.07 (-139.25, -74.90)
Absolute change in Mean Grade Score (0-3[d]) from the Histology Scoring System (EoEHSS) from baseline, LS mean (SE)	-0.879 (0.05)	0.023 (0.05)	-0.902 (-1.03, -0.77)
Absolute change in Mean Stage Score (0-3[d]) from the EoEHSS from baseline, LS mean (SE)	-0.835 (0.05)	0.048 (0.05)	-0.883 (-1.01, -0.76)
Absolute change in EoE-Endoscopic Reference Score(EoE-EREFS) (0-18[e]) from baseline, LS mean (SE)	-3.5 (0.42)	0.3 (0.45)	-3.8 (-4.94, -2.63)

[a] DUPIXENT was evaluated at tiered dosing regimens based on body weight: ≥5 to <15 kg (100 mg Q2W), ≥15 to <30 kg (200 mg Q2W), and ≥30 to <60 kg (300 mg Q2W).

[b] For histological remission, the difference in percentages is estimated using the Mantel-Haenszel method, adjusting for baseline weight group (≥5 to <15 kg, ≥15 to <30 kg, and ≥30 to <60 kg).

[c] The difference in absolute change or percent change is estimated using ANCOVA model with baseline measurement as covariate and the treatment, baseline weight group (≥5 to <15 kg, ≥15 to <30 kg, and ≥30 to <60 kg) strata as fixed factors.
[d] EoEHSS scores range from 0 to 3; higher scores indicate greater severity and extent of histological abnormalities.
[e] EoE-EREFS overall scores range from 0 to 18; higher scores indicate worse endoscopic inflammatory and remodeling findings.

In Part A, a greater proportion of patients randomized to dupilumab achieved histological remission (peak esophageal intraepithelial eosinophil count ≤6 eos/hpf) compared to placebo. The proportion of subjects with histological remission observed after 16 weeks of treatment in Part A was maintained for 52 weeks in Part B.

Numerical improvement in the proportion of days with 1 or more EoE signs (PESQ-C) was observed after 16 weeks of treatment in Part A and was maintained for 52 weeks in Part B.

Nominally significant improvement in the frequency and severity of EoE signs (PEESS-Caregiver) was observed after 16 weeks of treatment in Part A. PEESS-Caregiver was not measured in Part B.

Adults and Adolescents with eosinophilic esophagitis

For clinical data in adults and adolescents with eosinophilic esophagitis please refer to the dupilumab 300 mg Summary of Product Characteristics.

Clinical Efficacy in Chronic Spontaneous Urticaria (CSU)

The chronic spontaneous urticaria (CSU) development program was conducted under a master protocol (CUPID). CUPID Study A, Study B, and Study C were three randomized, double-blind, parallel-group, multicentre, placebo-controlled, 24-week treatment studies in adult and paediatric patients (Study A: 6 to 17 years of age, Study B: 12 to 17 years of age, and Study C: 6 to 17 years of age). Study A and Study C enrolled patients with CSU who were symptomatic despite the use of H1 antihistamines. Study B enrolled patients with CSU who were symptomatic despite the use of H1 antihistamines and were inadequate responders or intolerant to anti-IgE therapy. In all three studies, dupilumab 300 mg every two weeks, dupilumab 200 mg every two weeks, or placebo were evaluated in adults and paediatric patients (12 to 17 years of age)

CUPID Study A and Study C

CUPID Study A and CUPID Study C enrolled 289 patients of which 274 were adults, 10 were adolescent patients 12 to 17 years of age, and 5 were paediatric patients 6 to 11 years of age, randomized to receive either dupilumab 300 mg every two weeks (N=139), dupilumab 200 mg every two weeks (N=5), or placebo (N=145).

In CUPID Study A and Study C, the mean age was 43.1 years, the median weight was 73 kg, 68.2% of patients were female, 57.1% were White, 1.7% were Black, 16.6% were Hispanic or Latino and 33.6% were Asian. In CUPID Study A and Study C, the mean weekly itch and urticaria activity severity scores (ISS7, UAS7) at baseline were 15.5 and 29.8, respectively, despite use of an H1 antihistamine. Majority of patients (64.7%) had severe CSU disease activity at baseline with a UAS7 score of ≥28 The mean baseline UCT was 4.5, corresponding

to uncontrolled urticaria (UCT <12). The reported mean duration of CSU at enrollment across treatment groups was 6.1 years (with an overall subject-level range of 1 to 60 years). The primary efficacy endpoint was change from baseline in itch severity score over 7 days (ISS7) at Week 24. The ISS7 score was defined as the sum of the daily itch severity scores (ISS) recorded at the same time of the day for a 7-day period, ranging from 0 to 21.

The key secondary endpoint was change from baseline in urticaria activity score over 7 days (UAS7) at Week 24. Disease severity was measured by a weekly urticaria activity score (UAS7, range 0–42), which is a composite of the weekly itch severity score (ISS7, range 0–21) and the weekly hive count score (HSS7 range 0–21). Additional secondary endpoints included the change from baseline in hives severity score over 7 days (HSS7) and the urticaria control test (UCT) at Week 12 and Week 24. The UCT is a measure for assessing urticaria control based on 4 assessment elements (severity of urticaria symptom, frequency of treatment being not sufficient, quality-of-life impairment, and overall urticarial control), with a score ranging from 0 to 16. The demographics and baseline characteristics of CUPID Study A are provided in Table 21 below.

Table 21: Demographics and Baseline Characteristics of CUPID Study A and Study C

Parameter	**CUPID Study A (N=138)**	**CUPID Study C (N=151)**	**Pooled (N=289)**
Age (years), mean (SD)	41.3 (15.5)	44.7 (16.9)	43.1 (16.3)
% Male	34.1	29.8	31.8
BMI (kg/m^2), mean (SD)	27.67 (6.47)	26.81 (6.16)	27.22 (6.31)
Disease Duration, mean (SD)	5.7 (8.5)	6.5 (9.8)	6.1 (9.2)
Baseline ISS7 score, mean (SD)	15.9 (4.0)	15.1 (3.8)	15.5 (3.9)
Baseline UAS7 score, mean (SD)	31.3 (7.7)	28.3 (7.5)	29.8 (7.7)
Severe CSU disease activity (UAS7 ≥28)	70.3	59.6	64.7
Baseline HSS7 score, mean (SD)	15.4 (4.3)	13.2 (4.7)	14.2 (4.7)
Baseline UCT score, mean (SD)	3.7 (2.3)	5.2 (3.2)	4.5 (2.9)
Baseline Total IgE (IU/mL,) median	101.0	107.3	103.0

The results for primary and secondary endpoints in CUPID Study A and Study C are presented in the Table 22.

Table 22: Results of the Primary and Secondary Endpoints in CUPID Study A and Study C

	CUPID STUDY A			**CUPID Study C**		
	DUPIXENT (N=70)	**Placebo (N=68)**	**Difference (95% CI) for DUPIXENT vs. Placebo[b]**	**DUPIXENT (N=74)**	**Placebo (N=77)**	**Difference (95% CI) for DUPIXENT vs. Placebo[b]**
Primary Endpoint						
Change from baseline in ISS7 at Week 24[a]	-10.24 (0.91)	-6.01 (0.94)	-4.23 (-6.63, -1.84)	-8.64 (1.41)	-6.10 (1.40)	-2.54 (-4.65, -0.43)
Secondary Endpoints						
Change from baseline in UAS7 at Week 24[a]	-20.53 (1.76)	-12.00 (1.81)	-8.53 (-13.16, -3.90)	-15.86 (2.66)	-11.21 (2.65)	-4.65 (-8.65, -0.65)
Change from baseline in HSS7 at Week 24[a]	-10.28 (0.91)	-5.90 (0.93)	-4.38 (-6.78, -1.98)	-7.27 (1.32)	-5.11 (1.31)	-2.17 (-4.15, -0.19)

	DUPIXENT (N=70)	Placebo (N=68)	Odds Ratio (95% CI) for DUPIXENT vs. Placebo[b]	DUPIXENT (N=74)	Placebo (N=77)	Odds Ratio (95% CI) for DUPIXENT vs. Placebo[b]
Proportion of patients with UAS7 ≤6 at Week 24[a]	32 (45.7)	16 (23.5)	2.848 (1.301, 6.234)	30 (40.5)	18 (23.4)	3.137 (1.371, 7.176)
Proportion of patients with UAS7 = 0 at Week 24[a]	22 (31.4)	9 (13.2)	2.908 (1.173, 7.209)	22 (29.7)	14 (18.2)	2.677 (1.127, 6.359)
Proportion of participants with MID (ISS7 ≥ 5) response at Week 24	51 (72.9)	29 (42.6)	3.41 (1.60, 7.30)	52 (70.3)	40 (51.9)	2.51 (1.23, 5.11)

[a] Values presented are LS mean change from baseline (SE) for continuous variables and number and percent of responders for binary variables.
[b] Difference is LS mean difference for continuous variables and odds ratio for binary variables.

Dupilumab treatment led to an improvement over time in ISS7 and UAS7 through the 24-week treatment period (Figures 3 and 4).

Figure 3: LS mean change from baseline in ISS7 up to Week 24 in CUPID Study A and Study C ITT population

Study A Study C

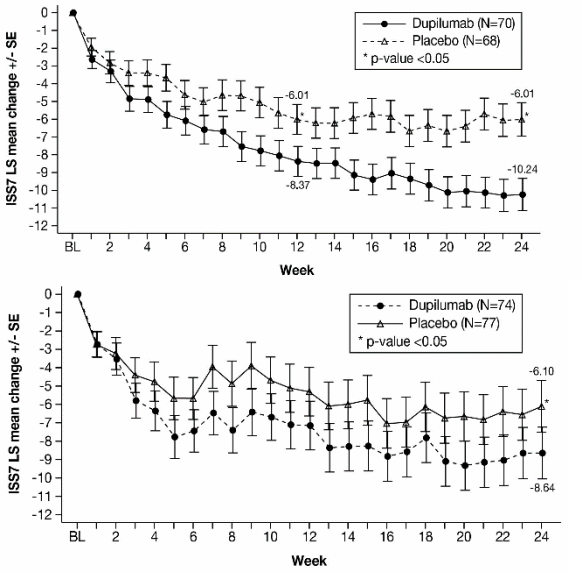
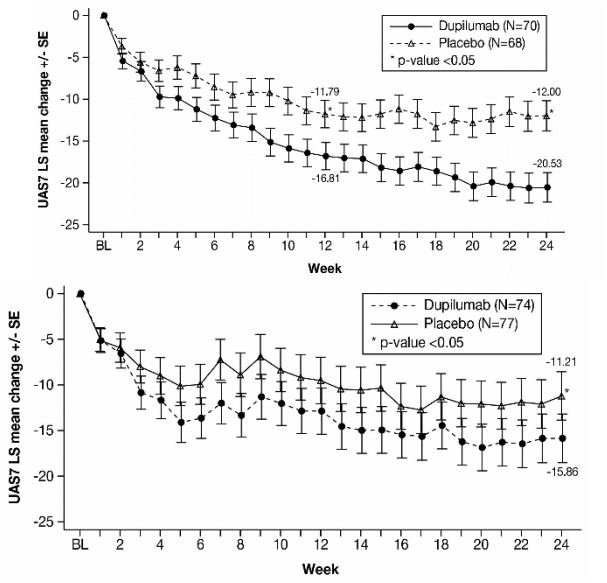


Figure 4: LS mean change from baseline in UAS7 up to Week 24 in CUPID Study A and Study C ITT population

Study A Study C



Similar improvement in HSS7 was observed over 24 weeks.

Improvements in ISS7 and UAS7 at Week 24 were consistent regardless of the patients' baseline IgE.

Dupilumab improved overall disease control compared to placebo as measured by UCT (higher score reflects greater disease control) at Week 24 (LS mean difference versus placebo of 2.84 [95% CI: 1.27: 4.40] in Study A and 0.93 [95% CI: -0.48, 2.34] in Study C) and at Week 12 (LS mean difference versus placebo of 1.86 [95% CI: 0.35: 3.36]).

Study A showed statistically significant improvement in ISS7 and UAS7 from baseline at Week 12 (LS mean difference versus placebo of -2.37 [95% CI: (-4.60, -0.13) for ISS7 and -5.02 [95% CI: (-9.32, -0.72)] for UAS7 respectively. Study C showed numerical differences in ISS7 and UAS7 from baseline at Week 12 (LS mean difference versus placebo of -1.84 [95% CI: (-3.78, 0.10)] for ISS7 and -3.36 [95% CI: (-7.07, 0.36)] for UAS7.The proportion of patients with UAS7 ≤6 at Week 12 was 34.3% and 31.1%for dupilumab and 17.6% and 16.9% for placebo [Odds Ratio: Study A: 2.645 [95% CI: (1.154, 6.061); Study C: 2.676 [95% CI:(1.169, 6.125)] for Study A and C respectively.

CUPID Study B

CUPID Study B evaluated the efficacy of dupilumab in patients with CSU who are inadequate responders (N=104) or intolerant (N=4) to anti-IgE therapy. This study enrolled 108 patients 12 years of age and older, and had same efficacy endpoints as Study A and Study C. Dupilumab did not meet statistical significance for reduction in the primary endpoint ISS7 at Week 24 (dupilumab -7.68, placebo -4.81, treatment difference, -2.87), but demonstrated nominally significant improvements for secondary endpoints UAS7 and HSS7 at Week 24 (UAS7: 'TM' -14.37, placebo -8.54, treatment difference -5.83; HSS7: 'TM' -6.64, placebo -3.63, treatment difference -3.01).

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 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.

Eosinophilic Esophagitis
The safety and efficacy of dupilumab for the treatment of EoE have been established in paediatric patients 1 to 17 years of age. Use of dupilumab in this population is supported by adequate and well-controlled studies and additional pharmacokinetic data. A total of 72 paediatric patients 12 to 17 years of age received dupilumab 300 mg QW or placebo for 24 weeks (TREET Parts A and B). Of these, there were 37 dupilumab treated patients in Parts A and B; 34 continued treatment with 300 mg QW

for an additional 28 weeks (TREET Part C). A total of 71 paediatric patients 1 to 11 years of age received dupilumab 100 mg Q2W, 200 mg Q2W, 300 mg Q2W, or placebo for 16 weeks (EoE KIDS Part A). Of these, there were 37 dupilumab treated patients in Part A all of whom continued treatment with these dupilumab regimens for an additional 36 weeks (EoE KIDS Part B). The use of dupilumab 300 mg QW in patients 1 to 11 years of age with EoE with a body weight 40 ≥ kg is also supported by a population pharmacokinetic analysis [see section 5.1]. The safety and efficacy of dupilumab in adults and paediatric patients were similar [see section 4.8 and section 5.1].

Chronic Spontaneous Urticaria
The safety and effectiveness of dupilumab for the treatment of CSU have been established in adolescent subjects 12 year of age and older. A total of 12 adolescents aged 12 to 17 years and 5 children aged 6 to 11 years with CSU were enrolled in CUPID Study A, B, and C who received doses of dupilumab 200 mg Q2W (30 kg to <60 kg), 300 mg Q2W (≥60 kg) or placebo. Two children 6 to 11 years of age (both in the dupilumab group), discontinued study treatment early (Week 4 and Week 10) and two adolescents aged 12 to 17 years of age (one in each treatment group) discontinued study treatment early (Week 12 and Week 22). An adverse event was reported in one adolescent treated with dupilumab. No adverse events were reported in children aged 6 to 11 years treated with dupilumab. The effectiveness of dupilumab for the treatment of CSU in adolescent patients 12 to 17 years of age is based on safety and efficacy in adults with this condition due to the similarity of pathophysiology, disease course, response to available therapies, and consistent dupilumab exposure established through PK modelling safety for dupilumab in adolescent patients 12 to 17 years of age with CSU is supported by available safety information from the paediatric AD indication. The recommended dosage in adolescent patients 12 years of age or older is based on body weight. Safety and effectiveness in paediatric patients younger than 12 years of age with CSU 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 and EoE have been fulfilled.

5.2 Pharmacokinetic properties

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

Of the 198 patients with CSU exposed to dupilumab, a total of 30 were 65 years of age and older including 7 patients 75 years of age and 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 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.

Eosinophilic esophagitis

In a clinical study (EoE KIDS Part A), dupilumab pharmacokinetics were investigated in 36 children 1 to 11 years of age with EoE receiving dupilumab [≥5 to <15 kg (100 mg Q2W), ≥15 to <30 kg (200 mg Q2W), and ≥30 to <60 kg (300 mg Q2W)], the mean ± SD steady-state trough concentration of dupilumab was 163±60.8 mcg/mL.

Simulations for paediatric patients 1 to 11 years of age were conducted with a population pharmacokinetic model to predict trough concentrations of dupilumab at steady-state as follows: ≥15 to <30 kg receiving 200 mg Q2W (170±78 mcg/mL); ≥30 to <40 kg receiving 300 mg Q2W (158±63 mcg/mL); or ≥40 kg receiving 300 mg QW (276±99 mcg/mL). Steady-state trough concentrations were also simulated for adult and paediatric patients 12 to 17 years of age and patients from ≥30 to <40 kg receiving 300 mg Q2W (159±61 mcg/mL).

Chronic Spontaneous Urticaria
Pharmacokinetics in paediatric patients (<12 years of age) with CSU have not been established.

A total of 12 adolescents aged 12 to 17 years with CSU were enrolled in CUPID Study A, B, and C. The observed steady-state trough concentrations of 5 adolescent patients with CSU who received dupilumab 300 mg Q2W or 200 mg Q2W for 24 weeks were within the range of the steady-state trough concentrations in adult patients with CSU who received dupilumab 300 mg Q2W for 24 weeks.

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 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

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

6.6 Special precautions for disposal

Comprehensive instructions for the administration of Dupixent in a pre-filled syringe 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 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 should not be exposed to heat or direct sunlight and should not be shaken.

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

7 MARKETING AUTHORISATION HOLDER

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9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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10 DATE OF REVISION OF THE TEXT

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