

デュピクセント皮下注300mgシリンジ に関する資料

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デュピルマブ（遺伝子組換え）

1.5 起原又は発見の経緯及び開発の経緯（鼻茸）

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1 起原又は発見の経緯及び開発の経緯

デュピルマブ（遺伝子組換え）（以下、デュピルマブ）は、インターロイキン（IL）-4 受容体及び IL-13 受容体複合体に共通する IL-4 受容体 α サブユニット（IL-4R α ）に特異的に結合することにより、IL-4 及び IL-13 シグナル伝達を阻害する遺伝子組換えヒト免疫グロブリン G4 モノクローナル抗体である。デュピルマブは、1 型受容体（IL-4R α / γ c）を介して IL-4 シグナル伝達を阻害し、2 型受容体（IL-4R α /IL-13R α ）を介して IL-4 及び IL-13 の両方のシグナル伝達を阻害する。

本邦ではデュピルマブは「既存治療で効果不十分なアトピー性皮膚炎」を効能・効果として 2018 年 1 月に医薬品製造販売承認され、さらに 2019 年 3 月に「気管支喘息（既存治療によっても喘息症状をコントロールできない重症又は難治の患者に限る）」の効能・効果を取得した。

慢性副鼻腔炎は、鼻腔及び副鼻腔の炎症、粘膜浮腫、鼻閉塞及び粘液産生増加を特徴とする多様な疾患であり、鼻閉、嗅覚障害、鼻漏といった症状が 12 週以上継続する。慢性副鼻腔炎は鼻茸の有無により 2 つのフェノタイプに分類され、鼻茸を伴う慢性副鼻腔炎では Type 2 炎症が優位に認められる。

今般、日本人患者を含む国際共同試験等において、鼻茸を伴う慢性副鼻腔炎に対するデュピルマブの有効性及び安全性が確認されたことから、医薬品製造販売承認事項一部変更承認申請を行うこととした。

1.1 開発の経緯

デュピルマブの開発の経緯を図 1 に示す。本剤の臨床試験では十分な患者説明及びトレーニングを実施した上で自己注射が行われた。なお、本申請に際して新たに提出する品質及び非臨床試験に関するデータはない。

1.5 起原又は発見の経緯及び開発の経緯
SAR231893 - デュピルマブ（遺伝子組換え）

図 1 デュピルマブに係る開発の経緯図

資料区分	試験項目			
	臨床試験	国際共同試験	第Ⅲ相試験	
第五部				

■ ■ ■ ■ ■ : 国際共同試験

数字は開始及び終了月を示す。

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デュピルマブ（遺伝子組換え）

1.6 外国における使用状況等に関する資料（鼻茸）

Total number of pages: 2

1 外国での承認及び使用状況

デュピルマブは米国では2017年3月に、欧州では2017年9月に、成人の中等症から重症のアトピー性皮膚炎の適応で承認された。

また、成人及び12歳以上の思春期患者を対象に、米国では2018年10月にフェノタイプが好酸球性の中等症から重症の喘息及びフェノタイプを問わない経口ステロイド薬依存性の喘息の適応が承認され、2019年5月に欧州にて重症のType 2喘息の適応で承認された。

さらに、鼻茸を伴う慢性副鼻腔炎に係る追加適応を2019年6月に米国で、2019年10月に欧州で取得した。

本剤の Company Core Data Sheet、USPI 及び SmPC を添付する。

DUPILUMAB
Solution for SC injection in pre-filled syringe

COMPANY CORE DATA SHEET


STRICTLY CONFIDENTIAL - FOR INTERNAL USE ONLY

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use DUPIXENT safely and effectively. See full prescribing information for DUPIXENT.

DUPIXENT® (dupilumab) injection, for subcutaneous use
Initial U.S. Approval: 2017

RECENT MAJOR CHANGES

Indications and Usage, Atopic Dermatitis (1.1)	03/2019
Indications and Usage, Asthma (1.2)	10/2018
Indications and Usage, CRSwNP (1.3)	06/2019
Dosage and Administration, Atopic Dermatitis (2.1; 2.4)	03/2019
Dosage and Administration, Asthma (2.2; 2.4; 2.5)	10/2018
Dosage and Administration, CRSwNP (2.3; 2.4)	06/2019
Warnings and Precautions (5.1; 5.2; 5.3; 5.4; 5.5; 5.6; 5.7)	10/2018
Warnings and Precautions (5.2; 5.6)	06/2019

INDICATIONS AND USAGE

DUPIXENT is an interleukin-4 receptor alpha antagonist indicated:

- for the treatment of patients aged 12 years and older with moderate-to-severe atopic dermatitis whose disease is not adequately controlled with topical prescription therapies or when those therapies are not advisable. DUPIXENT can be used with or without topical corticosteroids. (1.1)
 - as an add-on maintenance treatment in patients with moderate-to-severe asthma aged 12 years and older with an eosinophilic phenotype or with oral corticosteroid dependent asthma. (1.2)
- Limitation of Use**
Not for the relief of acute bronchospasm or status asthmaticus. (1.2)
- as an add-on maintenance treatment in adult patients with inadequately controlled chronic rhinosinusitis with nasal polyposis (CRSwNP). (1.3)

DOSAGE AND ADMINISTRATION

Administer by subcutaneous injection. (2)

Atopic Dermatitis

Adults

- The recommended dose is an initial dose of 600 mg (two 300 mg injections in different injection sites), followed by 300 mg given every other week. (2.1)

Adolescents

Body Weight	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

Asthma

- The recommended dose of DUPIXENT 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 or
 - an initial dose of 600 mg (two 300 mg injections) followed by 300 mg given every other week
 - for patients requiring concomitant oral corticosteroids or with co-morbid moderate-to-severe atopic dermatitis for which DUPIXENT is indicated,

start with an initial dose of 600 mg followed by 300 mg given every other week. (2.2)

Chronic Rhinosinusitis with Nasal Polyposis

- The recommended dose of DUPIXENT for adult patients is 300 mg given every other week. (2.3)

DOSAGE FORMS AND STRENGTHS

- Injection: 300 mg/2 mL solution in a single-dose pre-filled syringe with needle shield (3)
- Injection: 200 mg/1.14 mL solution in a single-dose pre-filled syringe with needle shield (3)

CONTRAINDICATIONS

Known hypersensitivity to DUPIXENT or any of its excipients. (4)

WARNINGS AND PRECAUTIONS

- Hypersensitivity:** Hypersensitivity reactions (urticaria, rash, erythema nodosum, anaphylaxis, and serum sickness) have occurred after administration of DUPIXENT. Discontinue DUPIXENT in the event of a hypersensitivity reaction. (5.1)
- Conjunctivitis and Keratitis:** Patients should report new onset or worsening eye symptoms to their healthcare provider. (5.2)
- Eosinophilic Conditions:** Be alert to vasculitic rash, worsening pulmonary symptoms, and/or neuropathy, especially upon reduction of oral corticosteroids. (5.3)
- Reduction of Corticosteroid Dosage:** Do not discontinue systemic, topical, or inhaled corticosteroids abruptly upon initiation of therapy with DUPIXENT. Decrease steroids gradually, if appropriate. (5.5)
- Parasitic (Helminth) Infections:** Treat patients with pre-existing helminth infections before initiating therapy with DUPIXENT. If patients become infected while receiving treatment with DUPIXENT and do not respond to anti-helminth treatment, discontinue treatment with DUPIXENT until the infection resolves. (5.7)

ADVERSE REACTIONS

Atopic Dermatitis: Most common adverse reactions (incidence $\geq 1\%$) are injection site reactions, conjunctivitis, blepharitis, oral herpes, keratitis, eye pruritus, other herpes simplex virus infection, and dry eye. (6.1)

Asthma: Most common adverse reactions (incidence $\geq 1\%$) are injection site reactions, oropharyngeal pain, and eosinophilia. (6.1)

Chronic Rhinosinusitis with Nasal Polyposis: Most common adverse reactions (incidence $\geq 1\%$) are injection site reactions, eosinophilia, insomnia, toothache, gastritis, arthralgia, and conjunctivitis. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Regeneron at 1-844-387-4936 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

Live Vaccines: Avoid use of live vaccines with DUPIXENT. (7.1)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 06/2019

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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

DUPIXENT is indicated for the following diseases:

1.1 Atopic Dermatitis

DUPIXENT is indicated for the treatment of patients aged 12 years and older with moderate-to-severe atopic dermatitis whose disease is not adequately controlled with topical prescription therapies or when those therapies are not advisable. DUPIXENT can be used with or without topical corticosteroids.

1.2 Asthma

DUPIXENT is indicated as an add-on maintenance treatment in patients with moderate-to-severe asthma aged 12 years and older with an eosinophilic phenotype or with oral corticosteroid dependent asthma.

Limitation of Use

DUPIXENT is not indicated for the relief of acute bronchospasm or status asthmaticus.

1.3 Chronic Rhinosinusitis with Nasal Polyposis

DUPIXENT is indicated as an add-on maintenance treatment in adult patients with inadequately controlled chronic rhinosinusitis with nasal polyposis (CRSwNP).

2 DOSAGE AND ADMINISTRATION

DUPIXENT is administered by subcutaneous injection.

2.1 Atopic Dermatitis

Dosing in Adults

The recommended dose of DUPIXENT for adult patients is an initial dose of 600 mg (two 300 mg injections), followed by 300 mg given every other week.

Dosing in Adolescents

The recommended dose of DUPIXENT for patients 12 to 17 years of age is specified in Table 1.

Table 1: Dose of DUPIXENT for Subcutaneous Administration in Adolescent Patients

Body Weight	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

Concomitant Topical Therapies

DUPIXENT 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.

2.2 Asthma

The recommended dose of DUPIXENT 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 or
- an initial dose of 600 mg (two 300 mg injections) followed by 300 mg given every other week
- for patients with oral corticosteroids-dependent asthma, or with co-morbid moderate-to-severe atopic dermatitis for which DUPIXENT is indicated, start with an initial dose of 600 mg followed by 300 mg given every other week

2.3 Chronic Rhinosinusitis with Nasal Polyposis

The recommended dose of DUPIXENT for adult patients is 300 mg given every other week.

2.4 Important Administration Instructions

DUPIXENT is intended for use under the guidance of a healthcare provider. A patient may self-inject DUPIXENT after training in subcutaneous injection technique using the pre-filled syringe. Provide proper training to patients and/or caregivers on the preparation and administration of DUPIXENT prior to use according to the “Instructions for Use”.

For atopic dermatitis and asthma patients taking an initial 600 mg dose, administer each of the two DUPIXENT 300 mg injections at different injection sites.

For asthma patients taking an initial 400 mg dose, administer each of the two DUPIXENT 200 mg injections at different injection sites.

Administer subcutaneous injection into the thigh or abdomen, except for the 2 inches (5 cm) around the navel. The upper arm can also be used if a caregiver administers the injection.

Rotate the injection site with each injection. DO NOT inject DUPIXENT into skin that is tender, damaged, bruised, or scarred.

If a dose is missed, instruct the patient to 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, instruct the patient to wait until the next dose on the original schedule.

The DUPIXENT “Instructions for Use” contains more detailed instructions on the preparation and administration of DUPIXENT [see *Instructions for Use*].

2.5 Preparation for Use of DUPIXENT Pre-filled Syringe with Needle Shield

Before injection, remove DUPIXENT pre-filled syringe from the refrigerator and allow DUPIXENT to reach room temperature (45 minutes for the 300 mg/2 mL pre-filled syringe and 30 minutes for the 200 mg/1.14 mL pre-filled syringe) without removing the needle cap.

Inspect DUPIXENT visually for particulate matter and discoloration prior to administration. DUPIXENT is a clear to slightly opalescent, colorless to pale yellow solution. Do not use if the liquid contains visible particulate matter, is discolored or cloudy (other than clear to slightly opalescent, colorless to pale yellow). DUPIXENT does not contain preservatives; therefore, discard any unused product remaining in the pre-filled syringe.

3 DOSAGE FORMS AND STRENGTHS

DUPIXENT is a clear to slightly opalescent, colorless to pale yellow solution available as:

- Injection: 300 mg/2 mL in a single-dose pre-filled syringe with needle shield
- Injection: 200 mg/1.14 mL in a single-dose pre-filled syringe with needle shield

4 CONTRAINDICATIONS

DUPIXENT is contraindicated in patients who have known hypersensitivity to dupilumab or any of its excipients [see *Warnings and Precautions* (5.1)].

5 WARNINGS AND PRECAUTIONS

5.1 Hypersensitivity

Hypersensitivity reactions, including generalized urticaria, rash, erythema nodosum and serum sickness or serum sickness-like reactions, were reported in less than 1% of subjects who received DUPIXENT in clinical trials. Two subjects in the atopic dermatitis development program experienced serum sickness or serum sickness-like reactions that were associated with high titers of antibodies to dupilumab. One subject in the asthma development program experienced anaphylaxis [see *Adverse Reactions* (6.2)]. If a clinically significant hypersensitivity reaction occurs, institute appropriate therapy and discontinue DUPIXENT [see *Adverse Reactions* (6.1, 6.2)].

5.2 Conjunctivitis and Keratitis

Conjunctivitis and keratitis occurred more frequently in atopic dermatitis subjects who received DUPIXENT. Conjunctivitis was the most frequently reported eye disorder. Most subjects with conjunctivitis recovered or were recovering during the treatment period. Keratitis was reported in <1% of the DUPIXENT group (1 per 100 subject-years) and in 0% of the placebo group (0 per 100 subject-years) in the 16-week atopic dermatitis monotherapy trials. In the 52-week DUPIXENT + topical corticosteroids (TCS) atopic dermatitis trial, keratitis was reported in 4% of the DUPIXENT + TCS group (12 per 100 subject-years) and in 0% of the placebo + TCS group (0 per 100 subject-years). Most subjects with keratitis recovered or were recovering during the treatment period [see *Adverse Reactions* (6.1)].

Among asthma subjects, the frequencies of conjunctivitis and keratitis were similar between DUPIXENT and placebo [see *Adverse Reactions* (6.1)].

In subjects with CRSwNP, the frequency of conjunctivitis was 2% in the DUPIXENT group compared to 1% in the placebo group in the 24-week safety pool; these subjects recovered. There were no cases of keratitis reported in the CRSwNP development program [see *Adverse Reactions* (6.1)].

Advise patients to report new onset or worsening eye symptoms to their healthcare provider.

5.3 Eosinophilic Conditions

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 may be associated with the reduction of oral corticosteroid therapy. Physicians should be alert to vasculitic rash, worsening pulmonary symptoms, cardiac complications, and/or neuropathy presenting in their patients with eosinophilia. Cases of eosinophilic pneumonia were reported in adult patients who participated in the asthma development program and cases of vasculitis consistent with eosinophilic granulomatosis with polyangiitis have been reported with DUPIXENT in adult patients who participated in the asthma development program as well as in adult patients with co-morbid asthma in the CRSwNP development program. A causal association between DUPIXENT and these conditions has not been established.

5.4 Acute Asthma Symptoms or Deteriorating Disease

DUPIXENT should not be used to treat acute asthma symptoms or acute exacerbations. Do not use DUPIXENT to treat acute bronchospasm or status asthmaticus. Patients should seek medical advice if their asthma remains uncontrolled or worsens after initiation of treatment with DUPIXENT.

5.5 Reduction of Corticosteroid Dosage

Do not discontinue systemic, topical, or inhaled corticosteroids abruptly upon initiation of therapy with DUPIXENT. 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.

5.6 Patients with Co-morbid Asthma

Advise patients with atopic dermatitis or CRSwNP who have co-morbid asthma not to adjust or stop their asthma treatments without consultation with their physicians.

5.7 Parasitic (Helminth) Infections

Patients with known helminth infections were excluded from participation in clinical studies. It is unknown if DUPIXENT will influence the immune response against helminth infections.

Treat patients with pre-existing helminth infections before initiating therapy with DUPIXENT. If patients become infected while receiving treatment with DUPIXENT and do not respond to anti-helminth treatment, discontinue treatment with DUPIXENT until the infection resolves.

6 ADVERSE REACTIONS

The following adverse reactions are discussed in greater detail elsewhere in the labeling:

- Hypersensitivity [*see Warnings and Precautions (5.1)*]
- Conjunctivitis and Keratitis [*see Warnings and Precautions (5.2)*]

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Adults with Atopic Dermatitis

Three randomized, double-blind, placebo-controlled, multicenter trials (Trials 1, 2, and 3) and one dose-ranging trial (Trial 4) evaluated the safety of DUPIXENT in subjects with moderate-to-severe atopic dermatitis. The safety population had a mean age of 38 years; 41% of subjects were female, 67% were white, 24% were Asian, and 6% were black; in terms of co-morbid conditions, 48% of the subjects had asthma, 49% had allergic rhinitis, 37% had food allergy, and 27% had allergic conjunctivitis. In these 4 trials, 1472 subjects were treated with subcutaneous injections of DUPIXENT, with or without concomitant topical corticosteroids (TCS).

A total of 739 subjects were treated with DUPIXENT for at least 1 year in the development program for moderate-to-severe atopic dermatitis.

Trials 1, 2, and 4 compared the safety of DUPIXENT monotherapy to placebo through Week 16. Trial 3 compared the safety of DUPIXENT + TCS to placebo + TCS through Week 52.

Weeks 0 to 16 (Trials 1 to 4):

In DUPIXENT monotherapy trials (Trials 1, 2, and 4) through Week 16, the proportion of subjects who discontinued treatment because of adverse events was 1.9% in both the DUPIXENT 300 mg Q2W and placebo groups.

Table 2 summarizes the adverse reactions that occurred at a rate of at least 1% in the DUPIXENT 300 mg Q2W monotherapy groups, and in the DUPIXENT + TCS group, all at a higher rate than in their respective comparator groups during the first 16 weeks of treatment.

Table 2: Adverse Reactions Occurring in $\geq 1\%$ of the DUPIXENT Monotherapy Group or the DUPIXENT + TCS Group in the Atopic Dermatitis Trials through Week 16

Adverse Reaction	DUPIXENT Monotherapy ^a		DUPIXENT + TCS ^b	
	DUPIXENT 300 mg Q2W ^c N=529 n (%)	Placebo N=517 n (%)	DUPIXENT 300 mg Q2W ^c + TCS N=110 n (%)	Placebo + TCS N=315 n (%)
Injection site reaction	51 (10)	28 (5)	11 (10)	18 (6)
Conjunctivitis ^d	51 (10)	12 (2)	10 (9)	15 (5)
Blepharitis	2 (<1)	1 (<1)	5 (5)	2 (1)
Oral herpes	20 (4)	8 (2)	3 (3)	5 (2)
Keratitis ^e	1 (<1)	0	4 (4)	0
Eye pruritus	3 (1)	1 (<1)	2 (2)	2 (1)
Other herpes simplex virus infection ^f	10 (2)	6 (1)	1 (1)	1 (<1)
Dry eye	1 (<1)	0	2 (2)	1 (<1)

^a Pooled analysis of Trials 1, 2, and 4.

^b Analysis of Trial 3 where subjects were on background TCS therapy.

^c DUPIXENT 600 mg at Week 0, followed by 300 mg every two weeks.

^d Conjunctivitis cluster includes conjunctivitis, allergic conjunctivitis, bacterial conjunctivitis, viral conjunctivitis, giant papillary conjunctivitis, eye irritation, and eye inflammation.

^e Keratitis cluster includes keratitis, ulcerative keratitis, allergic keratitis, atopic keratoconjunctivitis, and ophthalmic herpes simplex.

^f Other herpes simplex virus infection cluster includes herpes simplex, genital herpes, herpes simplex otitis externa, and herpes virus infection, but excludes eczema herpeticum.

Safety through Week 52 (Trial 3):

In the DUPIXENT with concomitant TCS trial (Trial 3) through Week 52, the proportion of subjects who discontinued treatment because of adverse events was 1.8% in DUPIXENT 300 mg Q2W + TCS group and 7.6% in the placebo + TCS group. Two subjects discontinued DUPIXENT because of adverse reactions: atopic dermatitis (1 subject) and exfoliative dermatitis (1 subject).

The safety profile of DUPIXENT + TCS through Week 52 was generally consistent with the safety profile observed at Week 16.

Adolescents with Atopic Dermatitis

The safety of DUPIXENT was assessed in a trial of 250 subjects 12 to 17 years of age with moderate-to-severe atopic dermatitis (Trial 6). The safety profile of DUPIXENT in these subjects through Week 16 was similar to the safety profile from studies in adults with atopic dermatitis.

The long-term safety of DUPIXENT was assessed in an open-label extension study in subjects 12 to 17 years of age with moderate-to-severe atopic dermatitis (Trial 7). The safety profile of DUPIXENT in subjects followed through Week 52 was similar to the safety profile observed at Week 16 in Trial 6. The long-term safety profile of DUPIXENT observed in adolescents was consistent with that seen in adults with atopic dermatitis.

Asthma

A total of 2888 adult and adolescent subjects with moderate-to-severe asthma (AS) were evaluated in 3 randomized, placebo-controlled, multicenter trials of 24 to 52 weeks duration (AS Trials 1, 2, and 3). Of these, 2678 had a history of 1 or more severe exacerbations in the year prior to enrollment despite regular use of medium to high-dose inhaled corticosteroids plus an additional controller(s) (AS Trials 1 and 2). A total of 210 subjects with oral corticosteroid-dependent asthma receiving high-dose inhaled corticosteroids plus up to two additional controllers were enrolled (AS Trial 3). The safety population (AS Trials 1 and 2) was 12-87 years of age, of which 63% were female, and 82% were white. DUPIXENT 200 mg or 300 mg was administered subcutaneously Q2W, following an initial dose of 400 mg or 600 mg, respectively.

In AS Trials 1 and 2, the proportion of subjects who discontinued treatment due to adverse events was 4% of the placebo group, 3% of the DUPIXENT 200 mg Q2W group, and 6% of the DUPIXENT 300 mg Q2W group.

Table 3 summarizes the adverse reactions that occurred at a rate of at least 1% in subjects treated with DUPIXENT and at a higher rate than in their respective comparator groups in Asthma Trials 1 and 2.

Table 3: Adverse Reactions Occurring in $\geq 1\%$ of the DUPIXENT Groups in Asthma Trials 1 and 2 and Greater than Placebo (6 Month Safety Pool)

Adverse Reaction	AS Trials 1 and 2		
	DUPIXENT 200 mg Q2W N=779 n (%)	DUPIXENT 300 mg Q2W N=788 n (%)	Placebo N=792 n (%)
Injection site reactions ^a	111 (14%)	144 (18%)	50 (6%)
Oropharyngeal pain	13 (2%)	19 (2%)	7 (1%)
Eosinophilia ^b	17 (2%)	16 (2%)	2 (<1%)

^a Injection site reactions cluster includes erythema, edema, pruritus, pain, and inflammation.

^b Eosinophilia = blood eosinophils $\geq 3,000$ cells/mcL, or deemed by the investigator to be an adverse event. None met the criteria for serious eosinophilic conditions [see *Warnings and Precautions (5.3)*].

Injection site reactions were most common with the loading (initial) dose.

The safety profile of DUPIXENT through Week 52 was generally consistent with the safety profile observed at Week 24.

Chronic Rhinosinusitis with Nasal Polyposis

A total of 722 adult subjects with chronic rhinosinusitis with nasal polyposis (CRSwNP) were evaluated in 2 randomized, placebo-controlled, multicenter trials of 24 to 52 weeks duration (CSNP Trials 1 and 2). The safety pool consisted of data from the first 24 weeks of treatment from both studies.

In the safety pool, the proportion of subjects who discontinued treatment due to adverse events was 5% of the placebo group and 2% of the DUPIXENT 300 mg Q2W group.

Table 4 summarizes the adverse reactions that occurred at a rate of at least 1% in subjects treated with DUPIXENT and at a higher rate than in their respective comparator group in CSNP Trials 1 and 2.

Table 4: Adverse Reactions Occurring in $\geq 1\%$ of the DUPIXENT Group in CRSwNP Trials 1 and 2 and Greater than Placebo (24 Week Safety Pool)

Adverse Reaction	CSNP Trials 1 and 2	
	DUPIXENT 300 mg Q2W N=440 n (%)	Placebo N=282 n (%)
Injection site reactions ^a	28 (6%)	12 (4%)
Conjunctivitis ^b	7 (2%)	2 (1%)
Arthralgia	14 (3%)	5 (2%)
Gastritis	7 (2%)	2 (1%)
Insomnia	6 (1%)	0 (<1%)
Eosinophilia	5 (1%)	1 (<1%)
Toothache	5 (1%)	1 (<1%)

^a Injection site reactions cluster includes injection site reaction, pain, bruising and swelling.

^b Conjunctivitis cluster includes conjunctivitis, allergic conjunctivitis, bacterial conjunctivitis, viral conjunctivitis, giant papillary conjunctivitis, eye irritation, and eye inflammation.

The safety profile of DUPIXENT through Week 52 was generally consistent with the safety profile observed at Week 24.

Specific Adverse Reactions

Conjunctivitis

During the 52-week treatment period of concomitant therapy atopic dermatitis trial (Trial 3), conjunctivitis was reported in 16% of the DUPIXENT 300 mg Q2W + TCS group (20 per 100 subject-years) and in 9% of the placebo + TCS group (10 per 100 subject-years). Among asthma subjects, the frequency of conjunctivitis was similar between DUPIXENT and placebo. In the 52-week CRSwNP study (CSNP Trial 2), the frequency of conjunctivitis was 3% in the DUPIXENT subjects and 1% in the placebo subjects; all of these subjects recovered. [see *Warnings and Precautions* (5.2)].

Eczema Herpeticum and Herpes Zoster

The rate of eczema herpeticum was similar in the placebo and DUPIXENT groups in the atopic dermatitis trials.

Herpes zoster was reported in <0.1% of the DUPIXENT groups (<1 per 100 subject-years) and in <1% of the placebo group (1 per 100 subject-years) in the 16-week atopic dermatitis monotherapy trials. In the 52-week DUPIXENT + TCS atopic dermatitis trial, herpes zoster was reported in 1% of the DUPIXENT + TCS group (1 per 100 subject-years) and 2% of the placebo + TCS group (2 per 100 subject-years). Among asthma subjects the frequency of herpes zoster was similar between DUPIXENT and placebo. Among CRSwNP subjects there were no reported cases of herpes zoster or eczema herpeticum.

Hypersensitivity Reactions

Hypersensitivity reactions were reported in <1% of DUPIXENT-treated subjects. These included serum sickness reaction, serum sickness-like reaction, generalized urticaria, rash, erythema nodosum, and anaphylaxis [see *Contraindications (4)*, *Warnings and Precautions (5.1)*, and *Adverse Reactions (6.2)*].

Eosinophils

DUPIXENT-treated subjects had a greater initial increase from baseline in blood eosinophil count compared to subjects treated with placebo. In subjects with atopic dermatitis, the mean and median increases in blood eosinophils from baseline to Week 4 were 100 and 0 cells/mcL respectively. In subjects with asthma, the mean and median increases in blood eosinophils from baseline to Week 4 were 130 and 10 cells/mcL respectively. In subjects with CRSwNP, the mean and median increases in blood eosinophils from baseline to Week 16 were 150 and 50 cells/mcL, respectively.

Across all indications, the incidence of treatment-emergent eosinophilia (≥ 500 cells/mcL) was similar in DUPIXENT and placebo groups. Treatment-emergent eosinophilia ($\geq 5,000$ cells/mcL) was reported in <2% of DUPIXENT-treated patients and <0.5% in placebo-treated patients. Blood eosinophil counts declined to near baseline levels during study treatment [see *Warnings and Precautions (5.3)*].

Cardiovascular

In the 1-year placebo controlled trial in subjects with asthma (AS Trial 2), cardiovascular thromboembolic events (cardiovascular deaths, non-fatal myocardial infarctions, and non-fatal strokes) were reported in 1 (0.2%) of the DUPIXENT 200 mg Q2W group, 4 (0.6%) of the DUPIXENT 300 mg Q2W group, and 2 (0.3%) of the placebo group.

In the 1-year placebo controlled trial in subjects with atopic dermatitis (Trial 3), cardiovascular thromboembolic events (cardiovascular deaths, non-fatal myocardial infarctions, and non-fatal strokes) were reported in 1 (0.9%) of the DUPIXENT + TCS 300 mg Q2W group, 0 (0.0%) of the DUPIXENT + TCS 300 mg QW group, and 1 (0.3%) of the placebo + TCS group.

In the 24-week placebo controlled trial in subjects with CRSwNP (CSNP Trial 1), cardiovascular thromboembolic events (cardiovascular deaths, non-fatal myocardial infarctions, and non-fatal strokes) were reported in 1 (0.7%) of the DUPIXENT group and 0 (0.0%) of the placebo group. In the 1-year placebo controlled trial in subjects with CRSwNP (CSNP Trial 2), there were no cases of cardiovascular thromboembolic events (cardiovascular deaths, non-fatal myocardial infarctions, and non-fatal strokes) reported in any treatment arm.

6.2 Immunogenicity

As with all therapeutic proteins, there is a potential for immunogenicity. The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody (including neutralizing antibody) positivity in an assay may be influenced by several factors, including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to dupilumab in the studies described below with the incidence of antibodies in other studies or to other products may be misleading.

Approximately 5% of subjects with atopic dermatitis, asthma, or CRSwNP who received DUPIXENT 300 mg Q2W for 52 weeks developed antibodies to dupilumab; approximately 2% exhibited persistent ADA responses, and approximately 2% had neutralizing antibodies.

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

Approximately 4% of subjects in the placebo groups in the 52-week studies were positive for antibodies to DUPIXENT; approximately 2% exhibited persistent ADA responses, and approximately 1% had neutralizing antibodies.

Approximately 16% of adolescent subjects with atopic dermatitis who received DUPIXENT 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 4% of adolescent subjects with atopic dermatitis in the placebo group were positive for antibodies to DUPIXENT; approximately 1% exhibited persistent ADA responses, and approximately 1% had neutralizing antibodies.

The antibody titers detected in both DUPIXENT and placebo subjects were mostly low. In subjects who received DUPIXENT, development of high titer antibodies to dupilumab was associated with lower serum dupilumab concentrations [see *Clinical Pharmacology* (12.3)].

Two subjects who experienced high titer antibody responses developed serum sickness or serum sickness-like reactions during DUPIXENT therapy [see *Warnings and Precautions* (5.1)].

7 DRUG INTERACTIONS

7.1 Live Vaccines

Avoid use of live vaccines in patients treated with DUPIXENT.

7.2 Non-Live Vaccines

Immune responses to vaccination were assessed in a study in which subjects with atopic dermatitis were treated once weekly for 16 weeks with 300 mg of dupilumab (twice the recommended dosing frequency). After 12 weeks of DUPIXENT administration, subjects were vaccinated with a Tdap vaccine (Adacel®) and a meningococcal polysaccharide vaccine (Menomune®). Antibody responses to tetanus toxoid and serogroup C meningococcal polysaccharide were assessed 4 weeks later. Antibody responses to both tetanus vaccine and meningococcal polysaccharide vaccine were similar in dupilumab-treated and placebo-treated subjects. Immune responses to the other active components of the Adacel and Menomune vaccines were not assessed.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Exposure Registry

There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to DUPIXENT during pregnancy.

Please contact 1-877-311-8972 or go to <https://mothertobaby.org/ongoing-study/dupixent/> to enroll in or to obtain information about the registry.

Risk Summary

Available data from case reports and case series with DUPIXENT use in pregnant women have not identified a drug-associated risk of major birth defects, miscarriage, or adverse maternal or fetal outcomes. Human IgG antibodies are known to cross the placental barrier; therefore, DUPIXENT may be transmitted from the mother to the developing fetus. There are adverse effects on maternal and fetal outcomes associated with asthma in pregnancy (*see Clinical Considerations*). In an enhanced pre- and post-natal developmental study, no adverse developmental effects were observed in offspring born to pregnant monkeys after subcutaneous administration of a homologous antibody against interleukin-4-receptor alpha (IL-4R α) during organogenesis through parturition at doses up to 10-times the maximum recommended human dose (MRHD) (*see Data*). The estimated background risk of major birth defects and miscarriage for the indicated populations are unknown. All pregnancies have a background risk of birth defect, loss or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Clinical Considerations

Disease-Associated Maternal and/or Embryo-fetal Risk

In women with poorly or moderately controlled asthma, evidence demonstrates that there is an increased risk of preeclampsia in the mother and prematurity, low birth weight, and small for gestational age in the neonate. The level of asthma control should be closely monitored in pregnant women and treatment adjusted as necessary to maintain optimal control.

Data

Animal Data

In an enhanced pre- and post-natal development toxicity study, pregnant cynomolgus monkeys were administered weekly subcutaneous doses of homologous antibody against IL-4R α up to 10 times the MRHD (on a mg/kg basis of 100 mg/kg/week) from the beginning of organogenesis to parturition. No treatment-related adverse effects on embryo-fetal toxicity or malformations, or on morphological, functional, or immunological development were observed in the infants from birth through 6 months of age.

8.2 Lactation

Risk Summary

There are no data on the presence of dupilumab in human milk, the effects on the breastfed infant, or the effects on milk production. Maternal IgG is known to be present in human milk. The effects of local gastrointestinal exposure and limited systemic exposure to dupilumab on the breastfed infant are unknown. The developmental and health benefits of breastfeeding should be

considered along with the mother's clinical need for DUPIXENT and any potential adverse effects on the breastfed child from DUPIXENT or from the underlying maternal condition.

8.4 Pediatric Use

Atopic Dermatitis

The safety and efficacy of DUPIXENT have been established in pediatric patients 12 years of age and older with moderate-to-severe atopic dermatitis. A total of 251 adolescents ages 12 to 17 years old with moderate-to-severe atopic dermatitis were enrolled in Trial 6. The safety and efficacy were generally consistent between adolescents and adults [*see Adverse Reactions (6.1) and Clinical Studies (14.1)*]. Safety and efficacy in pediatric patients (<12 years 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 AS Trial 2 and received either 200 mg (N=21) or 300 mg (N=18) DUPIXENT (or matching placebo either 200 mg [N=34] or 300 mg [N=34]) Q2W. Asthma exacerbations and lung function were assessed in both adolescents and adults. For both the 200 mg and 300 mg Q2W doses, improvements in FEV₁ (LS mean change from baseline at Week 12) were observed (0.36 L and 0.27 L, respectively). For the 200 mg Q2W dose, subjects had a reduction in the rate of severe exacerbations that was consistent with adults. Safety and efficacy in pediatric patients (<12 years of age) with asthma have not been established. Dupilumab exposure was higher in adolescent patients than that in adults at the respective dose level which was mainly accounted for by difference in body weight [*see Clinical Pharmacology (12.3)*].

The adverse event profile in adolescents was generally similar to the adults [*see Adverse Reactions (6.1)*].

CRSwNP

CRSwNP does not normally occur in children. Safety and efficacy in pediatric patients (<18 years of age) with CRSwNP have not been established.

8.5 Geriatric Use

Of the 1472 subjects with atopic dermatitis exposed to DUPIXENT in a dose-ranging study and placebo-controlled trials, 67 subjects were 65 years or older. Although no differences in safety or efficacy were observed between older and younger subjects, the number of subjects aged 65 and over is not sufficient to determine whether they respond differently from younger subjects [*see Clinical Pharmacology (12.3)*].

Of the 1977 subjects with asthma exposed to DUPIXENT, a total of 240 subjects were 65 years or older. Efficacy and safety in this age group was similar to the overall study population.

Of the 440 subjects with CRSwNP exposed to DUPIXENT, a total of 79 subjects were 65 years or older. Efficacy and safety in this age group were similar to the overall study population.

10 OVERDOSE

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

11 DESCRIPTION

Dupilumab, an interleukin-4 receptor alpha antagonist, is a human monoclonal antibody of the IgG4 subclass that binds to the IL-4R α subunit and inhibits IL-4 and IL-13 signaling. Dupilumab has an approximate molecular weight of 147 kDa.

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

DUPIXENT (dupilumab) Injection is supplied as a sterile, preservative-free, clear to slightly opalescent, colorless to pale yellow solution for subcutaneous injection. DUPIXENT is provided as a single-dose pre-filled syringe with needle shield in a siliconized Type-1 clear glass syringe. The needle cap is not made with natural rubber latex.

Each 300 mg pre-filled syringe delivers 300 mg dupilumab in 2 mL which also contains L-arginine hydrochloride (10.5 mg), L-histidine (6.2 mg), polysorbate 80 (4 mg), sodium acetate (2 mg), sucrose (100 mg), and water for injection, pH 5.9.

Each 200 mg pre-filled syringe delivers 200 mg dupilumab in 1.14 mL which also contains L-arginine hydrochloride (12 mg), L-histidine (3.5 mg), polysorbate 80 (2.3 mg), sodium acetate (1.2 mg), sucrose (57 mg), and water for injection, pH 5.9.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Dupilumab is a human monoclonal IgG4 antibody that inhibits interleukin-4 (IL-4) and interleukin-13 (IL-13) signaling by specifically binding to the IL-4R α subunit shared by the IL-4 and IL-13 receptor complexes. Dupilumab inhibits IL-4 signaling via the Type I receptor and both IL-4 and IL-13 signaling through the Type II receptor.

Inflammation is an important component in the pathogenesis of asthma, atopic dermatitis, and CRSwNP. Multiple cell types that express IL-4R α (e.g., mast cells, eosinophils, macrophages, lymphocytes, epithelial cells, goblet cells) and inflammatory mediators (e.g., histamine, eicosanoids, leukotrienes, cytokines, chemokines) are involved in inflammation. Blocking IL-4R α with dupilumab inhibits IL-4 and IL-13 cytokine-induced inflammatory responses, including the release of proinflammatory cytokines, chemokines, nitric oxide, and IgE; however, the mechanism of dupilumab action in asthma has not been definitively established.

12.2 Pharmacodynamics

Consistent with inhibition of IL-4 and IL-13 signaling, dupilumab treatment decreased certain biomarkers. In asthma subjects, fractional exhaled nitric oxide (FeNO) and circulating concentrations of eotaxin-3, total IgE, allergen specific IgE, TARC, and periostin were decreased relative to placebo. These reductions in biomarkers were comparable for the 300 mg Q2W and

200 mg Q2W regimens. These markers were near maximal suppression after 2 weeks of treatment, except for IgE which declined more slowly. These effects were sustained throughout treatment. The median percent reduction from baseline in total IgE concentrations with dupilumab treatments was 52% at Week 24 (AS Trial 1) and 70% at Week 52 (AS Trial 2). For FeNO, the mean percent reduction from baseline at Week 2 was 35% and 24% in AS Trials 1 and 2 respectively, and in the overall safety population, the mean FeNO level decreased to 20 ppb.

12.3 Pharmacokinetics

The pharmacokinetics of dupilumab is similar in subjects with atopic dermatitis, asthma, and CRSwNP.

Absorption

Following an initial subcutaneous (SC) dose of 600 mg, 400 mg, or 300 mg, dupilumab reached peak mean $\pm$ SD concentrations (C_{max}) of 70.1 ± 24.1 mcg/mL, 41.8 ± 12.4 mcg/mL, or 30.5 ± 9.39 mcg/mL respectively, by approximately 1 week post dose. Steady-state concentrations were achieved by Week 16 following the administration of 600 mg starting dose and 300 mg dose either weekly (twice the recommended dosing frequency) or Q2W, or 400 mg starting dose and 200 mg dose Q2W, or 300 mg Q2W without a loading dose. Across clinical trials, the mean $\pm$ SD steady-state trough concentrations ranged from 60.3 ± 35.1 mcg/mL to 80.2 ± 35.3 mcg/mL for 300 mg administered Q2W, from 173 ± 75.9 mcg/mL to 193 ± 77.0 mcg/mL for 300 mg administered weekly, and from 29.2 ± 18.7 to 36.5 ± 22.2 mg/L for 200 mg administered Q2W.

The bioavailability of dupilumab following a SC dose is similar between AD, asthma, and CRSwNP patients, ranging between 61% and 64%.

Distribution

The estimated total volume of distribution was approximately 4.8 ± 1.3 L.

Elimination

The metabolic pathway of dupilumab has not been characterized. As a human monoclonal IgG4 antibody, dupilumab is expected to be degraded into small peptides and amino acids via catabolic pathways in the same manner as endogenous IgG. After the last steady-state dose of 300 mg Q2W, 300 mg QW, or 200 mg Q2W dupilumab, the median times to non-detectable concentration (<78 ng/mL) are 10-12, 13, and 9 weeks, respectively.

Dose Linearity

Dupilumab exhibited nonlinear target-mediated pharmacokinetics with exposures increasing in a greater than dose-proportional manner. The systemic exposure increased by 30-fold when the dose increased 8-fold following a single dose of dupilumab from 75 mg to 600 mg (i.e., 0.25-times to 2-times the recommended dose).

Weight

Dupilumab trough concentrations were lower in subjects with higher body weight.

Age

Based on population pharmacokinetic analysis, age did not affect dupilumab clearance.

Immunogenicity

Development of antibodies to dupilumab was associated with lower serum dupilumab concentrations. A few subjects who had high antibody titers also had no detectable serum dupilumab concentrations.

Specific Populations

Geriatric Patients

In subjects who are 65 years and older, the mean $\pm$ SD steady-state trough concentrations of dupilumab were 69.4 $\pm$ 31.4 mcg/mL and 166 $\pm$ 62.3 mcg/mL, respectively, for 300 mg administered Q2W and weekly, and 39.7 $\pm$ 21.7 mcg/mL for 200 mg administered Q2W.

Pediatric Patients

Atopic Dermatitis

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 ($\geq$ 60 kg), the mean $\pm$ SD steady-state trough concentration of dupilumab was 54.5 $\pm$ 27.0 mcg/mL.

Asthma

A total of 107 adolescents aged 12 to 17 years with asthma were enrolled in AS Trial 2. The mean $\pm$ SD steady-state trough concentrations of dupilumab were 107 $\pm$ 51.6 mcg/mL and 46.7 $\pm$ 26.9 mcg/mL, respectively, for 300 mg or 200 mg administered Q2W.

Renal or Hepatic Impairment

No formal trial of the effect of hepatic or renal impairment on the pharmacokinetics of dupilumab was conducted.

Drug Interaction Studies

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

Cytochrome P450 Substrates

The effects of dupilumab on the pharmacokinetics of midazolam (metabolized by CYP3A4), warfarin (metabolized by CYP2C9), omeprazole (metabolized by CYP2C19), metoprolol (metabolized by CYP2D6), and caffeine (metabolized by CYP1A2) were evaluated in a study with 12-13 evaluable subjects with atopic dermatitis (a SC loading dose of 600 mg followed by 300 mg SC weekly for six weeks). No clinically significant changes in AUC were observed. The largest effect was observed for metoprolol (CYP2D6) with an increase in AUC of 29%.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Animal studies have not been conducted to evaluate the carcinogenic or mutagenic potential of dupilumab.

No effects on fertility parameters such as reproductive organs, menstrual cycle length, or sperm analysis were observed in sexually mature mice that were subcutaneously administered a homologous antibody against IL-4R α at doses up to 200 mg/kg/week.

14 CLINICAL STUDIES

14.1 Atopic Dermatitis

Adults with Atopic Dermatitis

Three randomized, double-blind, placebo-controlled trials (Trials 1, 2, and 3; NCT02277743, 02277769, and 02260986 respectively) enrolled a total of 2119 subjects 18 years of age and older with moderate-to-severe atopic dermatitis (AD) not adequately controlled by topical medication(s). Disease severity was defined by an 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 involvement of $\geq 10\%$. At baseline, 59% of subjects were male, 67% were white, 52% of subjects had a baseline IGA score of 3 (moderate AD), and 48% of subjects had a baseline IGA of 4 (severe AD). The baseline mean EASI score was 33 and the baseline weekly averaged Peak Pruritus Numeric Rating Scale (NRS) was 7 on a scale of 0-10.

In all three trials, subjects in the DUPIXENT group received subcutaneous injections of DUPIXENT 600 mg at Week 0, followed by 300 mg every other week (Q2W). In the monotherapy trials (Trials 1 and 2), subjects received DUPIXENT or placebo for 16 weeks.

In the concomitant therapy trial (Trial 3), subjects received DUPIXENT or placebo with concomitant topical corticosteroids (TCS) and as needed topical calcineurin inhibitors for problem areas only, such as the face, neck, intertriginous and genital areas for 52 weeks.

All three trials assessed the primary endpoint, the change from baseline to Week 16 in the proportion of subjects with an IGA 0 (clear) or 1 (almost clear) and at least a 2-point improvement. Other endpoints included the proportion of subjects with EASI-75 (improvement of at least 75% in EASI score from baseline), and reduction in itch as defined by at least a 4-point improvement in the Peak Pruritus NRS from baseline to Week 16.

Clinical Response at Week 16 (Trials 1, 2, and 3)

The results of the DUPIXENT monotherapy trials (Trials 1 and 2) and the DUPIXENT with concomitant TCS trial (Trial 3) are presented in Table 5.

Table 5: Efficacy Results of DUPIXENT With or Without Concomitant TCS at Week 16 (FAS)

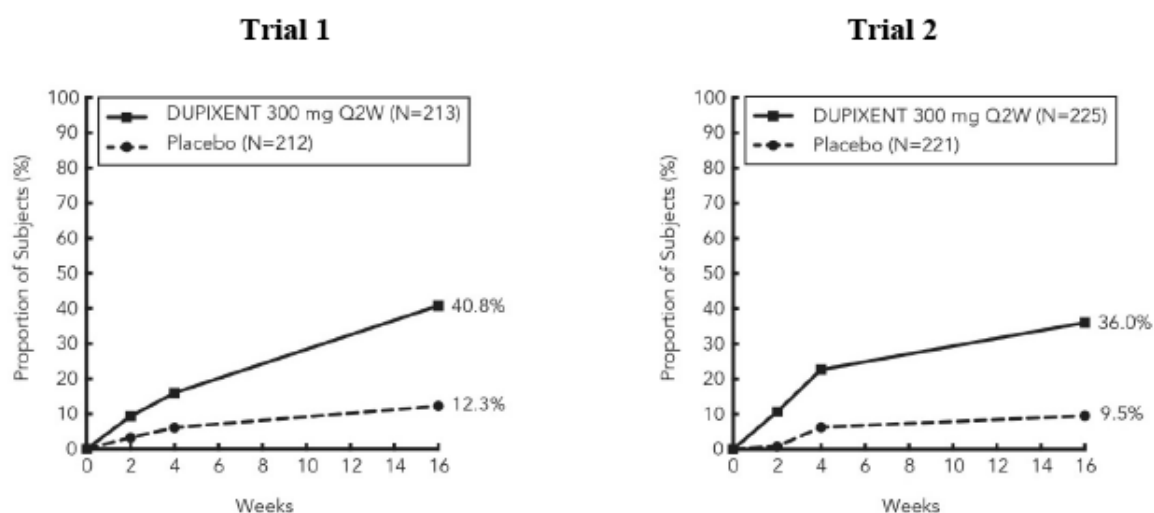
	Trial 1		Trial 2		Trial 3	
	DUPIXENT 300 mg Q2W	Placebo	DUPIXENT 300 mg Q2W	Placebo	DUPIXENT 300 mg Q2W + TCS	Placebo + TCS
Number of subjects randomized (FAS) ^a	224	224	233	236	106	315
IGA 0 or 1 ^{b,c}	38%	10%	36%	9%	39%	12%
EASI-75 ^c	51%	15%	44%	12%	69%	23%
EASI-90 ^c	36%	8%	30%	7%	40%	11%
Number of subjects with baseline Peak Pruritus NRS score ≥ 4	213	212	225	221	102	299
Peak Pruritus NRS (≥ 4 -point improvement) ^c	41%	12%	36%	10%	59%	20%

^a Full Analysis Set (FAS) includes all subjects randomized.

^b Responder was defined as a subject with an IGA 0 or 1 ("clear" or "almost clear") and a reduction of ≥ 2 points on a 0-4 IGA scale.

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

Figure 1: Proportion of Subjects with ≥ 4 -point Improvement on the Peak Pruritus NRS in Trial 1^a and Trial 2^a Studies (FAS)^b



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

^b Full Analysis Set (FAS) includes all subjects randomized.

In Trial 3, of the 421 subjects, 353 had been on study for 52 weeks at the time of data analysis. Of these 353 subjects, responders at Week 52 represent a mixture of subjects who maintained their efficacy from Week 16 (e.g., 53% of DUPIXENT IGA 0 or 1 responders at Week 16 remained responders at Week 52) and subjects who were non-responders at Week 16 who later responded to treatment (e.g., 24% of DUPIXENT IGA 0 or 1 non-responders at Week 16 became responders at Week 52). Results of supportive analyses of the 353 subjects in the DUPIXENT with concomitant TCS trial (Trial 3) are presented in Table 6.

Table 6: Efficacy Results (IGA 0 or 1) of DUPIXENT with Concomitant TCS at Week 16 and 52

	DUPIXENT 300 mg Q2W + TCS	Placebo + TCS
Number of Subjects ^a	89	264
Responder ^{b,c} at Week 16 and 52	22%	7%
Responder at Week 16 but Non-responder at Week 52	20%	7%
Non-responder at Week 16 and Responder at Week 52	13%	6%
Non-responder at Week 16 and 52	44%	80%
Overall Responder ^{b,c} Rate at Week 52	36%	13%

^a In Trial 3, of the 421 randomized and treated subjects, 68 subjects (16%) had not been on study for 52 weeks at the time of data analysis.

^b Responder was defined as a subject with an IGA 0 or 1 ("clear" or "almost clear") and a reduction of ≥ 2 points on a 0-4 IGA scale.

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

Treatment effects in subgroups (weight, age, gender, race, and prior treatment, including immunosuppressants) in Trials 1, 2, and 3 were generally consistent with the results in the overall study population.

In Trials 1, 2, and 3, a third randomized treatment arm of DUPIXENT 300 mg QW did not demonstrate additional treatment benefit over DUPIXENT 300 mg Q2W.

Subjects in Trials 1 and 2 who had an IGA 0 or 1 with a reduction of ≥ 2 points were re-randomized into Trial 5. Trial 5 evaluated multiple DUPIXENT monotherapy dose regimens for maintaining treatment response. The study included subjects randomized to continue with DUPIXENT 300 mg Q2W (62 subjects) or switch to placebo (31 subjects) for 36 weeks. IGA 0 or 1 responses at Week 36 were as follows: 33 (53%) in the Q2W group and 3 (10%) in the placebo group.

Adolescents with Atopic Dermatitis

The efficacy and safety of DUPIXENT monotherapy in adolescent subjects was evaluated in a multicenter, randomized, double-blind, placebo-controlled trial (Trial 6; NCT03054428) in 251 adolescent subjects 12 to 17 years of age, with moderate-to-severe AD 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 $\geq 10\%$. Eligible subjects enrolled into this trial had previous inadequate response to topical medication.

Subjects in the DUPIXENT group with baseline weight of <60 kg received an initial dose of 400 mg at Week 0, followed by 200 mg Q2W for 16 weeks. Subjects with baseline weight of ≥60 kg received an initial dose of 600 mg at Week 0, followed by 300 mg Q2W for 16 weeks. Subjects were permitted to receive rescue treatment at the discretion of the investigator. Subjects who received rescue treatment were considered non-responders.

In Trial 6, the mean age was 14.5 years, the median weight was 59.4 kg, 41% of subjects were female, 63% were White, 15% were Asian, and 12% were Black. At baseline 46% of subjects had an IGA score of 3 (moderate AD), 54% had an IGA score of 4 (severe AD), the mean BSA involvement was 57%, and 42% had received prior systemic immunosuppressants. Also, at baseline the mean EASI score was 36, and the weekly averaged Peak Pruritus NRS was 8 on a scale of 0-10. Overall, 92% of subjects had at least one co-morbid allergic condition; 66% had allergic rhinitis, 54% had asthma, and 61% had food allergies.

The primary endpoint was the proportion of subjects with an IGA 0 (clear) or 1 (almost clear) and at least a 2-point improvement from baseline to Week 16. Other evaluated outcomes included the proportion of subjects with EASI-75 or EASI-90 (improvement of at least 75% or 90% in EASI from baseline, respectively), and reduction in itch as measured by the Peak Pruritus NRS (≥4-point improvement).

The efficacy results at Week 16 for Trial 6 are presented in Table 7.

Table 7: Efficacy Results of DUPIXENT in Trial 6 at Week 16 (FAS)^a

	DUPIXENT^d 200 mg (<60 kg) or 300 mg (≥60 kg) Q2W N=82 ^a	Placebo N=85 ^a
IGA 0 or 1 ^{b,c}	24%	2%
EASI-75 ^c	42%	8%
EASI-90 ^c	23%	2%
Peak Pruritus NRS (≥4-point improvement) ^c	37%	5%

^a Full Analysis Set (FAS) includes all subjects randomized.

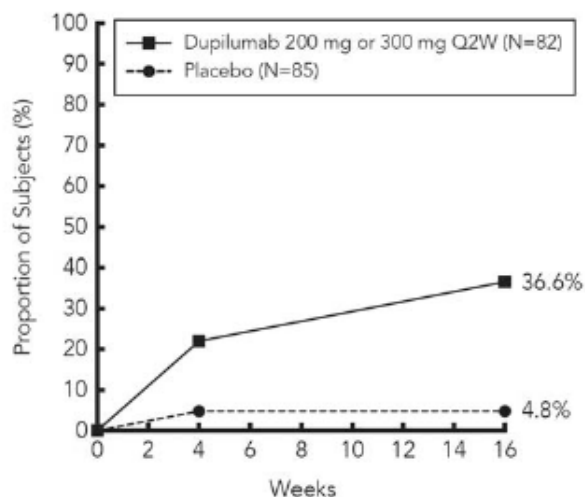
^b Responder was defined as a subject with an IGA 0 or 1 ("clear" or "almost clear") and a reduction of ≥2 points on a 0-4 IGA scale.

^c Subjects who received rescue treatment or with missing data were considered as non-responders (59% and 21% in the placebo and DUPIXENT arms, respectively).

^d At Week 0, subjects received 400 mg (baseline weight <60 kg) or 600 mg (baseline weight ≥60 kg) of DUPIXENT.

A greater proportion of subjects randomized to DUPIXENT achieved an improvement in the Peak Pruritus NRS compared to placebo (defined as ≥4-point improvement at Week 4). See Figure 2.

Figure 2: Proportion of Adolescent Subjects with ≥ 4 -point Improvement on the Peak Pruritus NRS in Trial 6^a (FAS)^b



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

^b Full Analysis Set (FAS) includes all subjects randomized.

14.2 Asthma

The asthma development program included three randomized, double-blind, placebo-controlled, parallel-group, multi-center trials (AS Trials 1, 2, and 3) of 24 to 52 weeks in treatment duration which enrolled a total of 2888 subjects (12 years of age and older). Subjects enrolled in AS Trials 1 and 2 were required to have a history of 1 or more asthma exacerbations that required treatment with systemic corticosteroids or emergency department visit or hospitalization for the treatment of asthma in the year prior to trial entry. Subjects enrolled in AS Trial 3 required dependence on daily oral corticosteroids in addition to regular use of high-dose inhaled corticosteroids plus an additional controller(s). In all 3 trials, subjects were enrolled without requiring a minimum baseline blood eosinophil count. In AS Trials 2 and 3 subjects with screening blood eosinophil level of >1500 cells/mcL ($<1.3\%$) were excluded. DUPIXENT was administered as add-on to background asthma treatment. Subjects continued background asthma therapy throughout the duration of the studies, except in AS Trial 3 in which OCS dose was tapered as described below.

AS Trial 1

AS Trial 1 was a 24-week dose-ranging study which included 776 subjects (18 years of age and older). DUPIXENT compared with placebo was evaluated in adult subjects with moderate-to-severe asthma on a medium or high-dose inhaled corticosteroid and a long acting beta agonist. Subjects were randomized to receive either 200 mg (N=150) or 300 mg (N=157) DUPIXENT every other week (Q2W) or 200 mg (N=154) or 300 mg (N=157) DUPIXENT every 4 weeks following an initial dose of 400 mg, 600 mg or placebo (N=158), respectively. The primary endpoint was mean change from baseline to Week 12 in FEV₁ (L) in subjects with baseline blood eosinophils ≥ 300 cells/mcL. Other endpoints included percent change from baseline in FEV₁ and annualized rate of severe asthma exacerbation events during the 24-week placebo controlled

treatment period. Results were evaluated in the overall population and subgroups based on baseline blood eosinophil count (≥ 300 cells/mcL and < 300 cells/mcL). Additional secondary endpoints included responder rates in the patient reported Asthma Control Questionnaire (ACQ-5) and Asthma Quality of Life Questionnaire, Standardized Version (AQLQ(S)) scores.

AS Trial 2

AS Trial 2 was a 52-week study which included 1902 subjects (12 years of age and older). DUPIXENT compared with placebo was evaluated in 107 adolescent and 1795 adult subjects with moderate-to-severe asthma on a medium or high-dose inhaled corticosteroid (ICS) and a minimum of one and up to two additional controller medications. Subjects were randomized to receive either 200 mg (N=631) or 300 mg (N=633) DUPIXENT Q2W (or matching placebo for either 200 mg [N=317] or 300 mg [N=321] Q2W) following an initial dose of 400 mg, 600 mg or placebo respectively. The primary endpoints were the annualized rate of severe exacerbation events during the 52-week placebo controlled period and change from baseline in pre-bronchodilator FEV₁ at Week 12 in the overall population (unrestricted by minimum baseline blood eosinophils count). Additional secondary endpoints included annualized severe exacerbation rates and FEV₁ in patients with different baseline levels of blood eosinophils as well as responder rates in the ACQ-5 and AQLQ(S) scores.

AS Trial 3

AS Trial 3 was a 24-week oral corticosteroid-reduction study in 210 subjects with asthma who required daily oral corticosteroids in addition to regular use of high dose inhaled corticosteroids plus an additional controller. After optimizing the OCS dose during the screening period, subjects received 300 mg DUPIXENT (N=103) or placebo (N=107) once Q2W for 24 weeks following an initial dose of 600 mg or placebo. Subjects 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 of oral corticosteroid dose at Weeks 20 to 24 compared with the baseline dose, while maintaining asthma control in the overall population (unrestricted by minimum baseline blood eosinophils count). Additional secondary endpoints included the annualized rate of severe exacerbation events during treatment period and responder rate in the ACQ-5 and AQLQ(S) scores.

The demographics and baseline characteristics of these 3 trials are provided in Table 8 below.

Table 8: Demographics and Baseline Characteristics of Asthma Trials

Parameter	Trial 1 (N=776)	Trial 2 (N=1902)	Trial 3 (N=210)
Mean age (years) (SD)	49 (13)	48 (15)	51 (13)
% Female	63	63	61
% White	78	83	94
Duration of Asthma (years), mean ($\pm$ SD)	22 (15)	21 (15)	20 (14)
Never smoked (%)	77	81	81
Mean exacerbations in previous year ($\pm$ SD)	2.2 (2.1)	2.1 (2.2)	2.1 (2.2)
High dose ICS use (%)	50	52	89
Pre-dose FEV ₁ (L) at baseline ($\pm$ SD)	1.84 (0.54)	1.78 (0.60)	1.58 (0.57)
Mean percent predicted FEV ₁ at baseline (%) ($\pm$ SD)	61 (11)	58 (14)	52 (15)
% Reversibility ($\pm$ SD)	27 (15)	26 (22)	19 (23)
Atopic Medical History % Overall	73	78	72
(AD %, NP %, AR %)	(8, 11, 62)	(10, 13, 69)	(8, 21, 56)
Mean FeNO ppb ($\pm$ SD)	39 (35)	35 (33)	38 (31)
Mean total IgE IU/mL ($\pm$ SD)	435 (754)	432 (747)	431 (776)
Mean baseline blood Eosinophil count ($\pm$ SD) cells/mcL	350 (430)	360 (370)	350 (310)

ICS = inhaled corticosteroid; FEV₁ = Forced expiratory volume in 1 second; AD = atopic dermatitis; NP = nasal polyposis; AR = allergic rhinitis; FeNO = fraction of exhaled nitric oxide

Exacerbations

AS Trials 1 and 2 evaluated the frequency of severe asthma exacerbations defined as deterioration of asthma requiring the use of systemic corticosteroids for at least 3 days or hospitalization or emergency room visit due to asthma that required systemic corticosteroids. In the primary analysis population (subjects with baseline blood eosinophil count of ≥ 300 cells/mcL in AS Trial 1 and the overall population in AS Trial 2), subjects receiving either DUPIXENT 200 mg or 300 mg Q2W had significant reductions in the rate of asthma exacerbations compared to placebo. In the overall population in AS Trial 2, the rate of severe exacerbations was 0.46 and 0.52 for DUPIXENT 200 mg Q2W and 300 mg Q2W, respectively, compared to matched placebo rates of 0.87 and 0.97. The rate ratio of severe exacerbations compared to placebo was 0.52 (95% CI: 0.41, 0.66) and 0.54 (95% CI: 0.43, 0.68) for DUPIXENT 200 mg Q2W and 300 mg Q2W, respectively. Results in subjects with baseline blood eosinophil counts ≥ 300 cells/mcL in AS Trials 1 and 2 are shown in Table 9.

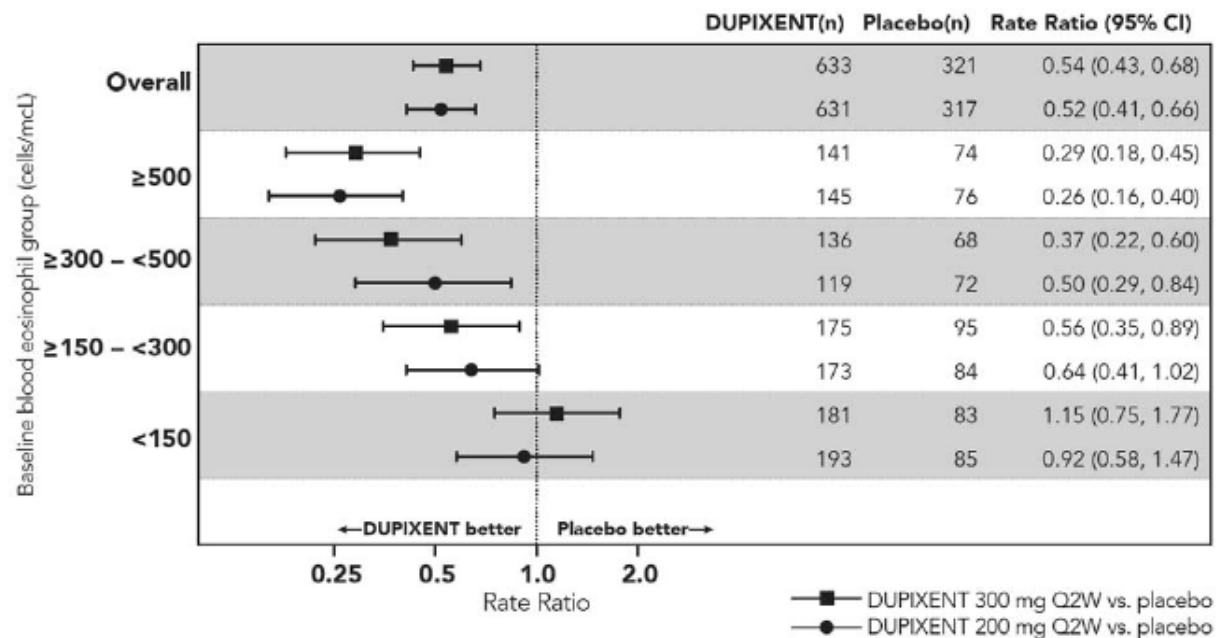
Response rates by baseline blood eosinophils for AS Trial 2 are shown in Figure 3. Pre-specified subgroup analyses of AS Trials 1 and 2 demonstrated that there were greater reductions in severe exacerbations in subjects with higher baseline blood eosinophil levels. In AS Trial 2, reductions in exacerbations were significant in the subgroup of subjects with baseline blood eosinophils ≥ 150 cells/mcL. In subjects with baseline blood eosinophil count < 150 cells/mcL, similar severe exacerbation rates were observed between DUPIXENT and placebo.

In AS Trial 2, the estimated rate ratio of exacerbations leading to hospitalizations and/or emergency room visits versus placebo was 0.53 (95% CI: 0.28, 1.03) and 0.74 (95% CI: 0.32, 1.70) with DUPIXENT 200 mg or 300 mg Q2W, respectively.

Table 9: Rate of Severe Exacerbations in AS Trials 1 and 2

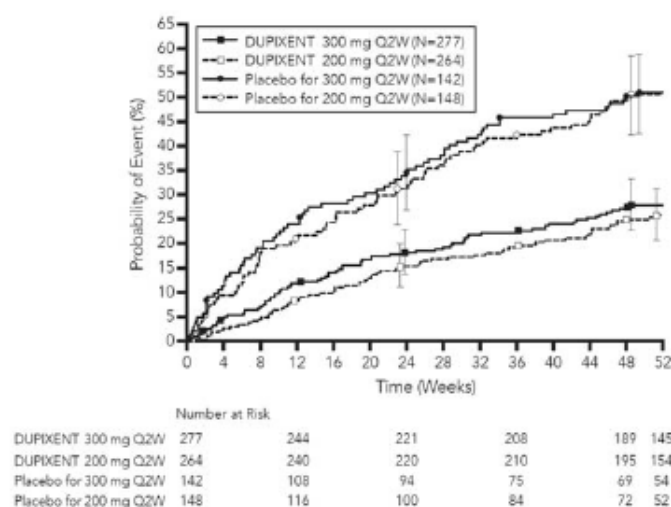
Trial	Treatment	Baseline Blood EOS ≥ 300 cells/mcL (primary analysis population, Trial 1)		
		N	Rate (95% CI)	Rate Ratio (95% CI)
AS Trial 1	DUPIXENT 200 mg Q2W	65	0.30 (0.13, 0.68)	0.29 (0.11, 0.76)
	DUPIXENT 300 mg Q2W	64	0.20 (0.08, 0.52)	0.19 (0.07, 0.56)
	Placebo	68	1.04 (0.57, 1.90)	
AS Trial 2	DUPIXENT 200 mg Q2W	264	0.37 (0.29, 0.48)	0.34 (0.24, 0.48)
	Placebo	148	1.08 (0.85, 1.38)	
	DUPIXENT 300 mg Q2W	277	0.40 (0.32, 0.51)	0.33 (0.23, 0.45)
	Placebo	142	1.24 (0.97, 1.57)	

Figure 3: Relative Risk in Annualized Event Rate of Severe Exacerbations across Baseline Blood Eosinophil Count (cells/mcL) in AS Trial 2



The time to first exacerbation was longer for the subjects receiving DUPIXENT compared to placebo in AS Trial 2 (Figure 4).

Figure 4: Kaplan Meier Incidence Curve for Time to First Severe Exacerbation in Subjects with Baseline Blood Eosinophils ≥ 300 cells/mcL (AS Trial 2)^a



^a At the time of the database lock, not all patients had completed Week 52

Lung Function

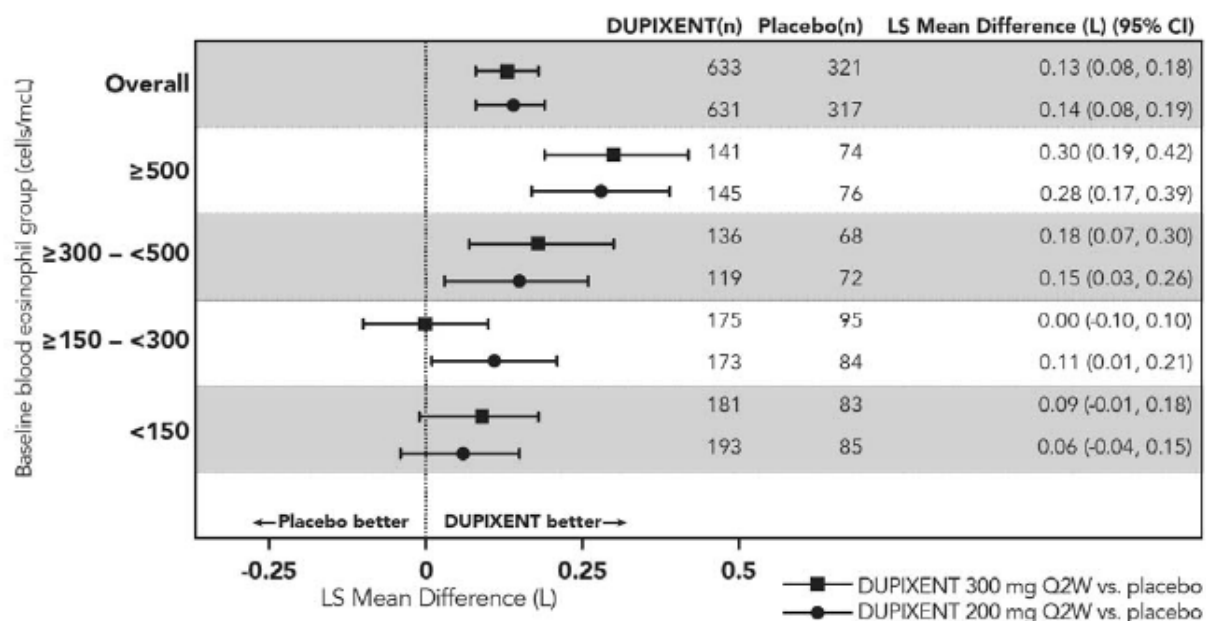
Significant increases in pre-bronchodilator FEV₁ were observed at Week 12 for AS Trials 1 and 2 in the primary analysis populations (subjects with baseline blood eosinophil count of ≥ 300 cells/mcL in AS Trial 1 and the overall population in AS Trial 2). In the overall population in AS Trial 2, the FEV₁ LS mean change from baseline was 0.32 L (21%) and 0.34 L (23%) for DUPIXENT 200 mg Q2W and 300 mg Q2W, respectively, compared to matched placebo means of 0.18 L (12%) and 0.21 L (14%). The mean treatment difference versus placebo was 0.14 L (95% CI: 0.08, 0.19) and 0.13 L (95% CI: 0.08, 0.18) for DUPIXENT 200 mg Q2W and 300 mg Q2W, respectively. Results in subjects with baseline blood eosinophil counts ≥ 300 cells/mcL in AS Trials 1 and 2 are shown in Table 10.

Improvements in FEV₁ by baseline blood eosinophils for AS Trial 2 are shown in Figure 5. Subgroup analysis of AS Trials 1 and 2 demonstrated greater improvement in subjects with higher baseline blood eosinophils.

Table 10: Mean Change from Baseline and vs Placebo in Pre-Bronchodilator FEV₁ at Week 12 in AS Trials 1 and 2

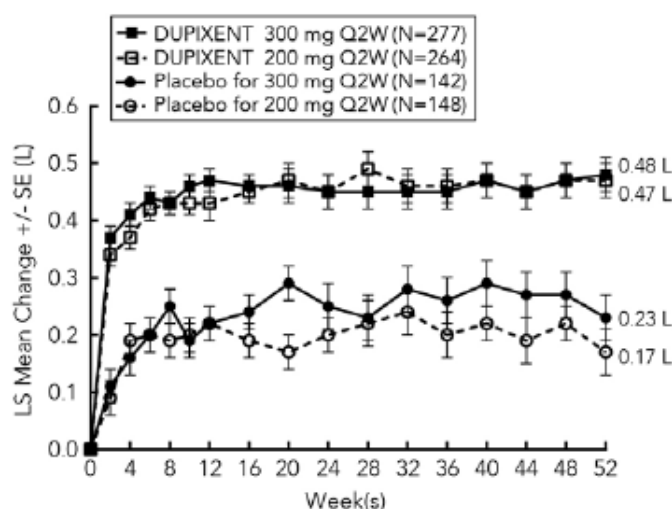
Trial	Treatment	Baseline Blood EOS ≥ 300 cells/mcL (primary analysis population, Trial 1)		
		N	LS Mean Change from baseline L (%)	LS Mean Difference vs. placebo (95% CI)
AS Trial 1	DUPIXENT 200 mg Q2W	65	0.43 (25.9)	0.26 (0.11, 0.40)
	DUPIXENT 300 mg Q2W	64	0.39 (25.8)	0.21 (0.06, 0.36)
	Placebo	68	0.18 (10.2)	
AS Trial 2	DUPIXENT 200 mg Q2W	264	0.43 (29.0)	0.21 (0.13, 0.29)
	Placebo	148	0.21 (15.6)	
	DUPIXENT 300 mg Q2W	277	0.47 (32.5)	0.24 (0.16, 0.32)
	Placebo	142	0.22 (14.4)	

Figure 5: LS Mean Difference in Change from Baseline vs Placebo to Week 12 in Pre-Bronchodilator FEV₁ across Baseline Blood Eosinophil Counts (cells/mcL) in AS Trial 2



Mean changes in FEV₁ over time in AS Trial 2 are shown in Figure 6.

Figure 6: Mean Change from Baseline in Pre-Bronchodilator FEV₁ (L) Over Time in Subjects with Baseline Blood Eosinophils ≥ 300 cells/mcL (AS Trial 2)



Additional Secondary Endpoints

ACQ-5 and AQLQ(S) were assessed in AS Trial 2 at 52 weeks. 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)).

- The ACQ-5 responder rate for DUPIXENT 200 mg and 300 mg Q2W in the overall population was 69% vs 62% placebo (odds ratio 1.37; 95% CI: 1.01, 1.86) and 69% vs 63% placebo (odds ratio 1.28; 95% CI: 0.94, 1.73), respectively; and the AQLQ(S) responder rates were 62% vs 54% placebo (odds ratio 1.61; 95% CI: 1.17, 2.21) and 62% vs 57% placebo (odds ratio 1.33; 95% CI: 0.98, 1.81), respectively.
- The ACQ-5 responder rate for DUPIXENT 200 mg and 300 mg Q2W in subjects with baseline blood eosinophils ≥ 300 cells/mcL was 75% vs 67% placebo (odds ratio: 1.46; 95% CI: 0.90, 2.35) and 71% vs 64% placebo (odds ratio: 1.39; 95% CI: 0.88, 2.19), respectively; and the AQLQ(S) responder rates were 71% vs 55% placebo (odds ratio: 2.02; 95% CI: 1.24, 3.32) and 65% vs 55% placebo (odds ratio: 1.79; 95% CI: 1.13, 2.85), respectively.

Oral Corticosteroid Reduction (AS Trial 3)

AS Trial 3 evaluated the effect of DUPIXENT on reducing the use of maintenance oral corticosteroids. The baseline mean oral corticosteroid dose was 12 mg in the placebo group and 11 mg in the group receiving DUPIXENT. The primary endpoint was the percent reduction from baseline of the final oral corticosteroid dose at Week 24 while maintaining asthma control.

Compared with placebo, subjects receiving DUPIXENT achieved greater reductions in daily maintenance oral corticosteroid dose, while maintaining asthma control. The mean percent reduction in daily OCS dose from baseline was 70% (median 100%) in subjects receiving DUPIXENT (95% CI: 60%, 80%) compared to 42% (median 50%) in subjects receiving placebo (95% CI: 33%, 51%). Reductions of 50% or higher in the OCS dose were observed in 82 (80%) subjects receiving DUPIXENT compared to 57 (53%) in those receiving placebo. The proportion of subjects with a mean final dose less than 5 mg at Weeks 24 was 72% for DUPIXENT and

37% for placebo (odds ratio 4.48 95% CI: 2.39, 8.39). A total of 54 (52%) subjects receiving DUPIXENT versus 31 (29%) subjects in the placebo group had a 100% reduction in their OCS dose.

In this 24-week trial, asthma exacerbations (defined as a temporary increase in oral corticosteroid dose for at least 3 days) were lower in subjects receiving DUPIXENT compared with those receiving placebo (annualized rate 0.65 and 1.60 for the DUPIXENT and placebo group, respectively; rate ratio 0.41 [95% CI 0.26, 0.63]) and improvement in pre-bronchodilator FEV₁ from baseline to Week 24 was greater in subjects receiving DUPIXENT compared with those receiving placebo (LS mean difference for DUPIXENT versus placebo of 0.22 L [95% CI: 0.09 to 0.34 L]). Effects on lung function and on oral steroid and exacerbation reduction were similar irrespective of baseline blood eosinophil levels. The ACQ-5 and AQLQ(S) were also assessed in AS Trial 3 and showed improvements similar to those in AS Trial 2.

14.3 Chronic Rhinosinusitis with Nasal Polyposis

The chronic rhinosinusitis with nasal polyposis (CRSwNP) development program included two randomized, double-blind, parallel-group, multicenter, placebo-controlled studies (CSNP Trial 1 and CSNP Trial 2) in 724 subjects aged 18 years and older on background intranasal corticosteroids (INCS). These studies included subjects with CRSwNP despite prior sino-nasal surgery or treatment with, or who were ineligible to receive or were intolerant to, systemic corticosteroids in the past 2 years. Patients with chronic rhinosinusitis without nasal polyposis were not included in these trials. Rescue with systemic corticosteroids or surgery was allowed during the studies at the investigator's discretion. In CSNP Trial 1, a total of 276 subjects were randomized to receive either 300 mg DUPIXENT (N=143) or placebo (N=133) every other week for 24 weeks. In CSNP Trial 2, 448 subjects were randomized to receive either 300 mg DUPIXENT (N=150) every other week for 52 weeks, 300 mg DUPIXENT (N=145) every other week until week 24 followed by 300 mg DUPIXENT every 4 weeks until week 52, or placebo (N=153). All subjects had evidence of sinus opacification on the Lund Mackay (LMK) sinus CT scan and 73% to 90% of subjects had opacification of all sinuses. Subjects were stratified based on their histories of prior surgery and co-morbid asthma/nonsteroidal anti-inflammatory drug exacerbated respiratory disease (NSAID-ERD). A total of 63% of subjects reported previous sinus surgery, with a mean number of 2.0 prior surgeries, 74% used systemic corticosteroids in the previous 2 years with a mean number of 1.6 systemic corticosteroid courses in the previous 2 years, 59% had co-morbid asthma, and 28% had NSAID-ERD.

The co-primary efficacy endpoints were change from baseline to Week 24 in bilateral endoscopic nasal polyps score (NPS; 0-8 scale) as graded by central blinded readers, and change from baseline to Week 24 in nasal congestion/obstruction score averaged over 28 days (NC; 0-3 scale), as determined by subjects using a daily diary. For NPS, polyps on each side of the nose were graded on a categorical scale (0=no polyps; 1=small polyps in the middle meatus not reaching below the inferior border of the middle turbinate; 2=polyps reaching below the lower border of the middle turbinate; 3=large polyps reaching the lower border of the inferior turbinate or polyps medial to the middle turbinate; 4=large polyps causing complete obstruction of the inferior nasal cavity). The total score was the sum of the right and left scores. Nasal congestion was rated daily by the subjects on a 0 to 3 categorical severity scale (0=no symptoms; 1=mild symptoms; 2=moderate symptoms; 3=severe symptoms).

In both studies, key secondary end-points at Week 24 included change from baseline in: LMK sinus CT scan score, daily loss of smell, and 22-item sino-nasal outcome test (SNOT-22). The LMK sinus CT scan score evaluated the opacification of each sinus using a 0 to 2 scale (0=normal; 1=partial opacification; 2=total opacification) deriving a maximum score of 12 per side and a total maximum score of 24 (higher scores indicate more opacification). Loss of smell was scored reflectively by the patient every morning on a 0-3 scale (0=no symptoms, 1=mild symptoms, 2=moderate symptoms, 3=severe symptoms). SNOT-22 includes 22 items assessing symptoms and symptom impact associated with CRSwNP with each item scored from 0 (no problem) to 5 (problem as bad as it can be) with a global score ranging from 0 to 110. SNOT-22 had a 2 week recall period. In the pooled efficacy results, the reduction in the proportion of subjects rescued with systemic corticosteroids and/or sino-nasal surgery (up to Week 52) were evaluated.

The demographics and baseline characteristics of these 2 trials are provided in Table 11 below.

Table 11: Demographics and Baseline Characteristics of CRSwNP Trials

Parameter	CSNP Trial 1 (N=276)	CSNP Trial 2 (N=448)
Mean age (years) (SD)	50 (13)	52 (12)
% Male	57	62
Mean CRSwNP duration (years) (SD)	11 (9)	11 (10)
Patients with ≥ 1 prior surgery (%)	72	58
Patients with systemic corticosteroid use in the previous 2 years (%)	65	80
Mean Bilateral endoscopic NPS ^a (SD), range 0-8	5.8 (1.3)	6.1 (1.2)
Mean Nasal congestion (NC) score ^a (SD), range 0-3	2.4 (0.6)	2.4 (0.6)
Mean LMK sinus CT total score ^a (SD), range 0-24	19 (4.4)	18 (3.8)
Mean loss of smell score ^a (AM), (SD) range 0-3	2.7 (0.5)	2.8 (0.5)
Mean SNOT-22 total score ^a (SD), range 0-110	49.4 (20.2)	51.9 (20.9)
Mean blood eosinophils (cells/mcL) (SD)	440 (330)	430 (350)
Mean total IgE IU/mL (SD)	212 (276)	240 (342)
Atopic Medical History	75%	82%
% Overall		
Asthma (%)	58	60
NSAID-ERD (%)	30	27

^aHigher scores indicate greater disease severity

SD = standard deviation; AM = morning; NPS = nasal polyps score; SNOT-22 = 22-item sino-nasal outcome test; NSAID-ERD = asthma/nonsteroidal anti-inflammatory drug exacerbated respiratory disease

Clinical Response (CSNP Trial 1 and CSNP Trial 2)

The results for primary endpoints in CRSwNP studies are presented in Table 12.

Table 12: Results of the Primary Endpoints in CRSwNP Trials

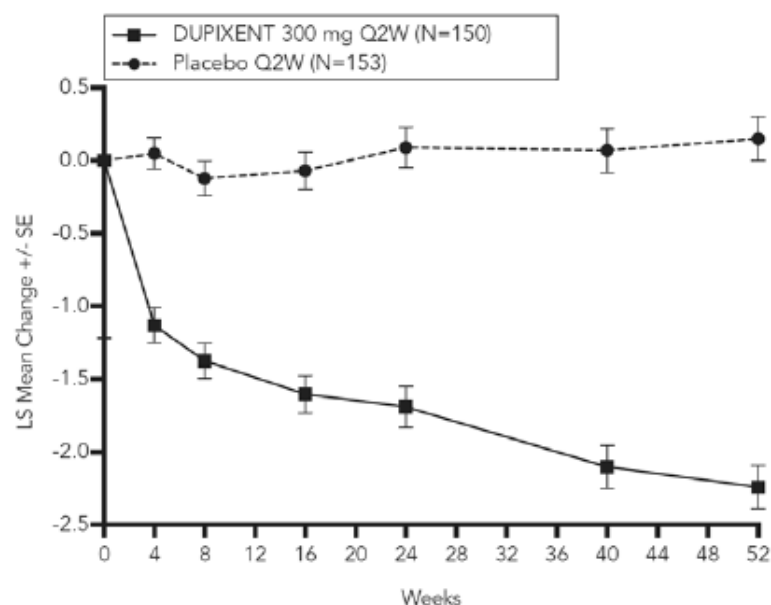
	CSNP Trial 1					CSNP Trial 2				
	Placebo (n=133)		DUPIXENT 300 mg Q2W (n=143)		LS mean difference vs. Placebo (95% CI)	Placebo (n=153)		DUPIXENT 300 mg Q2W (n=295)		LS mean difference vs. Placebo (95% CI)
Primary Endpoints at Week 24										
Scores	Baseline mean	LS mean change	Baseline mean	LS mean change		Baseline mean	LS mean change	Baseline mean	LS mean change	
NPS	5.86	0.17	5.64	-1.89	-2.06 (-2.43, -1.69)	5.96	0.10	6.18	-1.71	-1.80 (-2.10, -1.51)
NC	2.45	-0.45	2.26	-1.34	-0.89 (-1.07, -0.71)	2.38	-0.38	2.46	-1.25	-0.87 (-1.03, -0.71)

A reduction in score indicates improvement.

NPS = nasal polyps score; NC = nasal congestion/obstruction

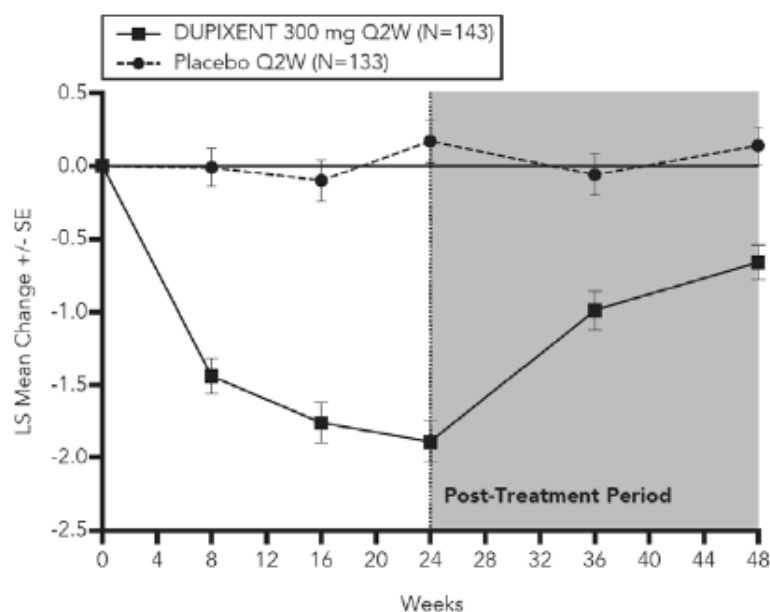
Statistically significant efficacy was observed in CSNP Trial 2 with regard to improvement in bilateral endoscopic NPS score at week 24 and week 52 (see Figure 7).

Figure 7: LS Mean Change from Baseline in Bilateral Nasal Polyps Score (NPS) up to Week 52 in CSNP Trial 2 - ITT Population



Similar results were seen in CSNP Trial 1 at Week 24. In the post-treatment period when subjects were off DUPIXENT, the treatment effect diminished over time (see Figure 8).

Figure 8: LS Mean Change from Baseline in Bilateral Nasal Polyps Score (NPS) up to Week 48 in CSNP Trial 1 - ITT Population



At Week 52, the LS mean difference for nasal congestion in the DUPIXENT group versus placebo was -0.98 (95% CI -1.17, -0.79). In both studies, significant improvements in nasal congestion were observed as early as the first assessment at Week 4. The LS mean difference for nasal congestion at Week 4 in the DUPIXENT group versus placebo was -0.41 (95% CI: -0.52, -0.30) in CSNP Trial 1 and -0.37 (95% CI: -0.46, -0.27) in CSNP Trial 2.

A significant decrease in the LMK sinus CT scan score was observed. The LS mean difference for LMK sinus CT scan score at Week 24 in the DUPIXENT group versus placebo was -7.44 (95% CI: -8.35, -6.53) in CSNP Trial 1 and -5.13 (95% CI: -5.80, -4.46) in CSNP Trial 2. At Week 52, in CSNP Trial 2 the LS mean difference for LMK sinus CT scan score in the DUPIXENT group versus placebo was -6.94 (95% CI: -7.87, -6.01).

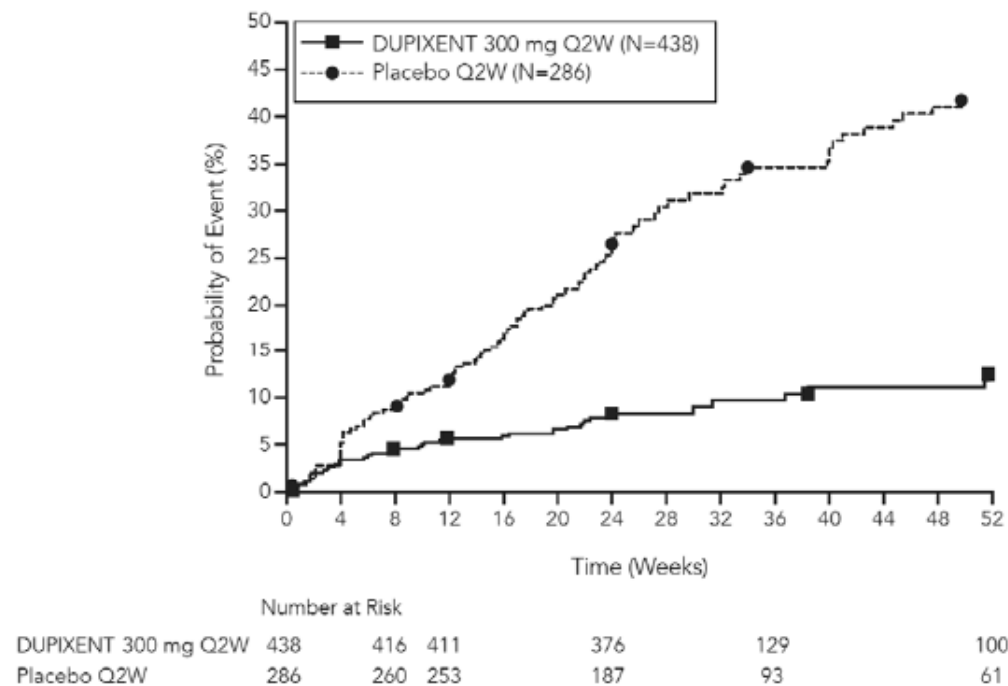
Dupilumab significantly improved the loss of smell compared to placebo. The LS mean difference for loss of smell at Week 24 in the DUPIXENT group versus placebo was -1.12 (95% CI: -1.31, -0.93) in CSNP Trial 1 and -0.98 (95% CI: -1.15, -0.81) in CSNP Trial 2. At Week 52, the LS mean difference for loss of smell in the DUPIXENT group versus placebo was -1.10 (95% CI -1.31, -0.89). In both studies, significant improvements in daily loss of smell severity were observed as early as the first assessment at Week 4.

Dupilumab significantly decreased sino-nasal symptoms as measured by SNOT-22 compared to placebo. The LS mean difference for SNOT-22 at Week 24 in the DUPIXENT group versus placebo was -21.12 (95% CI: -25.17, -17.06) in CSNP Trial 1 and -17.36 (95% CI: -20.87, -13.85) in CSNP Trial 2. At Week 52, the LS mean difference in the DUPIXENT group versus placebo was -20.96 (95% CI -25.03, -16.89).

In the pre-specified multiplicity-adjusted pooled analysis of two studies, treatment with DUPIXENT resulted in significant reduction of systemic corticosteroid use and need for sino-nasal surgery versus placebo (HR of 0.24; 95% CI: 0.17, 0.35) (see Figure 9). The

proportion of subjects who required systemic corticosteroids was reduced by 74% (HR of 0.26; 95% CI: 0.18, 0.38). The total number of systemic corticosteroid courses per year was reduced by 75% (RR of 0.25; 95% CI: 0.17, 0.37). The proportion of subjects who required surgery was reduced by 83% (HR of 0.17; 95% CI: 0.07, 0.46).

Figure 9: Kaplan Meier Curve for Time to First Systemic Corticosteroid Use and/or Sino-Nasal Surgery During Treatment Period - ITT population CSNP Trial 1 and CSNP Trial 2 Pooled



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

In subjects with co-morbid asthma, improvements in pre-bronchodilator FEV₁ were similar to patients in the asthma program.

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

DUPIXENT (dupilumab) Injection is a clear to slightly opalescent, colorless to pale yellow solution, supplied in single-dose pre-filled syringes with needle shield. Each pre-filled syringe with needle shield is designed to deliver either 300 mg of DUPIXENT in 2 mL (NDC 0024-5914-00) or 200 mg of DUPIXENT in 1.14 mL solution (NDC 0024-5918-00).

DUPIXENT is available in cartons containing 2 pre-filled syringes with needle shield.

Pack Size	300 mg/2 mL Pre-filled Syringe with Needle Shield	200 mg/1.14 mL Pre-filled Syringe with Needle Shield
Pack of 2 syringes	NDC 0024-5914-01	NDC 0024-5918-01

16.2 Storage and Handling

DUPIXENT is sterile and preservative-free. Discard any unused portion.

Store refrigerated at 36°F to 46°F (2°C to 8°C) in the original carton to protect from light.

If necessary, pre-filled syringes may be kept at room temperature up to 77°F (25°C) for a maximum of 14 days. Do not store above 77°F (25°C). After removal from the refrigerator, DUPIXENT must be used within 14 days or discarded.

Do not expose the pre-filled syringe to heat or direct sunlight.

Do NOT freeze. Do NOT shake.

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Patient Information and Instructions for Use).

Pregnancy Registry

There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to DUPIXENT during pregnancy. Encourage participation in the registry. *[see Use in Specific Populations (8.1)]*.

Administration Instructions

Provide proper training to patients and/or caregivers on proper subcutaneous injection technique, including aseptic technique, and the preparation and administration of DUPIXENT prior to use. Advise patients to follow sharps disposal recommendations *[see Instructions for Use]*.

Hypersensitivity

Advise patients to discontinue DUPIXENT and to seek immediate medical attention if they experience any symptoms of systemic hypersensitivity reactions *[see Warnings and Precautions (5.1)]*.

Conjunctivitis and Keratitis

Advise patients to consult their healthcare provider if new onset or worsening eye symptoms develop *[see Warnings and Precautions (5.2)]*.

Eosinophilic Conditions

Advise patients to notify their healthcare provider if they present with clinical features of eosinophilic pneumonia or vasculitis consistent with eosinophilic granulomatosis with polyangiitis *[see Warnings and Precautions (5.3)]*.

Not for Acute Asthma Symptoms or Deteriorating Disease

Inform patients that DUPIXENT does not treat acute asthma symptoms or acute exacerbations. Inform patients to seek medical advice if their asthma remains uncontrolled or worsens after initiation of treatment with DUPIXENT [see *Warnings and Precautions* (5.4)].

Reduction in Corticosteroid Dosage

Inform patients to not discontinue systemic or inhaled corticosteroids except under the direct supervision of a physician. Inform patients that reduction in corticosteroid dose may be associated with systemic withdrawal symptoms and/or unmask conditions previously suppressed by systemic corticosteroid therapy [see *Warnings and Precautions* (5.5)].

Patients with Co-morbid Asthma

Advise patients with atopic dermatitis or CRSwNP who have co-morbid asthma not to adjust or stop their asthma treatment without talking to their physicians [see *Warnings and Precautions* (5.6)].

REGENERON SANOFI GENZYME 

Manufactured by:

Regeneron Pharmaceuticals, Inc.

Tarrytown, NY 10591

U.S. License No. 1760

Marketed by:

sanofi-aventis U.S. LLC (Bridgewater, NJ 08807) and

Regeneron Pharmaceuticals, Inc. (Tarrytown, NY 10591)

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Revised: June 2019

ANNEX I
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 300 mg solution for injection in pre-filled syringe

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Dupilumab 300 mg solution for injection in pre-filled syringe

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

Dupilumab is a fully human monoclonal antibody against interleukin (IL)-4 receptor alpha that inhibits IL-4/IL-13 signalling, produced in Chinese Hamster Ovary (CHO) cells by recombinant DNA technology.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection (injection)

Clear to slightly opalescent, colourless to pale yellow solution, which is free from visible particulates.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Atopic Dermatitis

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.

Asthma

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 FeNO (see section 5.1), who are inadequately controlled with high dose ICS plus another medicinal product for maintenance treatment.

Chronic rhinosinusitis with nasal polyposis (CRSwNP)

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

4.2 Posology and method of administration

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

Posology

Atopic Dermatitis

Adults

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

Adolescents

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 years 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

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

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

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

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

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

Chronic rhinosinusitis with nasal polyposis (CRSwNP)

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

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

Missed dose

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

Special populations

Elderly patients (≥ 65 years)

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

Renal impairment

No dose adjustment is needed in patients with mild or moderate renal impairment. Very limited data are available in patients with severe renal impairment (see section 5.2).

Hepatic impairment

No data are available in patients with hepatic impairment (see section 5.2).

Body weight

No dose adjustment for body weight is recommended for patients with asthma 12 years of age and older or in adults with atopic dermatitis or CRSwNP (see section 5.2).

For patients 12 to 17 years of age with atopic dermatitis, the recommended every other week dose is 200 mg (< 60 kg) or 300 mg (≥ 60 kg).

Paediatric patients

The safety and efficacy of dupilumab in children with atopic dermatitis below the age of 12 years have not been established (see section 5.2). No data are available.

The safety and efficacy of dupilumab in children with severe asthma below the age of 12 years have not been established (see section 5.2). No data are available.

CRSwNP does not normally occur in children. The safety and efficacy in children with CRSwNP below the age of 18 years have not been established (see section 5.2). No data are available.

Method of administration

Subcutaneous use

Dupilumab is administered by subcutaneous injection into the thigh or abdomen, except for the 5 cm around the navel. If somebody else administers the injection, the upper arm can also be used.

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

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

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

4.3 Contraindications

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

4.4 Special warnings and precautions for use

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

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

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

Traceability

In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded.

Hypersensitivity

If a systemic hypersensitivity reaction (immediate or delayed) occurs, administration of dupilumab should be discontinued immediately and appropriate therapy initiated. Very rare cases of serum sickness/serum sickness-like reactions have been reported in the atopic dermatitis development program following the administration of dupilumab. Anaphylactic reaction has been reported very rarely in the asthma development program following the administration of dupilumab (section 4.8).

Eosinophilic conditions

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

Helminth infection

Patients with known helminth infections were excluded from participation in clinical studies. Dupilumab may influence the immune response against helminth infections by inhibiting IL-4/IL-13 signaling. Patients with pre-existing helminth infections should be treated before initiating dupilumab. If patients become infected while receiving treatment with dupilumab and do not respond to anti-helminth treatment, treatment with dupilumab should be discontinued until infection resolves.

Conjunctivitis related events

Patients treated with dupilumab who develop conjunctivitis that does not resolve following standard treatment should undergo ophthalmological examination (section 4.8).

Atopic dermatitis or CRSwNP patients with comorbid asthma

Patients on dupilumab for moderate-to-severe atopic dermatitis or severe CRSwNP who also have co-morbid asthma should not adjust or stop their asthma treatments without consultation with their physicians. Patients with comorbid asthma should be monitored carefully following discontinuation of dupilumab.

Vaccinations

Live and live attenuated vaccines should not be given concurrently with dupilumab as clinical safety and efficacy has not been established. Immune responses to Tdap vaccine and meningococcal polysaccharide vaccine were assessed, see section 4.5. It is recommended that patients should be brought up to date with live and live attenuated immunisations in agreement with current immunisation guidelines prior to treatment with dupilumab.

Sodium content

This medicinal product contains less than 1 mmol sodium (23 mg) per 300 mg dose, i.e. essentially “sodium-free”.

4.5 Interaction with other medicinal products and other forms of interaction

Immune responses to vaccination were assessed in a study in which patients with atopic dermatitis were treated once weekly for 16 weeks with 300 mg of dupilumab. After 12 weeks of dupilumab administration, patients were vaccinated with a Tdap vaccine (T cell-dependent), and a meningococcal polysaccharide vaccine (T cell-independent) and immune responses were assessed 4 weeks later. Antibody responses to both tetanus vaccine and meningococcal polysaccharide vaccine were similar in dupilumab-treated and placebo-treated patients. No adverse interactions between either of the non-live vaccines and dupilumab were noted in the study.

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

In a clinical study of AD patients, the effects of dupilumab on the pharmacokinetics (PK) of CYP substrates were evaluated. The data gathered from this study did not indicate clinically relevant effects of dupilumab on CYP1A2, CYP3A, CYP2C19, CYP2D6, or CYP2C9 activity.

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

4.6 Fertility, pregnancy and lactation

Pregnancy

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

Breast-feeding

It is unknown whether dupilumab is excreted in human milk or absorbed systemically after ingestion. A decision must be made whether to discontinue breast-feeding or to discontinue dupilumab therapy taking into account the benefit of breast feeding for the child and the benefit of therapy for the woman.

Fertility

Animal studies showed no impairment of fertility (see section 5.3).

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

Atopic dermatitis

Adults with atopic dermatitis

Summary of the safety profile

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

In the monotherapy studies, the proportion of patients who discontinued treatment due to adverse events was 1.9 % of the placebo group, 1.9 % of the dupilumab 300 mg Q2W group, 1.5 % of the dupilumab 300 mg QW group. In the concomitant TCS study, the proportion of patients who discontinued treatment due to adverse events was 7.6 % of the placebo + TCS group, 1.8 % of the dupilumab 300 mg Q2W + TCS group, and 2.9 % of the dupilumab 300 mg QW + TCS group.

Tabulated list of adverse reactions

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

Listed in Table 2 are adverse reactions observed in atopic dermatitis clinical trials presented by system organ class and frequency, using the following categories: very common ($\geq 1/10$); common ($\geq 1/100$ to $< 1/10$); uncommon ($\geq 1/1,000$ to $< 1/100$); rare ($\geq 1/10,000$ to $< 1/1,000$); very rare ($< 1/10,000$). Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Table 2: List of adverse reactions in atopic dermatitis

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

Adolescents with atopic dermatitis

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.

The long-term safety of dupilumab was assessed in an open-label extension study in patients 12 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 AD-1526 study. The long-term safety profile of dupilumab observed in adolescents was consistent with that seen in adults with atopic dermatitis.

Asthma

Summary of the safety profile

The most common adverse reaction was injection site erythema. Anaphylactic reaction has been reported very rarely in the asthma development program (see section 4.4).

In DRI12544 and QUEST studies, the proportion of patients who discontinued treatment due to adverse events was 4.3% of the placebo group, 3.2% of the dupilumab 200 mg Q2W group, and 6.1% of the dupilumab 300 mg Q2W group.

Tabulated list of adverse reactions

A total of 2,888 adult and adolescent patients with moderate-to-severe asthma were evaluated in 3 randomised, placebo-controlled, multicentre trials of 24 to 52 weeks duration (DRI12544, QUEST, and VENTURE). Of these, 2,678 had a history of 1 or more severe exacerbations in the year prior to enrolment despite regular use of medium-to-high dose inhaled corticosteroids plus an additional controller(s) (DRI12544 and QUEST). A total of 210 patients with oral corticosteroid-dependent asthma receiving high-dose inhaled corticosteroids plus up to two additional controllers were enrolled (VENTURE).

Listed in Table 3 are adverse reactions observed in asthma clinical trials presented by system organ class and frequency, using the following categories: very common ($\geq 1/10$); common ($\geq 1/100$ to $< 1/10$); uncommon ($\geq 1/1,000$ to $< 1/100$); rare ($\geq 1/10,000$ to $< 1/1,000$); very rare ($< 1/10,000$). Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Table 3: List of adverse reactions in asthma

MedDRA System Organ Class	Frequency	Adverse Reaction
<i>Immune system disorders</i>	Very rare	Anaphylactic reaction
<i>General disorders and administration site conditions</i>	Very common	Injection site erythema
	Common	Injection site oedema
	Common	Injection site pain
	Common	Injection site pruritus

Chronic rhinosinusitis with nasal polyposis (CRSwNP)

Summary of the safety profile

The most common adverse reactions were injection site reaction and injection site swelling.

In the safety pool, the proportion of patients who discontinued treatment due to adverse events was 2.0% of the dupilumab 300 mg Q2W group and 4.6% of the placebo group.

Tabulated list of adverse reactions

A total of 722 adult patients with CRSwNP were evaluated in 2 randomised, placebo-controlled, multicentre trials of 24 to 52 weeks duration (SINUS-24 and SINUS-52). The safety pool consisted of data from the first 24 weeks of treatment.

Listed in Table 4 are adverse reactions observed in CRSwNP clinical trials presented by system organ class and frequency, using the following categories: very common ($\geq 1/10$); common ($\geq 1/100$ to $< 1/10$); uncommon ($\geq 1/1,000$ to $< 1/100$); rare ($\geq 1/10,000$ to $< 1/1,000$); very rare ($< 1/10,000$). Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Table 4. List of adverse reactions in CRSwNP clinical studies

MedDRA System Organ Class	Frequency	Adverse Reaction
<i>Infections and infestations</i>	Common	Conjunctivitis
<i>Blood and lymphatic system disorders</i>	Common	Eosinophilia
<i>General disorders and administration site conditions</i>	Common	Injection site reaction Injection site swelling

Description of selected adverse reactions in atopic dermatitis, asthma, and CRSwNP indications

Hypersensitivity

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

Conjunctivitis and related events

Conjunctivitis occurred more frequently in atopic dermatitis patients who received dupilumab. Most patients with conjunctivitis recovered or were recovering during the treatment period. Among asthma patients frequency of conjunctivitis was low and similar between dupilumab and placebo. Among CRSwNP patients the frequency of conjunctivitis was higher in dupilumab than placebo, though lower than that observed in atopic dermatitis patients (see section 4.4).

Eczema herpeticum

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

Eosinophilia

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

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

Infections

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

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.

Immunogenicity

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

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

Approximately 5% of patients with atopic dermatitis, asthma, or CRSwNP who received dupilumab 300 mg Q2W for 52 weeks developed ADA to dupilumab; approximately 2% exhibited persistent ADA responses and approximately 2% had neutralizing antibodies.

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.

Across the 300 mg and 200 mg Q2W dosing regimens, approximately 4% of patients with atopic dermatitis, asthma, or CRSwNP in the placebo groups in the 52 week studies were also positive for antibodies to dupilumab; approximately 2% exhibited persistent ADA response and approximately 1% had neutralizing antibodies.

Less than 0.6% of patients exhibited high titer ADA responses associated with reduced exposure and efficacy. In addition, there was one patient with serum sickness and one with serum sickness-like reaction ($< 0.1\%$) associated with high ADA titers (see section 4.4).

Paediatric population

The safety profile observed in adolescents aged 12 to 17 years in atopic dermatitis clinical trials was similar to that seen in adults.

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.

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 national reporting system listed in [Appendix V](#).

4.9 Overdose

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

Mechanism of action

Dupilumab is a recombinant human IgG4 monoclonal antibody that inhibits interleukin-4 and interleukin-13 signaling. Dupilumab inhibits IL-4 signaling via the Type I receptor (IL-4R α / γ c), and both IL-4 and IL-13 signaling through the Type II receptor (IL-4R α /IL-13R α). IL-4 and IL-13 are major drivers of human type 2 inflammatory disease, such as atopic dermatitis, asthma, and CRSwNP. 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 asthma clinical trials, dupilumab treatment markedly decreased FeNO and circulating concentrations of eotaxin-3, total IgE, allergen specific IgE, TARC, and periostin in asthma subjects relative to placebo. These reductions in type 2 inflammatory biomarkers were comparable for the 200 mg Q2W and 300 mg Q2W regimens. These markers were near maximal suppression after 2 weeks of treatment, except for IgE which declined more slowly. These effects were sustained throughout treatment.

Clinical efficacy and safety in atopic dermatitis

Adults with atopic dermatitis

The efficacy and safety of dupilumab as monotherapy and with concomitant topical corticosteroids were evaluated in three pivotal randomised, double-blind, placebo-controlled studies (SOLO 1, SOLO 2, and CHRONOS) in 2,119 patients 18 years of age and older with moderate to severe atopic dermatitis (AD) defined by Investigator's Global Assessment (IGA) score ≥ 3 , an Eczema Area and Severity Index (EASI) score ≥ 16 , and a minimum body surface area (BSA) involvement of $\geq 10\%$. Eligible patients enrolled into the three studies had previous inadequate response to topical medication.

In all three studies, patients received 1) an initial dose of 600 mg dupilumab (two 300 mg injections) on day 1, followed by 300 mg once every two weeks (Q2W); 2) an initial dose of 600 mg dupilumab on day 1, followed by 300 mg once weekly (QW); or 3) matching placebo. Dupilumab was administered by subcutaneous (SC) injection in all studies. If needed to control intolerable symptoms of atopic dermatitis, patients were permitted to receive rescue treatment (which included higher potency topical steroids or systemic immunosuppressants) at the discretion of the investigator. Patients who received rescue treatment were considered non-responders.

SOLO 1 enrolled 671 patients (224 to placebo, 224 to dupilumab 300 mg Q2W, and 223 to dupilumab 300 mg QW) and had a treatment period of 16 weeks.

SOLO 2 enrolled 708 patients (236 to placebo, 233 to dupilumab 300 mg Q2W, and 239 to dupilumab 300 mg QW) and had a treatment period of 16 weeks.

CHRONOS enrolled 740 patients (315 to placebo + topical corticosteroid (TCS), 106 to dupilumab 300 mg Q2W + TCS, and 319 to dupilumab 300 mg QW + TCS) and had a treatment period of 52 weeks. Patients received dupilumab or placebo with concomitant use of TCS starting at baseline using a standardized regimen. Patients were also permitted to use topical calcineurin inhibitors (TCI).

Endpoints

In all three pivotal studies, the co-primary endpoints were the proportion of patients with IGA 0 or 1 (“clear” or “almost clear”) with a reduction of ≥ 2 points on a 0–4 IGA scale and the proportion of patients with improvement of at least 75 % in EASI (EASI-75) from baseline to week 16. Other evaluated outcomes included the proportion of patients with improvement of at least 50 % and 90 % in EASI (EASI-50 and EASI-90, respectively), reduction in itch as measured by the peak pruritus Numerical Rating Scale (NRS), and percent change in the SCORing Atopic Dermatitis (SCORAD) scale from baseline to week 16. Additional secondary endpoints included mean change from baseline to week 16 in the Patient Oriented Eczema Measure (POEM), Dermatology Life Quality Index (DLQI), and Hospital Anxiety and Depression Scale (HADS) scores. In CHRONOS, efficacy was also evaluated at week 52.

Baseline Characteristics

In the monotherapy studies (SOLO 1 and SOLO 2), across all treatment groups, the mean age was 38.3, the mean weight was 76.9 kg, 42.1% were female, 68.1% were white, 21.8% were Asian, and 6.8% were black. In these studies, 51.6 % of patients had a baseline IGA score of 3 (moderate AD), 48.3 % of patients had a baseline IGA of 4 (severe AD) and 32.4 % of patients had received prior systemic immunosuppressants. The baseline mean EASI score was 33.0, the baseline weekly averaged pruritus NRS was 7.4, the baseline mean SCORAD score was 67.8, the baseline mean POEM score was 20.5, the baseline mean DLQI was 15.0, and the baseline mean HADS total score was 13.3. In the concomitant TCS study (CHRONOS), across all treatment groups, the mean age was 37.1, the mean weight was 74.5 kg, 39.7 % were female, 66.2 % were white, 27.2 % were Asian, and 4.6 % were black. In this study, 53.1 % of patients had a baseline IGA score of 3 and 46.9 % of patients had a baseline IGA of 4 and 33.6 % of patients received prior systemic immunosuppressants. The baseline mean EASI score was 32.5, the baseline weekly pruritus NRS was 7.3, the baseline mean SCORAD score was 66.4, the baseline mean POEM score was 20.1, the baseline mean DLQI was 14.5, and the baseline mean HADS total score was 12.7.

Clinical Response

16-Week Monotherapy Studies (SOLO 1 and SOLO 2)

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

A significantly greater proportion of patients randomized to dupilumab achieved a rapid improvement in the pruritus NRS compared to placebo (defined as ≥ 4 -point improvement as early as week 2; $p < 0.01$) and the proportion of patients responding on the pruritus NRS continued to increase through the treatment period. The improvement in pruritus NRS occurred in conjunction with the improvement of objective signs of atopic dermatitis.

Figure 1 and Figure 2 show the mean percent change from baseline in EASI and the mean percent change from baseline in NRS, respectively up to week 16.

Table 5: Efficacy results of dupilumab monotherapy at week 16 (FAS)

	SOLO 1 (FAS) ^a			SOLO 2 (FAS) ^a		
	Placebo	Dupilumab 300 mg Q2W	Dupilumab 300 mg QW	Placebo	Dupilumab 300 mg Q2W	Dupilumab 300 mg QW
<i>Patients</i>	224	224	223	236	233	239

	SOLO 1 (FAS) ^a			SOLO 2 (FAS) ^a		
	Placebo	Dupilumab 300 mg Q2W	Dupilumab 300 mg QW	Placebo	Dupilumab 300 mg Q2W	Dupilumab 300 mg QW
<i>randomised</i>						
IGA 0 or 1 ^b , % responders ^c	10.3 %	37.9 % ^e	37.2 % ^e	8.5 %	36.1 % ^e	36.4 % ^e
EASI-50, % responders ^c	24.6 %	68.8 % ^e	61.0 % ^e	22.0 %	65.2 % ^e	61.1 % ^e
EASI-75, % responders ^c	14.7 %	51.3 % ^e	52.5 % ^e	11.9 %	44.2 % ^e	48.1 % ^e
EASI-90, % responders ^c	7.6 %	35.7 % ^e	33.2 % ^e	7.2 %	30.0 % ^e	30.5 % ^e
EASI, LS mean % change from baseline (+/- SE)	-37.6 % (3.28)	-72.3 % ^e (2.63)	-72.0 % ^e (2.56)	-30.9 % (2.97)	-67.1 % ^e (2.52)	-69.1 % ^e (2.49)
SCORAD, LS mean % change from baseline (+/- SE)	-29.0 % (3.21)	-57.7 % ^e (2.11)	-57.0 % ^e (2.11)	-19.7 % (2.52)	-51.1 % ^e (2.02)	-53.5 % ^e (2.03)
Pruritus NRS, LS mean % change from baseline (+/- SE)	-26.1 % (3.02)	-51.0 % ^e (2.50)	-48.9 % ^e (2.60)	-15.4 % (2.98)	-44.3 % ^e (2.28)	-48.3 % ^e (2.35)
<i>Number of patients with baseline pruritus NRS score ≥ 4</i>	212	213	201	221	225	228
Pruritus NRS (≥ 4-point improvement) , % responders ^{c, d}	12.3 %	40.8 % ^e	40.3 % ^e	9.5%	36.0 % ^e	39.0 % ^e

LS = least squares; SE= standard error

^a Full analysis set (FAS) includes all patients randomized.

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

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

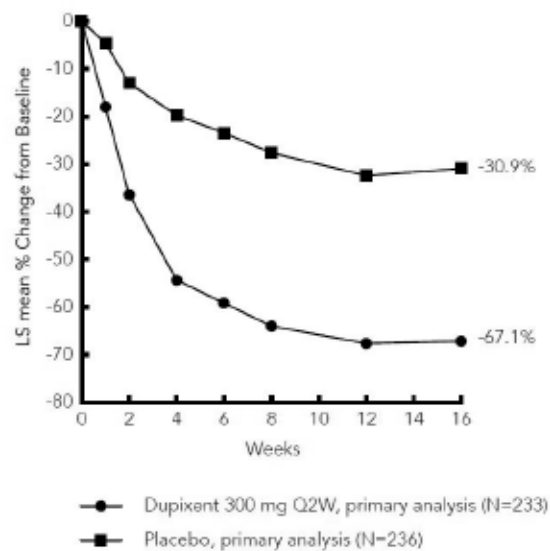
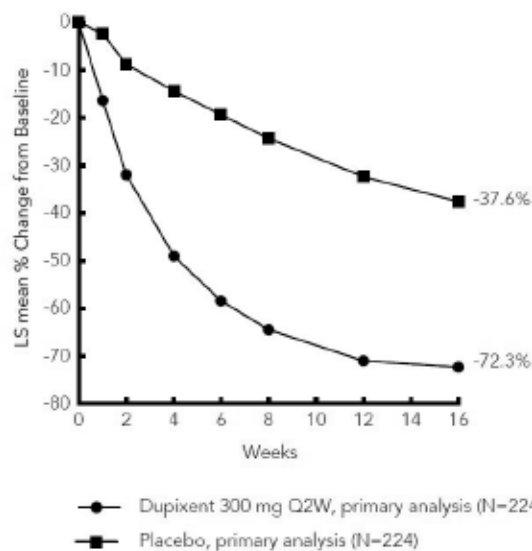
^d a significantly greater proportion of patients on dupilumab had improvement in pruritus NRS of ≥ 4 points compared to placebo at week 2 (p < 0.01).

^e p-value < 0.0001

Figure 1: Mean percent change from baseline in EASI in SOLO 1^a and SOLO 2^a (FAS)^b

SOLO 1

SOLO 2

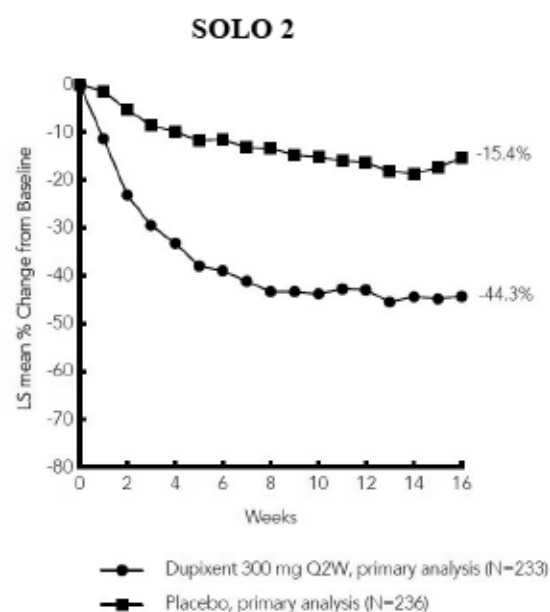
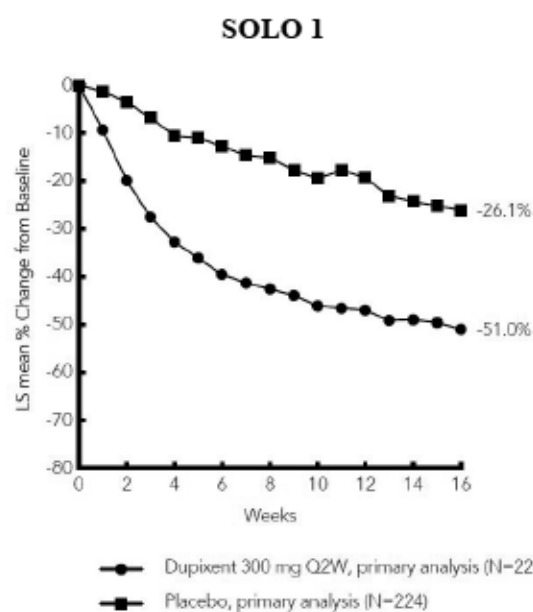


LS = least squares

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

^bFull analysis set (FAS) includes all patients randomized.

Figure 2: Mean percent change from baseline in NRS in SOLO 1^a and SOLO 2^a (FAS)^b



LS = least squares

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

^bFull analysis set (FAS) includes all patients randomized.

Treatment effects in subgroups (weight, age, gender, race, and background treatment, including immunosuppressants) in SOLO 1 and SOLO 2 were consistent with the results in the overall study population.

52-Week Concomitant TCS Study (CHRONOS)

In CHRONOS, a significantly greater proportion of patients randomized to dupilumab 300 mg Q2W + TCS achieved an IGA 0 or 1 response, EASI-75, and/or an improvement of ≥ 4 points on the pruritus NRS from baseline to week 16 and week 52 compared to placebo + TCS (see Table 6).

A significantly greater proportion of patients randomized to dupilumab + TCS achieved a rapid improvement in the pruritus NRS compared to placebo + TCS (defined as ≥ 4 -point improvement as early as week 2; $p < 0.05$) and the proportion of patients responding on the pruritus NRS continued to increase through the treatment period. The improvement in pruritus NRS occurred in conjunction with the improvement of objective signs of atopic dermatitis.

Figure 3 and Figure 4 show the mean percent change from baseline in EASI and the mean percent change from baseline in NRS, respectively, up to week 52 in CHRONOS.

Table 6: Efficacy results of dupilumab with concomitant TCS^a at Week 16 and Week 52 in CHRONOS

	Week 16 (FAS) ^b			Week 52 (FAS Week 52) ^b		
	Placebo + TCS	Dupilumab 300 mg Q2W + TCS	Dupilumab 300 mg QW + TCS	Placebo + TCS	Dupilumab 300 mg Q2W + TCS	Dupilumab 300 mg QW + TCS
<i>Patients randomized</i>	315	106	319	264	89	270
IGA 0 or 1 ^c , % responders ^d	12.4 %	38.7 % ^f	39.2 % ^f	12.5 %	36.0 % ^f	40.0 % ^f
EASI-50, % responders ^d	37.5 %	80.2 % ^f	78.1 % ^f	29.9 %	78.7 % ^f	70.0 % ^f
EASI-75, % responders ^d	23.2 %	68.9 % ^f	63.9 % ^f	21.6 %	65.2 % ^f	64.1 % ^f
EASI-90, % responders ^d	11.1 %	39.6 % ^f	43.3 % ^f	15.5 %	50.6 % ^f	50.7 % ^f
EASI, LS mean % change from baseline (+/- SE)	-48.4 % (3.82)	-80.5 % ^f (6.34)	- 81.5 % ^f (5.78)	-60.9 % (4.29)	-84.9 % ^g (6.73)	-87.8 % ^h (6.19)
SCORAD, LS mean % change from baseline (+/- SE)	-36.2 % (1.66)	-63.9 % ^f (2.52)	-65.9 % ^f (1.49)	-47.3 % (2.18)	-69.7 % ^f (3.06)	-70.4 % ^f (1.72)
Pruritus NRS, LS mean % change from baseline (+/- SE)	-30.3 % (2.36)	-56.6 % ^f (3.95)	-57.1 % ^f (2.11)	-31.7 % (3.95)	-57.0 % ⁱ (6.17)	-56.5 % ^f (3.26)
<i>Number of patients with baseline pruritus NRS score ≥ 4</i>	299	102	295	249	86	249
Pruritus NRS (≥ 4 -point improvement), % responders ^{d, e}	19.7 %	58.8 % ^f	50.8 % ^f	12.9 %	51.2 % ^f	39.0 % ^f

LS = least squares; SE = standard error

^a All patients were on background topical corticosteroids therapy and patients were permitted to use topical calcineurin inhibitors.

^b Full analysis set (FAS) includes all patients randomized. FAS week 52 includes all patients randomized at least one year before the cutoff date of the primary analysis.

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

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

^e a significantly greater proportion of patients on dupilumab had improvement in pruritus NRS of ≥ 4 points compared to placebo at week 2 ($p < 0.05$).

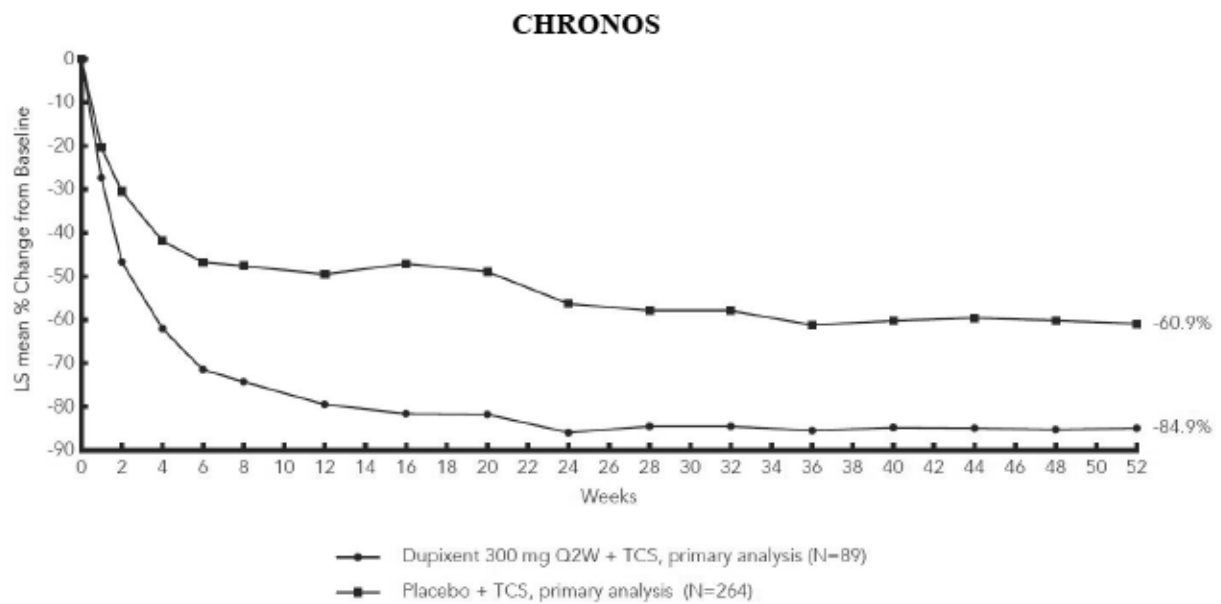
^f p-value < 0.0001

^g p-value = 0.0015

^h p-value = 0.0003

ⁱ p-value = 0.0005

Figure 3: Mean percent change from baseline in EASI in CHRONOS^a (FAS Week 52)^b

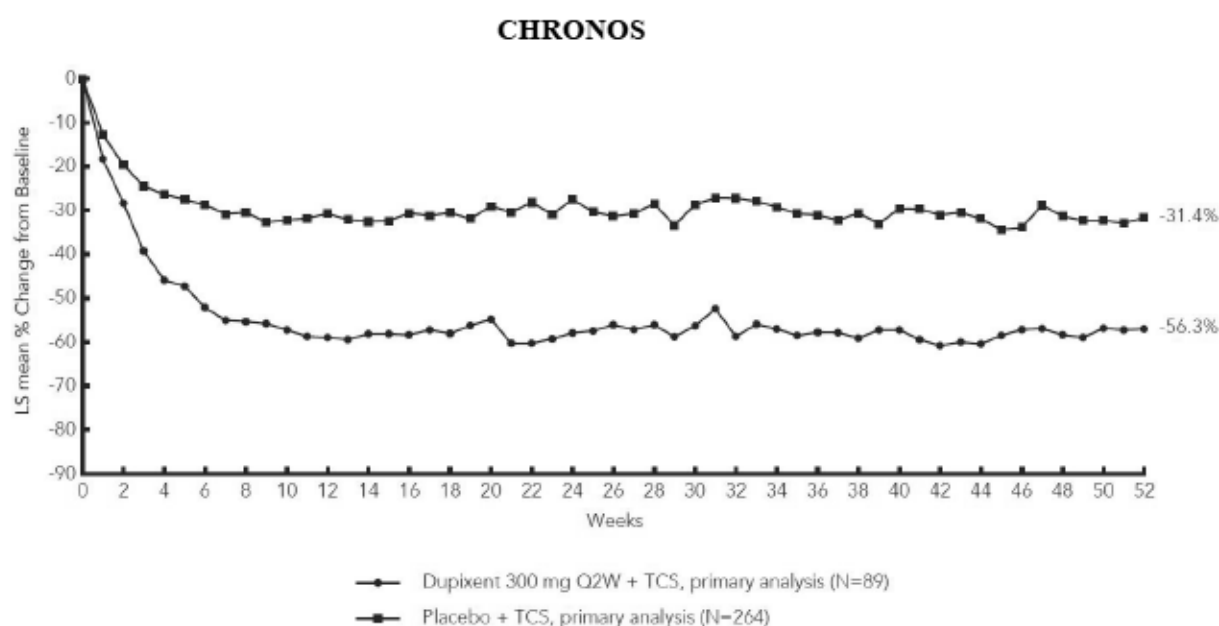


LS = least squares

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

^bFAS week 52 includes all patients randomized at least one year before the cutoff date of the primary analysis.

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



LS = least squares

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

^bFAS week 52 includes all patients randomized at least one year before the cutoff date of the primary analysis.

Treatment effects in subgroups (weight, age, gender, race, and background treatment, including immunosuppressants) in CHRONOS were consistent with the results in the overall study population.

Clinical Response in Patients Not Adequately Controlled with, Intolerant to, or for whom Ciclosporin Treatment was Inadvisable (CAFE study)

CAFE study evaluated the efficacy of dupilumab compared to placebo during a 16-week treatment period, administered with concomitant TCS, in adult patients with AD who are not adequately controlled with, or are intolerant to, oral ciclosporin, or when this treatment is currently contraindicated or not medically advisable.

A total of 325 patients were enrolled, with 210 patients who were previously exposed to ciclosporin and 115 patients who have never been exposed to ciclosporin because ciclosporin treatment was medically inadvisable. The mean age was 38.4 years, 38.8 % were female, the baseline mean EASI score was 33.1, the mean BSA was 55.7, the baseline weekly average pruritus NRS was 6.4, the baseline mean SCORAD score was 67.2, and the baseline mean DLQI was 13.8.

The primary endpoint was the proportion of patients with EASI-75 at week 16.

Primary and secondary endpoints for the 16 week CAFE study are summarized in table 7.

Table 7: Results of the primary and secondary endpoints in CAFE study

	Placebo + TCS	Dupilumab 300 mg Q2W + TCS	Dupilumab 300 mg QW+TCS
<i>Patients randomised</i>	108	107	110
EASI-75, % responders	29.6 %	62.6 %	59.1 %
EASI, LS mean % change from baseline (+/- SE)	-46.6 (2.76)	-79.8 (2.59)	-78.2 (2.55)
Pruritus NRS, LS mean % change from baseline (+/- SE)	-25.4 % (3.39)	-53.9 % (3.14)	-51.7 % (3.09)
SCORAD, LS mean % change from baseline (+/- SE)	-29.5 % (2.55)	-62.4 % (2.48)	-58.3 % (2.45)
DLQI, LS mean change from baseline (SE)	-4.5 (0.49)	-9.5 (0.46)	-8.8 (0.45)

(all p values <0.0001)

In the subgroup of patients resembling the CAFE study population within the 52 week CHRONOS study, 69.6 % of dupilumab 300 mg Q2W-treated patients reached EASI-75 vs 18.0 % placebo-treated patients at week 16, and 52.4 % of dupilumab 300 mg Q2W-treated vs 18.6 % placebo-treated at week 52. In this subset, the percent change of pruritus NRS from baseline was -51.4 % vs -30.2 % at week 16 and -54.8 % vs -30.9 % at week 52, for the dupilumab 300 mg Q2W and placebo groups respectively.

Maintenance and Durability of Response (SOLO CONTINUE study)

To evaluate maintenance and durability of response, subjects treated with dupilumab for 16 weeks in SOLO 1 and SOLO 2 studies who achieved IGA 0 or 1 or EASI-75 were re-randomized in SOLO CONTINUE study to an additional 36-week treatment of dupilumab or placebo, for a cumulative 52-week study treatment. Endpoints were assessed at weeks 51 or 52.

The co-primary endpoints were the difference between baseline (week 0) and week 36 in percent change in EASI from SOLO 1 and SOLO 2 studies baseline and percentage of patients with EASI-75 at week 36 in patients with EASI-75 at baseline.

Patients who continued on the same dose regimen received in the SOLO 1 and SOLO 2 studies (300 mg Q2W or 300 mg QW) showed the optimal effect in maintaining clinical response while efficacy for other dose regimens diminished in a dose-dependent manner.

Primary and secondary endpoints for the 52 week SOLO CONTINUE study are summarized in table 8.

Table 8: Results of the primary and secondary endpoints in SOLO CONTINUE study

	Placebo	Dupilumab 300 mg		
	N=83	Q8W N=84	Q4W N=86	Q2W/QW N=169
Co-Primary Endpoints				
LS mean change (SE) between baseline and week 36 in percent change in EASI Score from Parent Study baseline	21.7 (3.13)	6.8*** (2.43)	3.8*** (2.28)	0.1*** (1.74)
Percent of patients with EASI-75 at week 36 for patients with EASI-75 at baseline, n (%)	24/79 (30.4%)	45/82* (54.9%)	49/84** (58.3%)	116/162*** (71.6%)
Key Secondary Endpoints				
Percent of patients whose IGA response at week 36 was maintained within 1 point of baseline in the subset of patients with IGA (0,1) at baseline, n (%)	18/63 (28.6)	32/64† (50.0)	41/66** (62.1)	89/126*** (70.6)
Percent of patients with IGA (0,1) at week 36 in the subset of patients with IGA (0,1) at baseline, n (%)	9/63 (14.3)	21/64† (32.8)	29/66** (43.9)	68/126*** (54.0)
Percent of patients whose peak pruritus NRS increased by ≥ 3 points from baseline to week 35 in the subset of patients with peak pruritus NRS ≤ 7 at baseline, n (%)	56/80 (70.0)	45/81 (55.6)	41/83† (49.4)	57/168*** (33.9)

†P< 0.05, *P< 0.01, **P< 0.001, ***P≤ 0.0001

In SOLO CONTINUE, a trend for increased treatment-emergent ADA positivity with increased dosing intervals was observed. Treatment-emergent ADA: QW: 1.2%; Q2W: 4.3%; Q4W: 6.0%; Q8W: 11.7%. ADA responses lasting more than 12 weeks: QW: 0.0%; Q2W: 1.4%; Q4W: 0.0%; Q8W: 2.6%.

Quality of Life/Patient-Reported Outcomes in Atopic Dermatitis

In both monotherapy studies (SOLO 1 and SOLO 2), both dupilumab 300 mg Q2W and 300 mg QW groups significantly improved patient-reported symptoms and the impact of AD on sleep and health-related quality of life as measured by POEM and DLQI total scores, respectively, at 16 weeks compared to placebo. A significantly larger proportion of patients administered dupilumab groups had clinically meaningful reductions in POEM and DLQI total score (each defined as ≥ 4 points improvement) from baseline to week 16 compared to placebo group. In addition, anxiety and depression symptoms as measured by the HADS total score were significantly reduced in the dupilumab groups compared to placebo at 16 weeks. In a subset of patients with HADS-anxiety or HADS-depression subscale scores ≥ 8 at baseline (the cut-off value for anxiety or depression), a larger proportion of patients in the dupilumab groups achieved HADS-anxiety and HADS-depression scores < 8 at week 16 compared to placebo (See Table 9).

Table 9: Additional secondary endpoint results of dupilumab monotherapy at Week 16

	Monotherapy					
	SOLO 1 at Week 16			SOLO 2 at Week 16		
	Placebo	Dupilumab 300 mg Q2W	Dupilumab 300 mg QW	Placebo	Dupilumab 300 mg Q2W	Dupilumab 300 mg QW
<i>Patients randomized</i>	224	224	223	236	233	239
DLQI, LS mean change from baseline (SE)	-5.3 (0.50)	-9.3 ^a (0.40)	-9.0 ^a (0.40)	-3.6 (0.50)	-9.3 ^a (0.38)	-9.5 ^a (0.39)
POEM, LS mean change from baseline (SE)	-5.1 (0.67)	-11.6 ^a (0.49)	-11.0 ^a (0.50)	-3.3 (0.55)	-10.2 ^a (0.49)	-11.3 ^a (0.52)
HADS, LS mean change from baseline (SE)	-3.0 (0.65)	-5.2 ^b (0.54)	-5.2 ^b (0.51)	-0.8 (0.44)	-5.1 ^a (0.39)	-5.8 ^a (0.38)
<i>Number of patients with DLQI ≥ 4 at baseline</i>	213	209	209	225	223	234
DLQI (≥ 4-point improvement), % responders	30.5 %	64.1 % ^a	58.4 % ^a	27.6 %	73.1 % ^a	62.0 % ^a
<i>Number of patients with POEM ≥ 4 at baseline</i>	223	222	222	234	233	239
POEM (≥ 4-point improvement), % responders	26.9 %	67.6 % ^a	63.1 % ^a	24.4 %	71.7 % ^a	64.0 % ^a
<i>Number of patients with HADS-anxiety ≥ 8 or HADS-depression ≥ 8 at baseline</i>	97	100	102	115	129	136
Patients achieving HADS-anxiety and HADS-depression score < 8, %	12.4 %	41.0 % ^a	36.3 % ^b	6.1 %	39.5 % ^a	41.2 % ^a

LS = least squares; SE = standard error

^ap-value < 0.0001

^bp-value < 0.001

In the concomitant TCS study (CHRONOS), dupilumab 300 mg Q2W + TCS and dupilumab 300 mg QW + TCS improved patient-reported symptoms and the impact of AD on sleep and health-related quality of life as measured by POEM and DLQI total scores, respectively, at 52 weeks compared to placebo + TCS. A larger proportion of patients administered dupilumab 300 mg Q2W + TCS and 300 mg QW + TCS had clinically meaningful reductions in POEM and DLQI total score (each defined as ≥ 4-point improvement) from baseline to week 52 compared to the placebo + TCS. In addition, dupilumab 300 mg Q2W + TCS and 300 mg QW + TCS reduced anxiety and depression as measured

by the HADS total score at 52 weeks compared to placebo + TCS. In a post-hoc analysis in a subset of patients with HADS-anxiety or HADS-depression subscale scores ≥ 8 at baseline (the cut-off value for anxiety or depression), a larger proportion of patients in the dupilumab 300 mg Q2W + TCS and 300 mg QW + TCS groups achieved HADS-anxiety and HADS-depression scores < 8 at week 52 compared to placebo + TCS (See Table 10).

Table 10: Other secondary endpoint results of dupilumab with concomitant TCS at Week 16 and Week 52 in CHRONOS

	Concomitant Use of TCS					
	CHRONOS at Week 16			CHRONOS at Week 52		
	Placebo	Dupilumab 300 mg Q2W + TCS	Dupilumab 300 mg QW + TCS	Placebo +TCS	Dupilumab 300 mg Q2W + TCS	Dupilumab 300 mg QW + TCS
<i>Patients randomized</i>	315	106	319	264	89	270
DLQI, LS mean change from baseline (SE)	-5.8 (0.34)	-10.0 ^a (0.50)	-10.7 ^a (0.31)	-7.2 (0.40)	-11.4 ^a (0.57)	-11.1 ^a (0.36)
POEM, LS mean change from baseline (SE)	-5.3 (0.41)	-12.7 ^a (0.64)	-12.9 ^a (0.37)	-7.0 (0.57)	-14.2 ^a (0.78)	-13.2 ^a (0.45)
HADS, LS mean change from baseline (SE)	-4.0 (0.37)	-4.9 (0.58)	-5.4 ^c (0.35)	-3.8 (0.47)	-5.5 ^c (0.71)	-5.9 ^b (0.42)
<i>Number of patients with DLQI ≥ 4 at baseline</i>	300	100	311	254	85	264
DLQI (≥ 4 -point improvement), % responders	43.0 %	81.0 % ^a	74.3 % ^a	30.3 %	80.0 % ^a	63.3 % ^a
<i>Number of patients with POEM ≥ 4 at baseline</i>	312	106	318	261	89	269
POEM (≥ 4 -point improvement), % responders	36.9 %	77.4 % ^a	77.4 % ^a	26.1 %	76.4 % ^a	64.7 % ^a
<i>Number of patients with HADS-anxiety ≥ 8 or HADS-depression ≥ 8 at baseline</i>	148	59	154	133	53	138
Patients achieving HADS-anxiety	26.4 %	47.5 % ^c	47.4 % ^b	18.0 %	43.4 % ^b	44.9 % ^a

and HADS-depression < 8, %						
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LS = least squares; SE = standard error

^a p-value < 0.0001

^b p-value < 0.001

^c p-value < 0.05

Adolescents with atopic dermatitis

The efficacy and safety of dupilumab monotherapy in adolescent patients was evaluated in a multicentre, randomised, double-blind, placebo-controlled study (AD-1526) in 251 adolescent patients 12 to 17 years of age with moderate-to-severe atopic dermatitis (AD) defined by Investigator's Global Assessment (IGA) score ≥ 3 in the overall assessment of AD lesions on a severity scale of 0 to 4, an Eczema Area and Severity Index (EASI) score ≥ 16 on a scale of 0 to 72, and a minimum body surface area (BSA) involvement of $\geq 10\%$. Eligible patients enrolled into this study had previous inadequate response to topical medication.

Patients received 1) an initial dose of 400 mg dupilumab (two 200 mg injections) on day 1, followed by 200 mg once every other week (Q2W) for patients with baseline weight of < 60 kg or an initial dose of 600 mg dupilumab (two 300 mg injections) on day 1, followed by 300 mg Q2W for patients with baseline weight of ≥ 60 kg; 2) an initial dose of 600 mg dupilumab (two 300 mg injections) on day 1, followed by 300 mg every 4 weeks (Q4W) regardless of baseline body weight; or 3) matching placebo. Dupilumab was administered by subcutaneous (SC) injection. If needed to control intolerable symptoms, patients were permitted to receive rescue treatment at the discretion of the investigator. Patients who received rescue treatment were considered non-responders.

In this study, the mean age was 14.5 years, the median weight was 59.4 kg, 41.0 % were female, 62.5% were White, 15.1% were Asian, and 12.0% were Black. At baseline 46.2% of patients had a baseline IGA score of 3 (moderate AD), 53.8% of patients had a baseline IGA of 4 (severe AD), the mean BSA involvement was 56.5%, and 42.4 % of patients had received prior systemic immunosuppressants. Also at baseline the mean Eczema Area and Severity Index (EASI) score was 35.5, the baseline weekly averaged pruritus Numerical Rating Scale (NRS) was 7.6, the baseline mean SCORing Atopic Dermatitis (SCORAD) score was 70.3, the baseline mean Patient Oriented Eczema Measure (POEM) score was 21.0, and the baseline mean Children Dermatology Life Quality Index (CDLQI) was 13.6. Overall, 92.0% of patients had at least one co-morbid allergic condition; 65.6% had allergic rhinitis, 53.6% had asthma, and 60.8% had food allergies. The co-primary endpoint was the proportion of patients with IGA 0 or 1 ("clear" or "almost clear") least a 2-point improvement and the proportion of patients with EASI-75 (improvement of at least 75% in EASI), from baseline to week 16. Other evaluated outcomes included the proportion of subjects with EASI-50 or EASI-90 (improvement of at least 50% or 90% in EASI from baseline respectively), reduction in itch as measured by the peak pruritus NRS, and percent change in the SCORAD scale from baseline to week 16. Additional secondary endpoints included mean change from baseline to week 16 in the POEM and CDLQI scores.

Clinical Response

The efficacy results at week 16 for adolescent atopic dermatitis study are presented in Table 11.

Table 11: 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
<i>Patients randomised</i>	85^a	82^a
IGA 0 or 1 ^b , % responders ^c	2.4%	24.4%
EASI-50, % responders ^c	12.9%	61.0%
EASI-75, % responders ^c	8.2%	41.5%
EASI-90, % responders ^c	2.4%	23.2%
EASI, LS mean % change from baseline (+/-SE)	-23.6% (5.49)	-65.9% (3.99)
SCORAD, LS mean % change from baseline (+/- SE)	-17.6% (3.76)	-51.6% (3.23)
Pruritus NRS, LS mean % change from baseline (+/- SE)	-19.0% (4.09)	-47.9% (3.43)
Pruritus NRS (≥4-point improvement), % responders ^c	4.8%	36.6%
BSA LS mean % change from baseline (+/- SE)	-11.7% (2.72)	-30.1% (2.34)
CDLQI, LS mean change from baseline (+/-SE)	-5.1 (0.62)	-8.5 (0.50)
CDLQI, (≥6-point improvement), % responders	19.7%	60.6%
POEM, LS mean change from baseline (+/- SE)	-3.8 (0.96)	-10.1 (0.76)
POEM, (≥6-point improvement), % responders	9.5%	63.4%

^a Full Analysis Set (FAS) includes all patients 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.

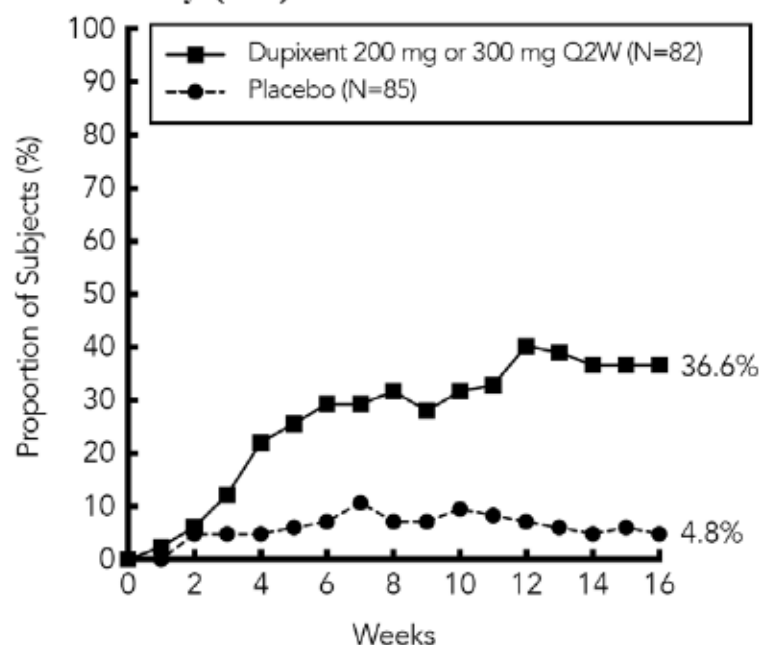
^c Patients who received rescue treatment or with missing data were considered as non-responders (58.8% and 20.7% in the placebo and dupilumab arms, respectively).

All p-values <0.0001

A larger percentage of patients randomised to placebo needed rescue treatment (topical corticosteroids, systemic corticosteroids, or systemic non-steroidal immunosuppressants) as compared to the dupilumab group (58.8% and 20.7%, respectively).

A significantly greater proportion of patients randomised to dupilumab achieved a rapid improvement in the pruritus NRS compared to placebo (defined as ≥4-point improvement as early as week 4; nominal p<0.001) and the proportion of patients responding on the pruritus NRS continued to increase through the treatment period (see Figure 5). The improvement in pruritus NRS occurred in conjunction with the improvement of objective signs of atopic dermatitis.

Figure 5: Proportion of adolescent patients with ≥ 4 -point improvement on the pruritus NRS in AD-1526 study^a (FAS)^b



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

^bFull Analysis Set (FAS) includes all subjects randomised.

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

The long-term efficacy of dupilumab in adolescent patients with moderate-to-severe AD who had participated in previous clinical trials of dupilumab was assessed in open-label extension study (AD-1434). Efficacy data from this study suggests that clinical benefit provided at week 16 was sustained through week 52.

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 biomarker (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 FEV₁ (L). Annualized 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 eosinophils 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. Patients were

randomised to receive either 200 mg (N=631) or 300 mg (N=633) Dupixent every other week (or matching placebo for either 200 mg (N = 317) or 300 mg (N= 321) every other week) following an initial dose of 400 mg, 600 mg or placebo respectively. The primary endpoints were the annualized rate of severe exacerbation events during the 52-week placebo controlled period and change from baseline in pre-bronchodilator FEV₁ at week 12 in the overall population (unrestricted by minimum baseline eosinophils or other type 2 inflammatory biomarkers) and subgroups based on baseline blood eosinophils 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. After optimizing the OCS dose during the screening period, patients received 300 mg dupilumab (n=103) or placebo (n=107) once every other week for 24 weeks following an initial dose of 600 mg or placebo. 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 12 below.

Table 12: Demographics and Baseline Characteristics of Asthma Trials

Parameter	DR12544 (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	77.8	71.4	71.4
≥ 300 cells/mcL	41.9	43.7	42.4

ICS = inhaled corticosteroid; FEV₁ = 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

^aThe 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 13 and Table 14).

Table 13: Rate of Severe Exacerbations in DRI12544 and QUEST (Baseline Blood Eosinophil Levels ≥ 150 and ≥ 300 cells/mcL)

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 ^a (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 ^e (0.34,0.58)	56%	264	0.37 (0.29, 0.48)	0.34 ^e (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)		

^ap-value = 0.0003, ^bp-value = 0.0001, ^cp-value = 0.0116, ^dp-value = 0.0024, ^ep-value <0.0001

Table 14. Rate of Severe Exacerbations in QUEST Defined by Baseline FeNO Subgroups

Treatment	Exacerbations per Year			Percent 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)		

^ap-value <0.0001

In the pooled analysis of DRI12544 and QUEST, hospitalizations 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 FEV₁ were observed at week 12 for DRI12544 and QUEST. There were greater improvements in FEV₁ in the subjects with higher baseline levels of type 2 inflammatory biomarkers such as blood eosinophils or FeNO (Table 15 and Table 16).

Significant improvements in FEV₁ 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 6).

Figure 6: Mean Change from Baseline in Pre-Bronchodilator FEV₁ (L) Over Time (Baseline Eosinophils $\geq$ 150 and $\geq$ 300 cells/mcL and FeNO $\geq$ 25 ppb) in QUEST

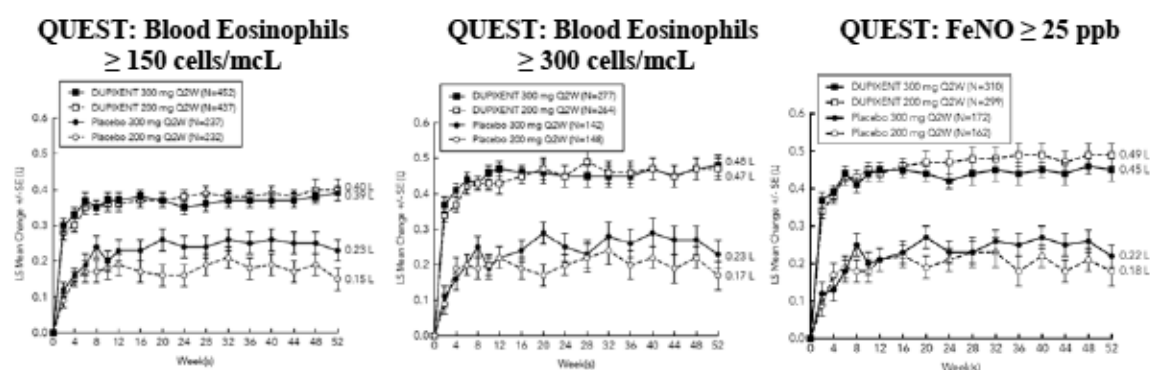


Table 15: Mean Change from Baseline in Pre-Bronchodilator FEV₁ at Week 12 in DRI12544 and QUEST (Baseline Blood Eosinophil Levels ≥ 150 and ≥ 300 cells/mcL)

Treatment	Baseline Blood EOS					
	≥ 150 cells/mcL			≥ 300 cells/mcL		
	N	LS Mean Δ From baseline L (%)	LS Mean Difference vs. placebo (95% CI)	N	LS mean Δ From baseline L (%)	LS Mean Difference vs. placebo (95% CI)
DRI12544 study						
Dupilumab 200 mg Q2W	120	0.32 (18.25)	0.23 ^a (0.13, 0.33)	65	0.43 (25.9)	0.26 ^c (0.11, 0.40)
Dupilumab 300 mg Q2W	129	0.26 (17.1)	0.18 ^b (0.08, 0.27)	64	0.39 (25.8)	0.21 ^d (0.06, 0.36)
Placebo	127	0.09 (4.36)		68	0.18 (10.2)	
QUEST study						
Dupilumab 200 mg Q2W	437	0.36 (23.6)	0.17 ^e (0.11, 0.23)	264	0.43 (29.0)	0.21 ^e (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)	

^ap-value <0.0001, ^bp-value = 0.0004, ^cp-value = 0.0008, ^dp-value = 0.0063, ^ep-value <0.0001

Table 16: Mean Change from Baseline in Pre-Bronchodilator FEV₁ at Week 12 and Week 52 in QUEST by Baseline FeNO Subgroups

QUEST by Baseline FeNO Subgroups					
Treatment	N	At Week 12		At Week 52	
		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%)	

^ap-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). 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. The ACQ-5 and AQLQ(S) responder rate results in patients with elevated baseline biomarkers of type 2 inflammation in QUEST at week 52 are presented in Table 17.

Table 17: 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 12. 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 (annualized 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 FEV₁ 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 18.

Table 18: 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
$\geq 90\%$	58.0	34.8	66.7	34.1	54.4	29.8
$\geq 75\%$	72.8	44.9	77.1	41.5	73.7	36.8
$\geq 50\%$	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)	

^aModel estimates by logistic regression

^bp-value <0.0001

^cp-value $=0.0001$

^dp-value $=0.0002$

Clinical efficacy in chronic rhinosinusitis with nasal polyposis (CRSwNP)

The chronic rhinosinusitis with nasal polyposis (CRSwNP) development program included two randomised, double-blind, parallel-group, multicentre, placebo-controlled studies (SINUS-24 and SINUS-52) in 724 patients aged 18 years and older on background intranasal corticosteroids (INCS). These studies included patients with severe CRSwNP despite prior sino-nasal surgery or treatment with, or who were ineligible to receive, systemic corticosteroids in the past 2 years. Rescue with systemic corticosteroids or surgery was allowed during the studies at the investigator's discretion. In SINUS-24, a total of 276 patients were randomised to receive either 300 mg dupilumab (N=143) or placebo (N=133) every other week for 24 weeks. In SINUS-52, 448 patients were randomised to receive either 300 mg dupilumab (N=150) every other week for 52 weeks, 300 mg dupilumab (N=145) every other week until week 24 followed by 300 mg dupilumab every 4 weeks until week 52, or placebo (N=153). All patients had evidence of sinus opacification on the Lund MacKay (LMK) sinus CT scan and 73% to 90% of patients had opacification of all sinuses. Patients were stratified based on their histories of prior surgery and co-morbid asthma/nonsteroidal anti-inflammatory drug exacerbated respiratory disease (NSAID-ERD).

The co-primary efficacy endpoints were change from baseline to week 24 in bilateral endoscopic nasal polyps score (NPS) as graded by central blinded readers, and change from baseline to week 24 in nasal congestion/obstruction score averaged over 28 days (NC), as determined by patients using a daily

diary. For NPS, polyps on each side of the nose were graded on a categorical scale (0=no polyps; 1=small polyps in the middle meatus not reaching below the inferior border of the middle turbinate; 2=polyps reaching below the lower border of the middle turbinate; 3=large polyps reaching the lower border of the inferior turbinate or polyps medial to the middle turbinate; 4=large polyps causing complete obstruction of the inferior nasal cavity). The total score was the sum of the right and left scores. Nasal congestion was rated daily by the subjects on a 0 to 3 categorical severity scale (0=no symptoms; 1=mild symptoms; 2=moderate symptoms; 3=severe symptoms).

In both studies, key secondary end-points at week 24 included change from baseline in: LMK sinus CT scan score, total symptoms score (TSS), University of Pennsylvania smell identification test (UPSIT), daily loss of smell, and 22-item Sino-Nasal Outcome Test (SNOT-22). In the pool of the two studies, the reduction in the proportion of patients rescued with systemic corticosteroid and/or sino-nasal surgery as well as the improvement in FEV₁ in the asthma subgroup were evaluated. Additional secondary endpoints included 6-item Asthma Control Questionnaire (ACQ-6) in the co-morbid asthma subgroup.

The demographics and baseline characteristics of these 2 studies are provided in Table 19 below.

Table 19: Demographics and Baseline Characteristics of CRSwNP Studies

Parameter	SINUS-24 (N=276)	SINUS-52 (N=448)
Mean age (years) (SD)	50.49 (13.39)	51.95 (12.45)
% Male	57.2	62.3
Mean CRSwNP duration (years)(SD)	11.11 (9.16)	10.94 (9.63)
Patients with ≥ 1 prior surgery (%)	71.7	58.3
Patients with systemic corticosteroid use in the previous 2 years (%)	64.9	80.1
Mean Bilateral endoscopic NPS ^a (SD), range 0–8	5.75 (1.28)	6.10 (1.21)
Mean Nasal congestion (NC) score ^a (SD) range 0–3	2.35 (0.57)	2.43 (0.59)
Mean LMK sinus CT total score ^a (SD), range 0–24	19.03 (4.44)	17.96 (3.76)
Mean Smell test (UPSIT) score ^a (SD), range 0–40	14.56 (8.48)	13.61 (8.02)
Mean loss of smell score ^a (AM), (SD) range 0–3	2.71 (0.54)	2.75 (0.52)
Mean SNOT-22 total score ^a (SD), range 0–110	49.40 (20.20)	51.86 (20.90)
Mean Rhinosinusitis severity scale ^a (VAS), (SD) 0–10 cm	7.68 (2.05)	8.00 (2.08)
Mean blood eosinophils (cells/mcL)(SD)	437 (333)	431 (353)
Mean total IgE IU/mL (SD)	211.97 (275.73)	239.84 (341.53)
Atopic (type 2 inflammatory disease) Medical History % Overall	75.4%	82.4%
Asthma (%)	58.3	59.6
Mean FEV ₁ (L)(SD)	2.69 (0.96)	2.57 (0.83)
Mean FEV ₁ percent predicted (%) (SD)	85.30 (20.23)	83.39 (17.72)
Mean ACQ-6 score ^a (SD)	1.62 (1.14)	1.58 (1.09)
NSAID-ERD (%)	30.4	26.8

^aHigher scores indicate greater disease severity except UPSIT where higher scores indicate lower disease severity; SD=standard deviation; AM = morning; NPS = nasal polyps score; UPSIT = University of Pennsylvania smell identification test; SNOT-22 = 22-item Sino-Nasal Outcome Test; VAS = visual analogue scale; FEV₁ = Forced expiratory volume in 1 second; ACQ-6 = Asthma Control Questionnaire-6; NSAID-ERD= aspirin/nonsteroidal anti-inflammatory drug exacerbated respiratory disease

Clinical Response (SINUS-24 and SINUS-52)

The results for primary and secondary endpoints in CRSwNP studies are presented in the Table 20.

Table 20: Results of the Primary and Secondary Endpoints in CRSwNP trials

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

A reduction in score indicates improvement, except UPSIT where an increase indicates improvement.

Total symptom score is a composite severity score consisting of the sum of daily symptoms of NC, loss of smell, and anterior/posterior rhinorrhoea.

NC = nasal congestion, NPS = nasal polyposis score; LMK = Lund-MacKay total CT score; UPSIT = University of Pennsylvania smell identification test; SNOT-22 = 22-item Sino-Nasal Outcome Test; TSS = total symptom score; VAS = visual analogue scale for rhinosinusitis (all p values <0.0001, nominal for VAS)

The results of SINUS-52 study at week 52 are presented in Table 21.

Table 21: Results of the efficacy at week 52 in SINUS-52 study

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

A reduction in score indicates improvement, except UPSIT where an increase indicates improvement.

Total symptom score is a composite severity score consisting of the sum of daily symptoms of NC, loss of smell, and anterior/posterior rhinorrhoea.

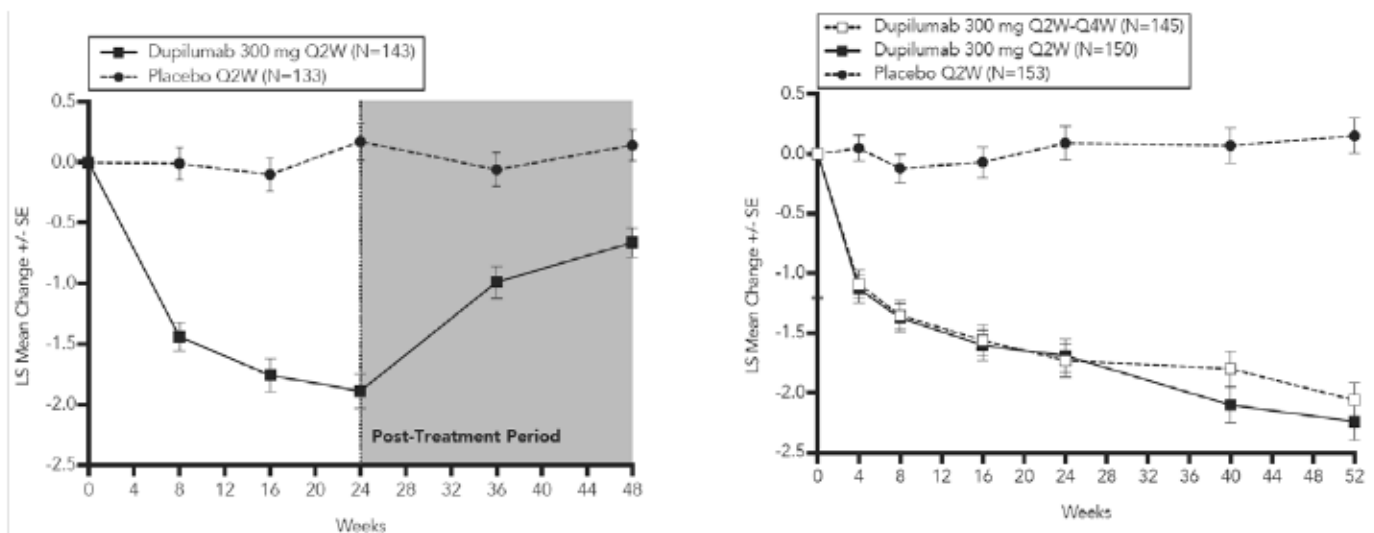
NC = nasal congestion, NPS = nasal polyposis score; LMK = Lund-MacKay total CT score; UPSIT = University of Pennsylvania smell identification test; SNOT-22 = 22-item Sino-Nasal Outcome Test; TSS = total symptom score; VAS = visual analogue scale for rhinosinusitis
(all p values <0.0001)

Statistically significant and clinically meaningful efficacy was observed in SINUS-24 with regard to improvement in bilateral endoscopic NPS score at week 24. In the post-treatment period when patients were off dupilumab, the treatment effect diminished over time (see Figure 7a). Similar results were also seen in SINUS-52 at both week 24 and week 52 with a progressive improvement over time (see Figure 7b).

Figure 7. LS mean change from baseline in bilateral nasal polyps score (NPS) in SINUS-24 and SINUS-52 - ITT population.

Figure 7a. SINUS-24

Figure 7b. SINUS-52

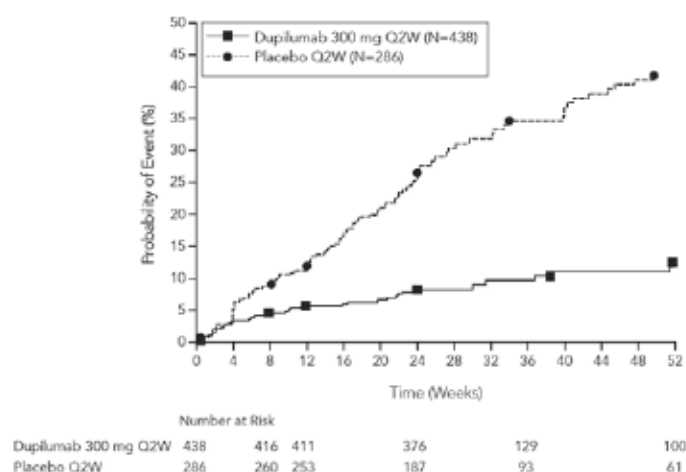


In both studies, significant improvements in NC and daily loss of smell severity were observed as early as the first assessment at week 4. The LS mean difference for NC at week 4 in the dupilumab group versus placebo was -0.41 (95% CI: -0.52, -0.30) in SINUS-24 and -0.37 (95% CI: -0.46, -0.27) in SINUS-52.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

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

In the pre-specified multiplicity-adjusted pooled analysis of two studies, treatment with dupilumab resulted in significant reduction of systemic corticosteroid use and need for sino-nasal surgery versus placebo (HR of 0.24; 95% CI: 0.17, 0.35) (see Figure8). The proportion of patients who required systemic corticosteroids was reduced by 74% (HR of 0.26; 95% CI: 0.18, 0.38). The total number of systemic corticosteroid courses per year was reduced by 75% (RR of 0.25; 95% CI: 0.17, 0.37). The mean individual annualised prescribed total dose of systemic corticosteroids (in mg) during the treatment period was 71% lower in the pooled dupilumab group compared with the pooled placebo group (60.5 [531.3] mg versus 209.5 [497.2] mg, respectively). The proportion of patients who required surgery was reduced by 83% (HR of 0.17; 95% CI: 0.07, 0.46).

Figure 8. Kaplan Meier Curve for time to first systemic corticosteroid use and/or sino-nasal surgery during treatment period - ITT population [SINUS-24 and SINUS-52 pooled]



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

In patients with co-morbid asthma, significant improvements in FEV₁ and ACQ-6 were observed at week 24 irrespective of baseline blood eosinophils levels. The pooled LS Mean change from baseline in FEV₁ at week 24 for dupilumab 300 mg Q2W was 0.14 vs -0.07 L for placebo, for a difference of 0.21 L (95% CI: 0.13, 0.29). In addition, improvements in FEV₁ were noted from the first post-baseline assessment, at week 8 in SINUS-24 and week 4 in SINUS-52. Improvements in ACQ-6 in patients with co-morbid asthma were observed in both studies. A response was defined as an improvement in score of 0.5 or more. The LS mean difference in the dupilumab group versus placebo at week 24 was -0.76 (95% CI: -1.00 to -0.51) in SINUS-24 and -0.94 (95% CI: -1.19, -0.69) in SINUS-52.

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

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

Paediatric population

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 FEV₁ (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. Safety and efficacy in paediatric patients (< 12 years of age) with severe asthma have not been established. The adverse event profile in adolescents was generally similar to the adults.

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 atopic dermatitis and asthma (see section 4.2 for information on paediatric use). The European Medicines Agency has waived the obligation to submit the results of studies with dupilumab in all subsets of the paediatric population in the treatment of nasal polyposis (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

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

Absorption

After a single subcutaneous (SC) dose of 75-600 mg dupilumab, median times to maximum concentration in serum (t_{max}) were 3-7 days. The absolute bioavailability of dupilumab following a SC dose is similar between AD, asthma, and CRSwNP patients, ranging between 61% and 64 %, as determined by a population pharmacokinetics (PK) analysis.

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

Distribution

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

Biotransformation

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

Elimination

Dupilumab elimination is mediated by parallel linear and nonlinear pathways. At higher concentrations, dupilumab elimination is primarily through a non-saturable proteolytic pathway, while at lower concentrations, the non-linear saturable IL-4R α target-mediated elimination predominates. After the last steady state dose, the median time for dupilumab concentrations to decrease below the lower limit of detection, estimated by population PK analysis, was 9 weeks for the 200 mg Q2W, 10-11 weeks for the 300 mg Q2W regimen and 13 weeks for the 300 mg QW regimen.

Linearity/non-linearity

Due to nonlinear clearance, dupilumab exposure, as measured by area under the concentration-time curve, increases with dose in a greater than proportional manner following single SC doses from 75-600 mg.

Special populations

Gender

Gender was not found to be associated with any clinically meaningful impact on the systemic exposure of dupilumab determined by population PK analysis.

Elderly patients

Of the 1,472 patients with atopic dermatitis exposed to dupilumab in a phase 2 dose-ranging study or phase 3 placebo-controlled studies, a total of 67 were 65 years or older. Although no differences in safety or efficacy were observed between older and younger adult atopic dermatitis patients, the number of patients aged 65 and over is not sufficient to determine whether they respond differently from younger patients.

Age was not found to be associated with any clinically meaningful impact on the systemic exposure of dupilumab determined by population PK analysis. However, there were only 61 patients over 65 years of age included in this analysis.

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

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

Race

Race was not found to be associated with any clinically meaningful impact on the systemic exposure of dupilumab by population PK analysis.

Hepatic impairment

Dupilumab, as a monoclonal antibody, is not expected to undergo significant hepatic elimination. No clinical studies have been conducted to evaluate the effect of hepatic impairment on the pharmacokinetics of dupilumab.

Renal impairment

Dupilumab, as a monoclonal antibody, is not expected to undergo significant renal elimination. No clinical studies have been conducted to evaluate the effect of renal impairment on the pharmacokinetics of dupilumab. Population PK analysis did not identify mild or moderate renal impairment as having a clinically meaningful influence on the systemic exposure of dupilumab. Very limited data are available in patients with severe renal impairment.

Body Weight

Dupilumab trough concentrations were lower in subjects with higher body weight with no meaningful impact on efficacy. There were only 6 patients exposed to dupilumab with body weight ≥ 130 kg in CRSwNP clinical studies.

Paediatric population

The pharmacokinetics of dupilumab in paediatric patients (< 12 years of age) 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 $\pm$ SD steady state trough concentration of dupilumab was 54.5 ± 27.0 mcg/mL.

A total of 107 adolescents aged 12 to 17 years with asthma were enrolled in QUEST study. The mean $\pm$ 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.

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

5.3 Preclinical safety data

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

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

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

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

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

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

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

arginine hydrochloride
histidine
polysorbate 80 (E433)
sodium acetate trihydrate
glacial acetic acid (E260)
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

30 months.

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

6.4 Special precautions for storage

Store 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

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

Dupixent 300 mg solution for injection in pre-filled syringe

Pack size:

- 1 pre-filled syringe

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

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

The instructions for the preparation and administration of Dupixent in a pre-filled syringe are given in the package leaflet.

The solution should be clear to slightly opalescent, colourless to pale yellow. If the solution is cloudy, discoloured or contains visible particulate matter, the solution should not be used.

After removing the 300 mg pre-filled syringe from the refrigerator, it should be allowed to reach room temperature up to 25°C by waiting for 45 min before injecting Dupixent.

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

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

7. MARKETING AUTHORISATION HOLDER

sanofi-aventis groupe
54, rue La Boétie
75008 Paris
France

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/17/1229/001
EU/1/17/1229/002
EU/1/17/1229/003
EU/1/17/1229/004
EU/1/17/1229/005
EU/1/17/1229/006
EU/1/17/1229/007
EU/1/17/1229/008

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 26 September 2017

10. DATE OF REVISION OF THE TEXT

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

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

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Dupilumab 200 mg solution for injection in pre-filled syringe

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

Dupilumab 200 mg solution for injection in pre-filled pen

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

Dupilumab is a fully human monoclonal antibody against interleukin (IL)-4 receptor alpha that inhibits IL-4/IL-13 signalling, produced in Chinese Hamster Ovary (CHO) cells by recombinant DNA technology.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection (injection)

Clear to slightly opalescent, colourless to pale yellow solution, which is free from visible particulates.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Atopic dermatitis

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.

Asthma

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 FeNO (see section 5.1), who are inadequately controlled with high dose ICS plus another medicinal product for maintenance treatment.

4.2 Posology and method of administration

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

Posology

Atopic Dermatitis

Adolescents

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 years 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

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.

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

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.

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

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

Missed dose

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

Special populations

Elderly patients (≥ 65 years)

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

Renal impairment

No dose adjustment is needed in patients with mild or moderate renal impairment. Very limited data are available in patients with severe renal impairment (see section 5.2).

Hepatic impairment

No data are available in patients with hepatic impairment (see section 5.2).

Body weight

No dose adjustment for body weight is recommended for patients with asthma 12 years of age and older or in adults with atopic dermatitis (see section 5.2).

For patients 12 to 17 years of age with atopic dermatitis, the recommended every other week dose is 200 mg (<60 kg) or 300 mg (≥60 kg).

Paediatric patients

The safety and efficacy of dupilumab in children with atopic dermatitis below the age of 12 years have not been established (see section 5.2). No data are available.

The safety and efficacy of dupilumab in children with severe asthma below the age of 12 years have not been established (see section 5.2). No data are available.

Method of administration

Subcutaneous use

Dupilumab is administered by subcutaneous injection into the thigh or abdomen, except for the 5 cm around the navel. If somebody else administers the injection, the upper arm can also be used.

For the initial 400 mg dose, two 200 mg injections should be administered consecutively in different injection sites.

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

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

4.3 Contraindications

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

4.4 Special warnings and precautions for use

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

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

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

Traceability

In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded.

Hypersensitivity

If a systemic hypersensitivity reaction (immediate or delayed) occurs, administration of dupilumab should be discontinued immediately and appropriate therapy initiated. Very rare cases of serum sickness/serum sickness-like reactions have been reported in the atopic dermatitis development program following the administration of dupilumab. Anaphylactic reaction has been reported very rarely in the asthma development program following the administration of dupilumab (section 4.8).

Eosinophilic conditions

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

Helminth infection

Patients with known helminth infections were excluded from participation in clinical studies. Dupilumab may influence the immune response against helminth infections by inhibiting IL-4/IL-13 signaling. Patients with pre-existing helminth infections should be treated before initiating dupilumab. If patients become infected while receiving treatment with dupilumab and do not respond to anti-helminth treatment, treatment with dupilumab should be discontinued until infection resolves.

Conjunctivitis related events

Patients treated with dupilumab who develop conjunctivitis that does not resolve following standard treatment should undergo ophthalmological examination (section 4.8).

Atopic dermatitis patients with comorbid asthma

Patients on dupilumab for moderate-to-severe atopic dermatitis who also have comorbid asthma should not adjust or stop their asthma treatments without consultation with their physicians. Patients with comorbid asthma should be monitored carefully following discontinuation of dupilumab.

Vaccinations

Live and live attenuated vaccines should not be given concurrently with dupilumab as clinical safety and efficacy has not been established. Immune responses to Tdap vaccine and meningococcal polysaccharide vaccine were assessed, see section 4.5. It is recommended that patients should be brought up to date with live and live attenuated immunisations in agreement with current immunisation guidelines prior to treatment with dupilumab.

Sodium content

This medicinal product contains less than 1 mmol sodium (23 mg) per 200 mg dose, i.e. essentially "sodium-free".

4.5 Interaction with other medicinal products and other forms of interaction

Immune responses to vaccination were assessed in a study in which patients with atopic dermatitis were treated once weekly for 16 weeks with 300 mg of dupilumab. After 12 weeks of dupilumab administration, patients were vaccinated with a Tdap vaccine (T cell-dependent), and a meningococcal polysaccharide vaccine (T cell-independent) and immune responses were assessed 4 weeks later. Antibody responses to both tetanus vaccine and meningococcal polysaccharide vaccine were similar in dupilumab-treated and placebo-treated patients. No adverse interactions between either of the non-live vaccines and dupilumab were noted in the study.

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

In a clinical study of AD patients, the effects of dupilumab on the pharmacokinetics (PK) of CYP substrates were evaluated. The data gathered from this study did not indicate clinically relevant effects of dupilumab on CYP1A2, CYP3A, CYP2C19, CYP2D6, or CYP2C9 activity.

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

4.6 Fertility, pregnancy and lactation

Pregnancy

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

Breast-feeding

It is unknown whether dupilumab is excreted in human milk or absorbed systemically after ingestion. A decision must be made whether to discontinue breast-feeding or to discontinue dupilumab therapy taking into account the benefit of breast feeding for the child and the benefit of therapy for the woman.

Fertility

Animal studies showed no impairment of fertility (see section 5.3).

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

Atopic dermatitis

Adults with atopic dermatitis

Summary of the safety profile

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

In the monotherapy studies, the proportion of patients who discontinued treatment due to adverse events was 1.9 % of the placebo group, 1.9 % of the dupilumab 300 mg Q2W group, 1.5 % of the dupilumab 300 mg QW group. In the concomitant TCS study, the proportion of patients who discontinued treatment due to adverse events was 7.6 % of the placebo + TCS group, 1.8 % of the dupilumab 300 mg Q2W + TCS group, and 2.9 % of the dupilumab 300 mg QW + TCS group.

Tabulated list of adverse reactions

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

Listed in Table 2 are adverse reactions observed in atopic dermatitis clinical trials presented by system organ class and frequency, using the following categories: very common ($\geq 1/10$); common ($\geq 1/100$ to $< 1/10$); uncommon ($\geq 1/1,000$ to $< 1/100$); rare ($\geq 1/10,000$ to $< 1/1,000$); very rare ($< 1/10,000$). Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Table 2: List of adverse reactions in atopic dermatitis

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

Adolescents with atopic dermatitis

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.

The long-term safety of dupilumab was assessed in an open-label extension study in patients 12 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 AD-1526 study. The long-term safety profile of dupilumab observed in adolescents was consistent with that seen in adults with atopic dermatitis.

Asthma

Summary of the safety profile

The most common adverse reaction was injection site erythema. Anaphylactic reaction has been reported very rarely in the asthma development program (see section 4.4).

In DRI12544 and QUEST studies, the proportion of patients who discontinued treatment due to adverse events was 4.3% of the placebo group, 3.2% of the dupilumab 200 mg Q2W group, and 6.1% of the dupilumab 300 mg Q2W group.

Tabulated list of adverse reactions

A total of 2,888 adult and adolescent patients with moderate-to-severe asthma were evaluated in 3 randomised, placebo-controlled, multicentre trials of 24 to 52 weeks duration (DRI12544, QUEST, and VENTURE). Of these, 2,678 had a history of 1 or more severe exacerbations in the year prior to enrolment despite regular use of medium-to-high dose inhaled corticosteroids plus an additional controller(s) (DRI12544 and QUEST). A total of 210 patients with oral corticosteroid-dependent asthma receiving high-dose inhaled corticosteroids plus up to two additional controllers were enrolled (VENTURE).

Listed in Table 3 are adverse reactions observed in asthma clinical trials presented by system organ class and frequency, using the following categories: very common ($\geq 1/10$); common ($\geq 1/100$ to $< 1/10$); uncommon ($\geq 1/1,000$ to $< 1/100$); rare ($\geq 1/10,000$ to $< 1/1,000$); very rare ($< 1/10,000$). Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Table 3: List of adverse reactions in asthma

MedDRA System Organ Class	Frequency	Adverse Reaction
<i>Immune system disorders</i>	Very rare	Anaphylactic reaction
<i>General disorders and administration site conditions</i>	Very common	Injection site erythema
	Common	Injection site oedema
	Common	Injection site pain
	Common	Injection site pruritus

Description of selected adverse reactions in atopic dermatitis and asthma indications

Hypersensitivity

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

Conjunctivitis and related events

Conjunctivitis occurred more frequently in atopic dermatitis patients who received dupilumab. Most patients with conjunctivitis recovered or were recovering during the treatment period. Among asthma patients frequency of conjunctivitis was low and similar between dupilumab and placebo (see section 4.4).

Eczema herpeticum

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

Eosinophilia

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

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

Infections

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

Immunogenicity

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

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

Approximately 6 % of patients with atopic dermatitis or asthma who received dupilumab 300 mg Q2W for 52 weeks developed ADA to dupilumab; approximately 2 % exhibited persistent ADA responses and approximately 2 % had neutralizing antibodies.

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

Less than 0.4 % of patients exhibited high titer ADA responses associated with reduced exposure and efficacy. In addition, there was one patient with serum sickness and one with serum sickness-like reaction (< 0.1 %) associated with high ADA titers (see section 4.4).

Paediatric population

The safety profile observed in the adolescents aged 12 to 17 years in atopic dermatitis clinical trials was similar to that seen in adults.

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.

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 national reporting system listed in Appendix V.

4.9 Overdose

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

Mechanism of action

Dupilumab is a recombinant human IgG4 monoclonal antibody that inhibits interleukin-4 and interleukin-13 signaling. Dupilumab inhibits IL-4 signaling via the Type I receptor (IL-4R α / γ c), and both IL-4 and IL-13 signaling through the Type II receptor (IL-4R α /IL-13R α). IL-4 and IL-13 are major drivers of human type 2 inflammatory disease, such as atopic dermatitis and asthma. Blocking the IL-4/IL-13 pathway with dupilumab in patients decreases many of the mediators of type 2 inflammation.

Pharmacodynamic effects

In atopic dermatitis clinical trials, treatment with dupilumab was associated with decreases from baseline in concentrations of type 2 immunity biomarkers, such as thymus and activation-regulated chemokine (TARC/CCL17), total serum IgE and allergen-specific IgE in serum. A reduction of lactate dehydrogenase (LDH), a biomarker associated with AD disease activity and severity, was observed with dupilumab treatment.

In asthma clinical trials, dupilumab treatment markedly decreased FeNO and circulating concentrations of eotaxin-3, total IgE, allergen specific IgE, TARC, and periostin in asthma subjects relative to placebo. These reductions in type 2 inflammatory biomarkers were comparable for the 200 mg Q2W and 300 mg Q2W regimens. 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

The efficacy and safety of dupilumab monotherapy in adolescent patients was evaluated in a multicentre, randomised, double-blind, placebo-controlled study (AD-1526) in 251 adolescent patients 12 to 17 years of age with moderate-to-severe atopic dermatitis (AD) defined by Investigator's Global Assessment (IGA) score ≥ 3 in the overall assessment of AD lesions on a severity scale of 0 to 4, an Eczema Area and Severity Index (EASI) score ≥ 16 on a scale of 0 to 72, and a minimum body surface area (BSA) involvement of $\geq 10\%$. Eligible patients enrolled into this study had previous inadequate response to topical medication.

Patients received 1) an initial dose of 400 mg dupilumab (two 200 mg injections) on day 1, followed by 200 mg once every other week (Q2W) for patients with baseline weight of < 60 kg or an initial dose of 600 mg dupilumab (two 300 mg injections) on day 1, followed by 300 mg Q2W for patients with baseline weight of ≥ 60 kg; 2) an initial dose of 600 mg dupilumab (two 300 mg injections) on day 1, followed by 300 mg every 4 weeks (Q4W) regardless of baseline body weight; or 3) matching placebo. Dupilumab was administered by subcutaneous (SC) injection. If needed to control intolerable symptoms, patients were permitted to receive rescue treatment at the discretion of the investigator. Patients who received rescue treatment were considered non-responders.

In this study, the mean age was 14.5 years, the median weight was 59.4 kg, 41.0 % were female, 62.5% were White, 15.1% were Asian, and 12.0% were Black. At baseline 46.2% of patients had a baseline IGA score of 3 (moderate AD), 53.8% of patients had a baseline IGA of 4 (severe AD), the mean BSA involvement was 56.5%, and 42.4 % of patients had received prior systemic immunosuppressants. Also at baseline the mean Eczema Area and Severity Index (EASI) score was 35.5, the baseline weekly averaged pruritus Numerical Rating Scale (NRS) was 7.6, the baseline mean SCORing Atopic Dermatitis (SCORAD) score was 70.3, the baseline mean Patient Oriented Eczema Measure (POEM) score was 21.0, and the baseline mean Children Dermatology

Life Quality Index (CDLQI) was 13.6. Overall, 92.0% of patients had at least one co-morbid allergic condition; 65.6% had allergic rhinitis, 53.6% had asthma, and 60.8% had food allergies. The co-primary endpoint was the proportion of patients with IGA 0 or 1 ("clear" or "almost clear") least a 2-point improvement and the proportion of patients with EASI-75 (improvement of at least 75% in EASI), from baseline to week 16. Other evaluated outcomes included the proportion of subjects with EASI-50 or EASI-90 (improvement of at least 50% or 90% in EASI from baseline respectively), reduction in itch as measured by the peak pruritus NRS, and percent change in the SCORAD scale from baseline to week 16. Additional secondary endpoints included mean change from baseline to week 16 in the POEM and CDLQI scores.

Clinical Response

The efficacy results at week 16 for adolescent atopic dermatitis study are presented in Table 4.

Table 4: 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%
EASI-50, % responders ^c	12.9%	61.0%
EASI-75, % responders ^c	8.2%	41.5%
EASI-90, % responders ^c	2.4%	23.2%
EASI, LS mean % change from baseline (+/-SE)	-23.6% (5.49)	-65.9% (3.99)
SCORAD, LS mean % change from baseline (+/- SE)	-17.6% (3.76)	-51.6% (3.23)
Pruritus NRS, LS mean % change from baseline (+/- SE)	-19.0% (4.09)	-47.9% (3.43)
Pruritus NRS (≥4-point improvement), % responders ^c	4.8%	36.6%
BSA LS mean % change from baseline (+/- SE)	-11.7% (2.72)	-30.1% (2.34)
CDLQI, LS mean change from baseline (+/-SE)	-5.1 (0.62)	-8.5 (0.50)
CDLQI, (≥6-point improvement), % responders	19.7%	60.6%
POEM, LS mean change from baseline (+/- SE)	-3.8 (0.96)	-10.1 (0.76)
POEM, (≥6-point improvement), % responders	9.5%	63.4%

^a Full Analysis Set (FAS) includes all patients 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).

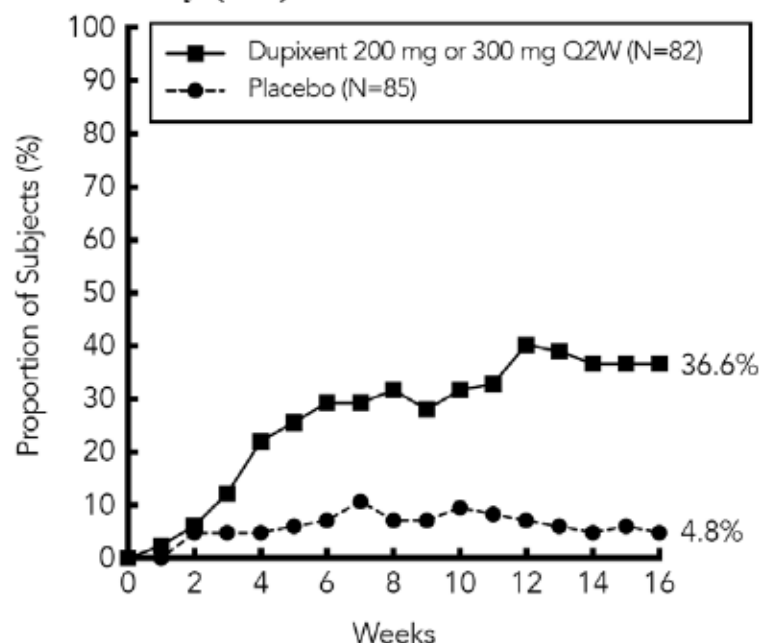
All p-values <0.0001

A larger percentage of patients randomised to placebo needed rescue treatment (topical corticosteroids, systemic corticosteroids, or systemic non-steroidal immunosuppressants) as compared to the dupilumab group (58.8% and 20.7%, respectively).

A significantly greater proportion of patients randomised to dupilumab achieved a rapid improvement in the pruritus NRS compared to placebo (defined as ≥4-point improvement as early as week 4; nominal p<0.001) and the proportion of patients responding on the pruritus NRS continued to increase

through the treatment period (see Figure 1). The improvement in pruritus NRS occurred in conjunction with the improvement of objective signs of atopic dermatitis.

Figure 1: Proportion of adolescent patients with ≥ 4 -point improvement on the pruritus NRS in AD-1526 study^a (FAS)^b



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

^bFull Analysis Set (FAS) includes all subjects randomised.

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

The long-term efficacy of dupilumab in adolescent patients with moderate-to-severe AD who had participated in previous clinical trials of dupilumab was assessed in open-label extension study (AD-1434). Efficacy data from this study suggests that clinical benefit provided at week 16 was sustained through week 52.

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 FEV₁ (L). Annualized 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. Patients were randomised to receive either 200 mg (N=631) or 300 mg (N=633) Dupixent every other week (or matching placebo for either 200 mg (N = 317) or 300 mg (N= 321) every other week) following an initial dose of 400 mg, 600 mg or placebo respectively. The primary endpoints were the annualized rate of severe exacerbation events during the 52-week placebo controlled period and change from baseline in pre-bronchodilator FEV₁ at week 12 in the overall population (unrestricted by minimum baseline eosinophils or other type 2 inflammatory biomarkers) and subgroups based on baseline blood eosinophils 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. After optimizing the OCS dose during the screening period, patients received 300 mg dupilumab (n=103) or placebo (n=107) once every other week for 24 weeks following an initial dose of 600 mg or placebo. 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 5 below.

Table 5: 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 $\pm$ 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 $\pm$ 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 $\pm$ SD	1.84 (0.54)	1.78 (0.60)	1.58 (0.57)
Mean percent predicted FEV ₁ at baseline (%) ($\pm$ SD)	60.77 (10.72)	58.43 (13.52)	52.18 (15.18)
% Reversibility ($\pm$ SD)	26.85 (15.43)	26.29 (21.73)	19.47 (23.25)
Mean ACQ-5 score ($\pm$ SD)	2.74 (0.81)	2.76 (0.77)	2.50 (1.16)
Mean AQLQ score ($\pm$ 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 ($\pm$ 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 ($\pm$ SD)	435.05 (753.88)	432.40 (746.66)	430.58 (775.96)
Mean baseline Eosinophil count ($\pm$ 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; FEV₁ = 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

^aThe 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 6 and Table 7).

Table 6: 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 ^e (0.34,0.58)	56%	264	0.37 (0.29, 0.48)	0.34 ^e (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)		

^ap-value = 0.0003, ^bp-value = 0.0001, ^cp-value = 0.0116, ^dp-value = 0.0024, ^ep-value <0.0001

Table 7: Rate of Severe Exacerbations in QUEST Defined by Baseline FeNO Subgroups

Treatment	Exacerbations per Year			Percent 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)		

^ap-value <0.0001

In the pooled analysis of DRI12544 and QUEST, hospitalizations 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 FEV₁ were observed at week 12 for DRI12544 and QUEST. There were greater improvements in FEV₁ in the subjects with higher baseline levels of type 2 inflammatory biomarkers such as blood eosinophils or FeNO (Table 8 and Table 9).

Significant improvements in FEV₁ 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 2).

Figure 2: Mean Change from Baseline in Pre-Bronchodilator FEV₁ (L) Over Time (Baseline Eosinophils ≥ 150 and ≥ 300 cells/mcL and FeNO ≥ 25 ppb) in QUEST

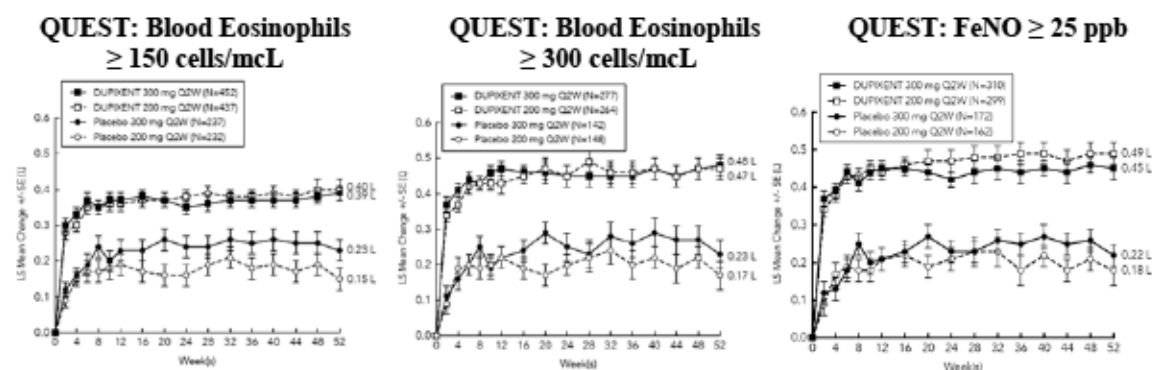


Table 8: Mean Change from Baseline in Pre-Bronchodilator FEV₁ at Week 12 in DRI12544 and QUEST (Baseline Blood Eosinophil Levels ≥ 150 and ≥ 300 cells/mcL)

Treatment	Baseline Blood EOS					
	≥ 150 cells/mcL			≥ 300 cells/mcL		
	N	LS Mean Δ From baseline L (%)	LS Mean Difference vs. placebo (95% CI)	N	LS mean Δ From baseline L (%)	LS Mean Difference vs. placebo (95% CI)
DRI12544 study						
Dupilumab 200 mg Q2W	120	0.32 (18.25)	0.23 ^a (0.13, 0.33)	65	0.43 (25.9)	0.26 ^c (0.11, 0.40)
Dupilumab 300 mg Q2W	129	0.26 (17.1)	0.18 ^b (0.08, 0.27)	64	0.39 (25.8)	0.21 ^d (0.06, 0.36)
Placebo	127	0.09 (4.36)		68	0.18 (10.2)	
QUEST study						
Dupilumab 200 mg Q2W	437	0.36 (23.6)	0.17 ^e (0.11, 0.23)	264	0.43 (29.0)	0.21 ^e (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)	

^ap-value <0.0001, ^bp-value = 0.0004, ^cp-value = 0.0008, ^dp-value = 0.0063, ^ep-value <0.0001

Table 9: Mean Change from Baseline in Pre-Bronchodilator FEV₁ at Week 12 and Week 52 in QUEST by Baseline FeNO Subgroups

Treatment		At Week 12		At Week 52	
	N	LS Mean Δ ^a From baseline L (%)	LS Mean Difference vs. placebo (95% CI)	LS Mean Δ ^a 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%)	

^ap-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). 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. The ACQ-5 and AQLQ(S) responder rate results in patients with elevated baseline biomarkers of type 2 inflammation in QUEST at week 52 are presented in Table 10.

Table 10: 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 5. 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 (annualized 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 FEV₁ 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 11.

Table 11: 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
$\geq 90\%$	58.0	34.8	66.7	34.1	54.4	29.8
$\geq 75\%$	72.8	44.9	77.1	41.5	73.7	36.8
$\geq 50\%$	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)	

^aModel estimates by logistic regression

^bp-value <0.0001

^cp-value =0.0001

^dp-value =0.0002

Paediatric population

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 FEV₁ (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. Safety and efficacy in paediatric patients (< 12 years of age) with severe asthma have not been established. The adverse event profile in adolescents was generally similar to the adults.

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 atopic dermatitis and asthma (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

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

Absorption

After a single subcutaneous (SC) dose of 75-600 mg dupilumab, median times to maximum concentration in serum (t_{max}) were 3-7 days. The absolute bioavailability of dupilumab following a SC dose is similar between AD and asthma patients, ranging between 61% and 64 %, as determined by a population pharmacokinetics (PK) analysis.

Steady-state concentrations were achieved by week 16 following the administration of 600 mg starting dose and 300 mg dose every other week. Across clinical trials, the mean $\pm$ SD steady-state trough concentrations ranged from 60.3 $\pm$ 35.1 mcg/mL to 79.9 $\pm$ 41.4 mcg/mL for 300 mg dose and from 29.2 $\pm$ 18.7 to 36.5 $\pm$ 22.2 mcg/mL for 200 mg dose administered every other week.

Distribution

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

Biotransformation

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

Elimination

Dupilumab elimination is mediated by parallel linear and nonlinear pathways. At higher concentrations, dupilumab elimination is primarily through a non-saturable proteolytic pathway, while at lower concentrations, the non-linear saturable IL-4R α target-mediated elimination predominates. After the last steady state dose, the median time for dupilumab concentrations to decrease below the lower limit of detection, estimated by population PK analysis, was 9 weeks for the 200 mg Q2W, 10-11 weeks for the 300 mg Q2W regimen and 13 weeks for the 300 mg QW regimen.

Linearity/non-linearity

Due to nonlinear clearance, dupilumab exposure, as measured by area under the concentration-time curve, increases with dose in a greater than proportional manner following single SC doses from 75-600 mg.

Special populations

Gender

Gender was not found to be associated with any clinically meaningful impact on the systemic exposure of dupilumab determined by population PK analysis.

Elderly patients

Of the 1,472 patients with atopic dermatitis exposed to dupilumab in a phase 2 dose-ranging study or phase 3 placebo-controlled studies, a total of 67 were 65 years or older. Although no differences in safety or efficacy were observed between older and younger adult atopic dermatitis patients, the number of patients aged 65 and over is not sufficient to determine whether they respond differently from younger patients.

Age was not found to be associated with any clinically meaningful impact on the systemic exposure of dupilumab determined by population PK analysis. However, there were only 61 patients over 65 years of age included in this analysis.

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

Race

Race was not found to be associated with any clinically meaningful impact on the systemic exposure of dupilumab by population PK analysis.

Hepatic impairment

Dupilumab, as a monoclonal antibody, is not expected to undergo significant hepatic elimination. No clinical studies have been conducted to evaluate the effect of hepatic impairment on the pharmacokinetics of dupilumab.

Renal impairment

Dupilumab, as a monoclonal antibody, is not expected to undergo significant renal elimination. No clinical studies have been conducted to evaluate the effect of renal impairment on the pharmacokinetics of dupilumab. Population PK analysis did not identify mild or moderate renal impairment as having a clinically meaningful influence on the systemic exposure of dupilumab. Very limited data are available in patients with severe renal impairment.

Body Weight

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

Paediatric population

The pharmacokinetics of dupilumab in paediatric patients (< 12 years of age) 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.

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.

5.3 Preclinical safety data

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

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

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

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

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

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

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

arginine hydrochloride
histidine
polysorbate 80 (E433)
sodium acetate trihydrate
glacial acetic acid (E260)
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

18 months.

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

6.4 Special precautions for storage

Store 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 or pre-filled pen, with a fixed 27 gauge 12.7 mm (½ inch), thin wall stainless steel staked needle.

Dupixent 200 mg solution for injection in pre-filled syringe

Pack size:

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

Dupixent 200 mg solution for injection in pre-filled pen

Pack size:

- 1 pre-filled pen
- 2 pre-filled pens
- 3 pre-filled pens
- 6 pre-filled pens

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

The instructions for the preparation and administration of Dupixent in a pre-filled syringe or in a pre-filled pen are given in the package leaflet.

The solution should be clear to slightly opalescent, colourless to pale yellow. If the solution is cloudy, discoloured or contains visible particulate matter, the solution should not be used.

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

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

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

7. MARKETING AUTHORISATION HOLDER

sanofi-aventis groupe
54, rue La Boétie
75008 Paris
France

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/17/1229/009
EU/1/17/1229/010

EU/1/17/1229/011
EU/1/17/1229/012
EU/1/17/1229/013
EU/1/17/1229/014
EU/1/17/1229/015
EU/1/17/1229/016

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 26 September 2017

10. DATE OF REVISION OF THE TEXT

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

サノフィ株式会社

デュピルマブ（遺伝子組換え）

1.7 同種同効品一覧

※ 最新の添付文書を参照してください。

Total number of pages: 2

1.7 同種同効品一覧

SAR231893 – デュピルマブ（遺伝子組換え）

鼻茸を伴う慢性副鼻腔炎（CRSwNP）に対する利用可能な治療法は、鼻用ステロイド薬の長期使用、症状が悪化した場合の全身性ステロイド薬（SCS）の短期使用、あるいは手術に限られる。これらの治療選択肢には大きな制約があり、この疾患の一部（すなわち鼻腔内の局所炎症）のみを治療していることから、鼻茸を生じさせる根本的な要因である副鼻腔の炎症性疾患を治療することはできない。唯一の全身療法である SCS は、長期使用に伴う副作用がよく知られているため、間欠的にのみ使用される。その結果、本疾患を引き起こす根本的な炎症反応は既存治療では十分に抑制されず、不十分な治療効果、鼻茸の手術後の高い再発率、全体的な健康関連 QoL の低下をもたらす。こうしたことから、本疾患を引き起こす Type 2 炎症を安全かつ効果的に抑制することができ、CRSwNP の臨床症状全てを治療し、SCS 及び手術の必要性を最小限にし、併存疾患（特に喘息）の負荷を低減することのできる治療薬が期待されている。

デュピルマブ（遺伝子組換え）（以下、デュピルマブ）は、インターロイキン（IL）-4 受容体 α サブユニット（IL-4R α ）に特異的に結合することにより、Type 2 炎症の重要な誘発因子であり CRSwNP に特徴的なエフェクター細胞（例：肥満細胞、好酸球、マクロファージ、リンパ球、上皮細胞、杯細胞）を動員する IL-4 及び IL-13 シグナル伝達を阻害する新規の作用機序となる標的免疫調整薬で、鼻用ステロイド薬や SCS といった既存の治療薬とは投与経路も異なる薬剤であり、既存療法に用いられている SCS 及び手術の必要性を最小限にし、併存疾患（特に喘息）の負荷を低減することが期待できる薬剤であることから、現時点で承認されている同種同効品は存在しない。

貯 法: 凍結を避け、2~8℃にて保存

有効期間: 24 箇月

生物由来製品、劇薬、処方箋医薬品: 注意—医師等の処方箋により使用すること

ヒト型抗ヒト IL-4/13 受容体モノクローナル抗体
デュピルマブ (遺伝子組換え) 製剤
デュピクセント®皮下注 300mg シリンジ
DUPIXENT® S.C. Injection

SANOFI

1. 警告

本剤の投与は、適応疾患の治療に精通している医師のもとで行うこと。

2. 禁忌 (次の患者には投与しないこと)

本剤の成分に対し過敏症の既往歴のある患者

3. 組成・性状

3.1 組成

成分	1 シリンジ (2mL) 中の分量
有効成分	デュピルマブ (遺伝子組換え) ^(注1)
	300mg
添加剤	L-ヒスチジン、L-ヒスチジン塩酸塩水和物
	6.2mg ^(注2)
	L-アルギニン塩酸塩
	8.7mg ^(注3)
	酢酸ナトリウム水和物、水酢酸
	1.5mg ^(注4)
	精製白糖
	100mg
	ポリソルベート 80
	4mg

注1) 本剤は遺伝子組換え技術によりチャイニーズハムスター卵巣細胞を用いて製造される。

注2) L-ヒスチジンと L-ヒスチジン塩酸塩水和物の合計量を L-ヒスチジンとしての量として示す。

注3) L-アルギニン塩酸塩の分量を L-アルギニンとしての量として示す。

注4) 酢酸ナトリウム水和物と水酢酸の合計量を酢酸イオンとしての量として示す。

3.2 製剤の性状

性状・剤形	無色～微黄色の澄明又はわずかに乳白光を呈する液 (注射剤)
pH	5.6~6.2
浸透圧比	約 1.0 (生理食塩液に対する比)

4. 効能又は効果

- 既存治療で効果不十分なアトピー性皮膚炎
- 気管支喘息 (既存治療によっても喘息症状をコントロールできない重症又は難治の患者に限る)
- 鼻茸を伴う慢性副鼻腔炎 (既存治療で効果不十分な患者に限る)

5. 効能又は効果に関連する注意

〈アトピー性皮膚炎〉

- 5.1 ステロイド外用剤やタクロリムス外用剤等の抗炎症外用剤による適切な治療を一定期間施行しても、十分な効果が得られず、強い炎症を伴う皮疹が広範囲に及ぶ患者に用いること。
[17.1.1、17.1.2 参照]

- 5.2 原則として、本剤投与時にはアトピー性皮膚炎の病変部位の状態に応じて抗炎症外用剤を併用すること。

- 5.3 本剤投与時も保湿外用剤を継続使用すること。

〈気管支喘息〉

- 5.4 最新のガイドライン等を参考に、中用量又は高用量の吸入ステロイド薬とその他の長期管理薬を併用しても、全身性ステロイド薬の投与等が必要な喘息増悪をきたす患者に本剤を追加して投与すること。

- 5.5 本剤は IL-4 及び IL-13 シグナル伝達を阻害することにより、喘息の病態に関与する 2 型炎症反応を抑制することから、臨床試験で認められた本剤投与前の 2 型炎症に関連するバイオマーカー (血中好酸球数、FeNO、IgE 等) の値と有効性の関係を十分に理解し、患者の当該バイオマーカーの値を考慮した上で、適応患者の選択を行うこと。[17.1.3 参照]

- 5.6 本剤は既に起きている気管支喘息の発作や症状を速やかに軽減する薬剤ではないので、急性の発作に対しては使用しないこと。

〈鼻茸を伴う慢性副鼻腔炎〉

- 5.7 本剤は全身性ステロイド薬、手術等ではコントロールが不十分な患者に用いること。

6. 用法及び用量

〈アトピー性皮膚炎〉

通常、成人にはデュピルマブ (遺伝子組換え) として初回に 600mg を皮下投与し、その後は 1 回 300mg を 2 週間隔で皮下投与する。

〈気管支喘息〉

通常、成人及び 12 歳以上の小児にはデュピルマブ (遺伝子組換え) として初回に 600mg を皮下投与し、その後は 1 回 300mg を 2 週間隔で皮下投与する。

〈鼻茸を伴う慢性副鼻腔炎〉

通常、成人にはデュピルマブ (遺伝子組換え) として 1 回 300mg を 2 週間隔で皮下投与する。なお、症状安定後には、1 回 300mg を 4 週間隔で皮下投与できる。

7. 用法及び用量に関連する注意

〈アトピー性皮膚炎〉

- 7.1 本剤による治療反応は、通常投与開始から 16 週までには得られる。16 週までに治療反応が得られない場合は、投与中止を考慮すること。

8. 重要な基本的注意

〈効能共通〉

- 8.1 本剤の投与によって合併する他のアレルギー性疾患の症状が変化する可能性があり、当該アレルギー性疾患に対する適切な治療を怠った場合、症状が急激に悪化し、喘息等では死亡に至るおそれもある。本剤の投与間隔変更後及び

投与中止後の疾患管理も含めて、本剤投与中から、合併するアレルギー性疾患を担当する医師と適切に連携すること。患者に対して、医師の指示なく、それらの疾患に対する治療内容を変更しないよう指導すること。

8.2 ショック、アナフィラキシーがあらわれることがあるので、観察を十分に行い、適切に対処できるようにしておくこと。[11.1.1 参照]

8.3 長期ステロイド療法を受けている患者において、本剤投与開始後にステロイド薬を急に中止しないこと。ステロイド薬の減量が必要な場合には、医師の管理下で徐々に行うこと。

8.4 本剤の臨床試験において、好酸球性肺炎及び好酸球性多発血管炎性肉芽腫症の発現が認められている。本剤投与中は、好酸球数の推移、並びに血管炎性皮疹、肺症状の悪化、心臓合併症及びニューロパチー等に注意すること。

8.5 本剤はIL-4及びIL-13の阻害作用により2型免疫応答を抑制する。2型免疫応答は寄生虫感染に対する生体防御機能に関与している可能性がある。患者が本剤投与中に寄生虫感染を起こし、抗寄生虫薬による治療が無効な場合には、寄生虫感染が治癒するまで本剤の投与を一時中止すること。[9.1.1 参照]

8.6 本剤投与中の生ワクチンの接種は、安全性が確認されていないので避けること。

8.7 本剤の投与開始にあたっては、医療施設において、必ず医師によるか、医師の直接の監督のもとで投与を行うこと。自己投与の適用については、医師がその妥当性を慎重に検討し、十分な教育訓練を実施した後、本剤投与による危険性と対処法について患者が理解し、患者自ら確実に投与できることを確認した上で、医師の管理指導のもとで実施すること。また、適用後、本剤による副作用が疑われる場合や自己投与の継続が困難な状況となる可能性がある場合には、直ちに自己投与を中止させ、医師の管理下で慎重に観察するなど適切な処置を行うこと。また、本剤投与後に副作用の発現が疑われる場合は、医療機関へ連絡するよう患者に指導を行うこと。使用済みの注射器を再使用しないよう患者に注意を促し、すべての器具の安全な廃棄方法に関する指導の徹底を行うとともに、使用済みの注射器を廃棄する容器を提供すること。

〈アトピー性皮膚炎〉

8.8 本剤が疾病を完治させる薬剤でなく、本剤投与中も保湿外用剤等を併用する必要があることを患者に対して説明し、患者が理解したことを確認したうえで投与すること。

〈気管支喘息〉

8.9 本剤の投与開始後に喘息症状がコントロール不良であったり、悪化した場合には、医師の診療を受けるよう患者に指導すること。

9. 特定の背景を有する患者に関する注意

9.1 合併症・既往歴等のある患者

9.1.1 寄生虫感染患者

本剤を投与する前に寄生虫感染の治療を行うこと。[8.5 参照]

9.5 妊婦

妊婦又は妊娠している可能性のある女性には、治療上の有益性が危険性を上回ると判断される場合にのみ投与すること。本剤はヒトIgG4モノクローナル抗体であり、ヒトIgGは胎盤関門を通過することが知られている。また、本剤のサル相同抗体を妊娠カニクイザルへ投与した場合、胎盤を通過して胎児に移行することが確認されている。

9.6 授乳婦

治療上の有益性及び母乳栄養の有益性を考慮し、授乳の継続又は中止を検討すること。本剤のヒト乳汁への移行は不明であるが、本剤はヒトIgG4モノクローナル抗体であり、ヒトIgGは乳汁中に移行することが知られている。

9.7 小児等

〈アトピー性皮膚炎〉

小児等を対象とした臨床試験は実施していない。

〈気管支喘息〉

12歳未満の小児等を対象とした臨床試験は実施していない。

〈鼻茸を伴う慢性副鼻腔炎〉

小児等を対象とした臨床試験は実施していない。

9.8 高齢者

一般的に生理機能（免疫機能等）が低下している。

11. 副作用

次の副作用があらわれることがあるので、観察を十分に行い、異常が認められた場合には投与を中止するなど適切な処置を行うこと。

11.1 重大な副作用

11.1.1 重篤な過敏症

アナフィラキシー（0.1%未満）が報告されている。血圧低下、呼吸困難、意識消失、めまい、嘔気、嘔吐、そう痒感、潮紅等があらわれる可能性がある。[8.2 参照]

11.2 その他の副作用

	5%以上	5%未満	頻度不明
感染症および寄生虫症		結膜炎、細菌性結膜炎、口腔ヘルペス、単純ヘルペス	
眼障害		アレルギー性結膜炎、眼瞼炎、眼乾燥	眼そう痒症
血液およびリンパ系障害		好酸球増加症	
注射部位	注射部位紅斑	注射部位反応、注射部位そう痒感、注射部位浮腫	
神経系障害		頭痛	
その他		発熱	血清病、血清病様反応

14. 適用上の注意

14.1 薬剤投与前の注意

14.1.1 投与前に45分以上かけて室温に戻しておくことが望ましい。

14.1.2 溶液が白濁したり、着色したり、微粒子がみられた場合及びシリンジに損傷がみられた場合には本剤は使用しないこと。

14.1.3 投与直前まで本剤の注射針のキャップを外さないこと。キャップを外したら直ちに投与すること。

14.2 薬剤投与時の注意

14.2.1 皮下注射は腹部、大腿部又は上腕部に行うこと。腹部へ投与する場合は、へその周り5cmを外して投与すること。注射部位反応が報告されているので、同一箇所へ繰り返し注射することは避けること。

14.2.2 正常な皮膚の部位に注射すること。皮膚が敏感な部位、皮膚に損傷、打撲や傷のある部位、アトピー性皮膚炎の強い炎症を伴う部位には注射しないこと。

14.2.3 他の薬剤と混合しないこと。

14.2.4 本剤は1回使用の製剤であり、再使用しないこと。

15. その他の注意

15.1 臨床使用に基づく情報

デュピルマブ300mg隔週投与の52週間投与後のアトピー性皮膚炎患者、気管支喘息患者、又は鼻茸を伴う慢性副鼻腔炎患者の約5%が抗薬物抗体（ADA）陽性反応を示し、約2%が持続するADA陽性反応を示し、約2%が中和抗体陽性であった。プラセボ群で

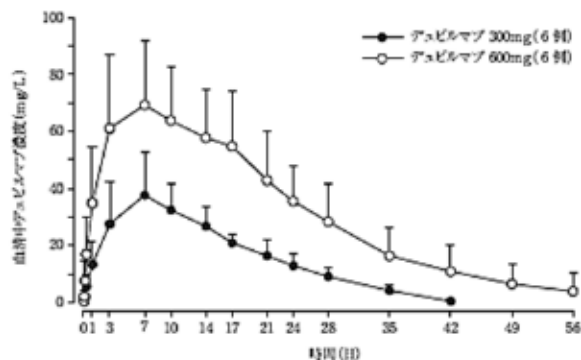
は約4%がADA陽性反応を示し、約2%が持続するADA陽性反応を示し、約1%が中和抗体陽性であった。高抗体価(10,000超)のADAの発現例(発現頻度0.6%未満)では、本剤の薬物動態及び有効性への影響が示唆された。加えて、高抗体価のADAに関連した血清病及び血清病様反応が認められた。

16. 薬物動態

16.1 血中濃度

16.1.1 単回投与

日本人健康成人に本剤300mg又は600mgを単回皮下投与したときのデュピルマブの血中濃度推移及び薬物動態パラメータは以下のとおりであった¹⁾。



本剤300mg又は600mgを単回皮下投与したときの血中濃度推移

本剤300mg又は600mgを単回皮下投与したときの薬物動態パラメータ

投与量 (mg)	C _{max} (mg/L)	t _{max} ^{注1)} (day)	AUC _{0-∞} (mg・day/L)	t _{1/2} ^{注2)} (day)
300 (6例)	38.3±15.3	7.01 (6.99-10.00)	700±234	5.13±1.42
600 (6例)	70.1±24.1	7.00 (3.00-7.02)	1780±699	8.77±5.18

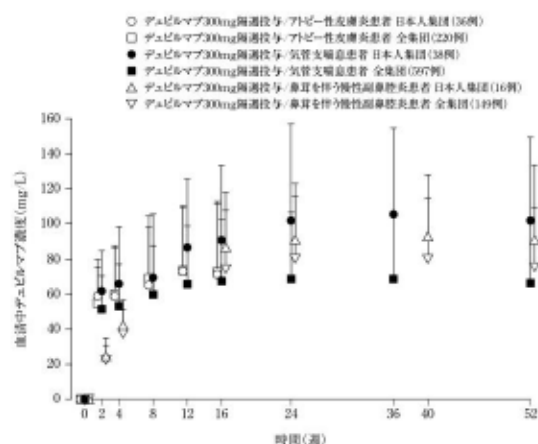
(平均値±標準偏差)

注1): 中央値(最小値-最大値)

注2): 血中濃度の経時的推移を片対数プロットしたときの最終消失相の回帰直線の傾きから算出

16.1.2 反復投与

アトピー性皮膚炎患者を対象とし本剤(初回600mg、以降300mg隔週投与)を16週間反復皮下投与したとき、並びに気管支喘息患者では本剤(初回600mg、以降300mg隔週投与)を、鼻茸を伴う慢性副鼻腔炎患者では本剤(300mg隔週投与)を52週間反復皮下投与したときの日本人部分集団と全患者集団でデュピルマブの曝露量は以下に示すとおりであった^{2), 5), 6)}。



16週間又は52週間反復皮下投与したときの血中濃度推移

16.1.3 母集団薬物動態解析

本剤は主に血管内のコンパートメントに分布し、母集団薬物動態解析により推定される分布容積は約4.6Lであった。

母集団薬物動態解析により、定常状態時の最終投与から本剤の血中濃度が定量下限未満に低下する時間の中央値は、300mg隔週投与で10~12週間と推定された。

16.2 吸収

母集団薬物動態解析により推定される皮下投与時の絶対バイオアベイラビリティは、アトピー性皮膚炎、気管支喘息及び鼻茸を伴う慢性副鼻腔炎患者の間で類似しており、61~64%であった。

17. 臨床成績

17.1 有効性及び安全性に関する試験

〈アトピー性皮膚炎〉

17.1.1 国際共同第Ⅲ相併用療法試験

日本の分類でストロングクラス以上に相当するステロイド外用薬で効果不十分な、18歳以上の中等症から重症^{注1)}のアトピー性皮膚炎(AD)患者740例(日本人患者117例を含む)を対象に、ステロイド外用薬に上乗せして本剤300mgを2週に1回(Q2W)又は毎週1回(QW)、若しくはプラセボを52週間投与した。本剤群では投与1日目に初回用量として本剤600mgの投与を行った^{注2)}。ベースラインの医師による全般評価(IGA)スコアは3.5±0.5、Eczema Area and Severity Index(EASI)スコアは32.5±12.9であった。主要有効性評価項目とした投与後16週時点のIGA≤1達成率^{注3)}及びEASI-75達成率^{注4)}において、本剤群はプラセボ群に比べ統計的に有意な(P<0.0001)改善効果を示した³⁾。

注1) IGAスコアが3以上、EASIスコアが16以上、及び体表面積に占めるAD病変の割合が10%以上、そう痒NRSスコアの日内最大値の週平均が3点以上

注2) 投与期間中は保湿剤の併用を必須とし、経口シクロスポリン、経口ステロイド等の全身療法及び光線療法の併用を禁止した

注3) IGAスコアが0(消失)又は1(ほぼ消失)かつベースラインから2点以上減少(改善)を達成した患者の割合

注4) EASIスコアがベースラインから75%以上改善した患者の割合

アトピー性皮膚炎・国際共同第Ⅲ相併用療法試験の成績

全体集団		Q2W 群	プラセボ群	プラセボ群との差 [95%信頼区間] p 値 ^{(注1)(注2)}
16 週	IGA ≤1 達成率	38.7 (41/106)	12.4 (39/315)	26.3 [16.3, 36.3] <0.0001
	EASI-75 達成率	68.9 (73/106)	23.2 (73/315)	45.7 [35.7, 55.7] <0.0001
	そう痒 NRS ≥4 点 改善達成率 ^(注3)	58.8 (60/106)	19.7 (59/299)	39.1 [28.5, 49.7]
52 週	IGA ≤1 達成率	34.9 (37/106)	12.4 (39/264)	22.5 [12.8, 32.3]
	EASI-75 達成率	62.3 (66/106)	21.9 (69/315)	40.4 [30.1, 50.7]
	そう痒 NRS ≥4 点 改善達成率 ^(注3)	48.0 (49/102)	13.4 (40/299)	34.7 [24.2, 45.1]
日本人部分集団		Q2W 群	プラセボ群	プラセボ群との差 [95%信頼区間]
16 週	IGA ≤1 達成率	18.8 (3/16)	3.7 (2/54)	15.0 [-13.2, 41.7]
	EASI-75 達成率	62.5 (10/16)	22.2 (12/54)	40.3 [12.5, 65.0]
	そう痒 NRS ≥4 点 改善達成率 ^(注3)	40.0 (6/15)	18.9 (10/53)	21.1 [-7.82, 48.5]
52 週	IGA ≤1 達成率	31.3 (5/16)	11.1 (6/54)	20.1 [-7.78, 46.5]

EASI-75 達成率	50.0 (8/16)	24.1 (13/54)	25.9 [-2.15, 52.3]
そう痒 NRS ≥ 4 点改善達成率 ^(注7)	33.3 (5/15)	17.0 (9/53)	16.4 [-12.5, 44.0]

承認用法・用量である 300mg Q2W のみ提示

% (例数)

中止例又は救済治療例は Non-responder とした

注 5) 地域及びベースライン時の重症度 (IGA スコア 3 又は 4) を層とした Cochran-Mantel-Haenszel 検定 (主要有効性評価項目についてのみ表中に表示)

注 6) プラセボ群と各本剤群の比較における有意水準をそれぞれ両側 2.5% と設定することで、検定の多重性を調整

注 7) そう痒 NRS スコアの日内最大値の週平均がベースラインから 4 点以上改善した患者の割合 (スコアの最大は 10)

本剤 Q2W 投与群での副作用は 33.6% (37/110 例) に、プラセボ群の副作用は 28.6% (90/315 例) に認められ、主な副作用は本剤 Q2W 群で注射部位反応 10.9%、アレルギー性結膜炎 4.5%、眼瞼炎 3.6%、アトピー性皮膚炎 3.6%、頭痛 3.6%であった。

17.1.2 国際共同第Ⅲ相単独療法試験

日本の分類でストロングクラス以上に相当するステロイド外用薬で効果不十分な、又は安全性上の理由等^(注8) からステロイド外用薬が推奨されない、18 歳以上の中等症から重症^(注9) の AD 患者 671 例 (日本人患者 106 例を含む) を対象に、本剤 300mg を Q2W 又は QW、若しくはプラセボを 16 週間投与した^(注10)。本剤群では投与 1 日目に初回用量として本剤 600 mg の投与を行った。ベースラインの IGA スコアは 3.5 ± 0.5、EASI スコアは 33.6 ± 14.0 であった。主要有効性評価項目とした投与後 16 週時点の IGA ≤ 1 達成率^(注11) 及び EASI-75 達成率^(注12) において、本剤群はプラセボ群に比べ統計的に有意な (P < 0.0001) 改善効果を示した⁽⁴⁾。

注 8) ステロイド外用薬治療により副作用 (治療不耐容、過敏症反応、顕著な皮膚萎縮、全身性の影響など) を認めた患者

注 9) IGA スコアが 3 以上、EASI スコアが 16 以上、及び体表面積に占める AD 病変の割合が 10% 以上、そう痒 NRS スコアの日内最大値の週平均が 3 点以上

注 10) 投与期間中は保湿剤の併用を必須とし、経口シクロスポリン、経口ステロイド等の全身療法及び光線療法の併用を禁止した

注 11) IGA スコアが 0 (消失) 又は 1 (ほぼ消失) かつベースラインから 2 点以上減少 (改善) を達成した患者の割合

注 12) EASI スコアがベースラインから 75% 以上改善した患者の割合

アトピー性皮膚炎・国際共同第Ⅲ相単独療法試験の成績

全体集団	Q2W 群	プラセボ群	プラセボ群との差 [95%信頼区間] p 値 ^{(注13) (注14)}
IGA ≤ 1 達成率	37.9 (85/224)	10.3 (23/224)	27.7 [20.2, 35.2] <0.0001
EASI-75 達成率	51.3 (115/224)	14.7 (33/224)	36.6 [28.6, 44.6] <0.0001
そう痒 NRS ≥ 4 点改善 達成率 ^(注15)	40.8 (87/213)	12.3 (26/212)	28.6 [20.7, 36.5]
日本人部分集団	Q2W 群	プラセボ群	プラセボ群との差 [95%信頼区間]
IGA ≤ 1 達成率	19.4 (7/36)	2.9 (1/35)	16.6 [-6.36, 38.8]
EASI-75 達成率	25.0 (9/36)	0.0 (0/35)	25.0 [2.16, 46.5]
そう痒 NRS ≥ 4 点改善 達成率 ^(注15)	25.0 (8/32)	0.0 (0/34)	25.0 [1.35, 47.6]

承認用法・用量である 300mg Q2W のみ提示

% (例数)

中止例又は救済治療例は Non-responder とした

注 13) 地域及びベースライン時の重症度 (IGA スコア 3 又は 4) を層とした Cochran-Mantel-Haenszel 検定 (主要有効性評価項目についてのみ)

注 14) プラセボ群と各本剤群の比較における有意水準をそれぞれ両側 2.5% と設定することで、検定の多重性を調整

注 15) そう痒 NRS スコアの日内最大値の週平均がベースラインから 4 点以上改善した患者の割合 (スコアの最大は 10)

本剤 Q2W 投与群での副作用は 28.8% (66/229 例) に、プラセボ群に 18.0% (40/222 例) に認められ、主な副作用は本剤 Q2W 群に注射部位反応 7.4%、アトピー性皮膚炎 3.5%、頭痛 3.1%であった。

〈気管支喘息〉

17.1.3 国際共同第Ⅲ相試験

中用量又は高用量の吸入ステロイド薬及び他の長期管理薬で治療しても喘息増悪をきたす 12 歳以上の気管支喘息患者 1902 例^(注16) (日本人患者 114 例を含む) を対象に、既存治療の併用下で、本剤 200 mg^(注17) 又は 300 mg^(注18)、もしくはそれぞれに対応するプラセボを 52 週間 Q2W 投与した。主要有効性評価項目とした喘息増悪 (全身ステロイド薬による 3 日間以上の治療、又は全身ステロイド薬による治療が必要な喘息による入院若しくは救急外来の受診) の発生率^(注19) 及び 12 週時点の FEV₁ の変化量^(注20) で、本剤 300mg 群はプラセボ群と比べて統計的に有意な効果を示した⁽⁵⁾。

注 16) ベースライン時の血中好酸球数が 1,500/μL 超の患者は除外した

注 17) 投与開始時には初回用量としてそれぞれ 400 mg 又は 600 mg を投与

注 18) 52 週間の治療薬投与期間中における重度喘息増悪の年換算発生率

注 19) 投与開始後 12 週時点における気管支拡張薬投与前の FEV₁ のベースラインからの変化量

投与 52 週後までの年間重度喘息増悪発生率 (ITT 集団)

全体集団	300 mg 群 (633 例)	プラセボ群 (321 例)
総観察期間 (人・年)	612.5	313.2
喘息増悪発件数 (回)	343	342
年間増悪発生率 (回/人・年)	0.560	1.092
年間増悪発生率 ^(注20) (回/人・年)	0.524	0.970
[95% 信頼区間]	[0.450, 0.611]	[0.810, 1.160]
プラセボ群との比 ^(注20)	0.540	/
[95% 信頼区間]	[0.430, 0.680]	
p 値 ^(注20)	<0.0001	
日本人部分集団	300 mg 群 (41 例)	プラセボ群 (17 例)
総観察期間 (人・年)	40.2	17.0
喘息増悪発件数 (回)	17	21
年間増悪発生率 (回/人・年)	0.423	1.238
年間増悪発生率 ^(注20) (回/人・年)	0.309	1.232
[95% 信頼区間]	[0.139, 0.687]	[0.502, 3.025]
プラセボ群との比 ^(注20)	0.251	/
[95% 信頼区間]	[0.072, 0.874]	

注 20) 投与群、年齢、地域、ベースライン時の血中好酸球数区分、ベースライン時の ICS 用量、1 年以内の重度喘息増悪の発生回数を説明変数とし、観察期間の対数変換値をオフセット変数とした負の二項回帰モデル

投与 12 週後の気管支拡張薬投与前 FEV₁ (L) の変化量 (ITT 集団)

全体集団	300 mg 群	プラセボ群
ベースライン	1.78 ± 0.60 (633)	1.75 ± 0.57 (321)
投与 12 週後	2.09 ± 0.70 (610)	1.93 ± 0.68 (313)
ベースラインからの変化量	0.31 ± 0.43 (610)	0.18 ± 0.39 (313)

プラセボ群との差 ^{注21)}	0.13	
[95% 信頼区間]	[0.08, 0.18]	
p 値 ^{注21)}	<0.0001	
日本人部分集団	300 mg 群	プラセボ群
ベースライン	1.75±0.64 (41)	1.76±0.43 (17)
投与 12 週後	2.02±0.63 (41)	1.88±0.55 (17)
ベースラインからの変化量	0.28±0.43 (41)	0.12±0.32 (17)
プラセボ群との差 ^{注21)}	0.17	
[95% 信頼区間]	[-0.04, 0.37]	

平均値±標準偏差 (例数)

注 21) 投与群、年齢、性別、身長、地域、ベースライン時の血中好酸球数区分、ベースライン時の ICS 用量、評価時点、投与群と評価時点の交互作用、ベースライン値、ベースライン値と評価時点の交互作用を説明変数とした MMRM 法、相関構造には unstructured を仮定した。

バイオマーカーの区分別の投与 52 週後までの年間重症喘息増悪発生率 (ITT 集団)

マーカー	区分 (ベースライン時)	重症喘息増悪の年間発生率		プラセボ群との比 ^{注22)} [95% 信頼区間]
		300 mg 群	プラセボ群	
血中好酸球数	150/μL 未満	0.805 (181)	0.779 (83)	1.149 [0.747, 1.767]
	150/μL 以上	0.475 (175)	0.845 (95)	0.557 [0.350, 0.888]
	300/μL 未満			
	300/μL 以上	0.496 (136)	1.393 (68)	0.366 [0.225, 0.596]
	500/μL 未満			
アレル	500/μL 以上	0.413 (141)	1.486 (74)	0.287 [0.184, 0.449]
	25ppb 未満	0.639 (317)	0.863 (144)	0.792 [0.572, 1.098]
	25ppb 以上	0.489 (186)	1.183 (97)	0.442 [0.282, 0.693]
	50ppb 未満			
総 IgE 濃度	50ppb 以上	0.485 (124)	1.444 (75)	0.305 [0.188, 0.494]
	61 IU/mL 未満	0.681 (149)	0.792 (83)	0.817 [0.511, 1.307]
	61 IU/mL 以上	0.535 (156)	1.344 (74)	0.420 [0.275, 0.641]
	167 IU/mL 未満			
	167 IU/mL 以上	0.616 (164)	1.008 (84)	0.685 [0.424, 1.106]
	449 IU/mL 未満			
	449 IU/mL 以上	0.402 (157)	1.291 (77)	0.375 [0.232, 0.606]

回/人・年 (例数)

注 22) 投与群、年齢、地域、ベースライン時の血中好酸球数区分、ベースライン時の ICS 用量、1 年以内の重症喘息増悪の発生回数を説明変数とし、観察期間の対数変換値をオフセット変数とした負の二項回帰モデル

バイオマーカーの区分別の投与 12 週後の気管支拡張薬投与前 FEV₁ (L) の変化量 (ITT 集団)

マーカー	区分 (ベースライン時)	ベースラインからの変化量		プラセボ群との差 ^{注22)} [95% 信頼区間]
		300 mg 群	プラセボ群	
血中好酸球数	150/μL 未満	0.19±0.37 (176)	0.11±0.41 (83)	0.09 [-0.01, 0.18]
	150/μL 以上	0.22±0.45 (168)	0.22±0.36 (90)	-0.00 [-0.10, 0.10]
	300/μL 未満			
	300/μL 以上	0.36±0.39 (131)	0.17±0.39 (66)	0.18 [0.07, 0.30]
	500/μL 未満			
アレル	500/μL 以上	0.50±0.45 (135)	0.22±0.41 (73)	0.30 [0.19, 0.42]
	25ppb 未満	0.20±0.37 (309)	0.17±0.36 (141)	0.03 [-0.04, 0.10]
	25ppb 以上	0.32±0.40 (182)	0.18±0.37 (94)	0.12 [0.03, 0.21]
	50ppb 未満			
	50ppb 以上	0.59±0.51 (113)	0.20±0.48 (73)	0.39 [0.26, 0.52]

総 IgE 濃度	61 IU/mL 未満	0.21±0.36 (143)	0.19±0.39 (78)	0.05 [-0.04, 0.14]
	61 IU/mL 以上	0.28±0.38 (151)	0.23±0.40 (73)	0.05 [-0.05, 0.15]
	167 IU/mL 未満			
	167 IU/mL 以上	0.34±0.47 (156)	0.08±0.31 (83)	0.26 [0.15, 0.36]
	449 IU/mL 未満			
	449 IU/mL 以上	0.39±0.49 (154)	0.24±0.46 (76)	0.13 [0.01, 0.25]

平均値±標準偏差 (例数)

注 23) 投与群、年齢、性別、身長、地域、ベースライン時の血中好酸球数区分、ベースライン時の ICS 用量、評価時点、投与群と評価時点の交互作用、ベースライン時の FEV₁ 値、ベースラインと評価時点の交互作用を説明変数とした MMRM 法、相関構造には unstructured を仮定した。

本剤 300mg 投与群での副作用は 22.6% (143/632 例) に、プラセボ群では 14.0% (45/321 例) に認められ、主な副作用は本剤 300mg に注射部位紅斑 14.9%、注射部位浮腫 5.9%、注射部位そう痒症 4.7%であった。

〈鼻茸を伴う慢性副鼻腔炎〉

17.1.4 国際共同第Ⅲ相試験

手術や全身ステロイド薬 (推奨されない場合を除く) によっても効果不十分^{注24)}な、18 歳以上の鼻茸を伴う慢性副鼻腔炎患者 448 例 (日本人患者 49 例を含む) を対象に、鼻噴霧用ステロイド薬に追加して本剤 300 mg を 52 週間 2 週に 1 回 (Q2W) (Q2W 群) 又は最初の 24 週間は Q2W その後 52 週まで 4 週に 1 回 (Q4W) 投与 (Q2W-Q4W 群)、若しくはプラセボを 52 週間投与した。3 つの主要有効性評価項目である投与後 24 週時点の鼻茸スコア、鼻閉重症度スコア、Lund-Mackay (LMK) スコアのベースラインからの変化量において、本剤併合群 (Q2W 群及び Q2W-Q4W 群) はプラセボ群に比べ統計的に有意な改善を示した (全て p<0.0001)

6)

ベースラインからの変化量の調整平均及び群間差 (ITT 集団)

評価項目		本剤併合群 ^{注25)} (295 例)	プラセボ群 (153 例)
鼻茸スコア ^{注26)}	投与前 ^{注26)}	6.18	5.96
	変化量 ^{注27)}	-1.71	0.10
	プラセボ群との差 [95% 信頼区間] ^{注28)}	-1.80 [-2.10, -1.51]	
	注		
鼻閉重症度 ^{注29)}	投与前 ^{注29)}	2.46	2.38
	変化量 ^{注27)}	-1.25	-0.38
	プラセボ群との差 [95% 信頼区間] ^{注28)}	-0.87 [-1.03, -0.71]	
	注		
LMK スコア ^{注30)}	投与前 ^{注30)}	18.12	17.65
	変化量 ^{注27)}	-5.21	-0.09
	プラセボ群との差 [95% 信頼区間] ^{注28)}	-5.13 [-5.80, -4.46]	
	注		
UPSIT ^{注31)}	投与前 ^{注31)}	13.53	13.78
	変化量 ^{注27)}	9.71	-0.81
	プラセボ群との差 [95% 信頼区間] ^{注28)}	10.52 [8.98, 12.07]	

評価項目		本剤 Q2W 群 (150 例)	本剤 Q2W-Q4W 群 (145 例)	プラセボ群 (153 例)	
投与後 24 週時点	鼻茸スコア ^{注26)}	投与前 ^{注26)}	6.07	6.29	5.96

与後 52 週 時 点		変化量 ^{注27)}	-2.24	-2.06	0.15
		プラセボ群との差	-2.40	-2.21	
		[95%信頼区間] ^{注28)}	[-2.77, -2.02]	[-2.59, -1.83]	
	鼻閉重症度 ^{注29)}	投与前 ^{注30)}	2.48	2.44	2.38
		変化量 ^{注27)}	-1.35	-1.48	-0.37
		プラセボ群との差	-0.98	-1.10	
	LMK スコア ^{注31)}	[95%信頼区間] ^{注28)}	[-1.17, -0.79]	[-1.29, -0.91]	
		投与前 ^{注30)}	18.42	17.81	17.65
		変化量 ^{注27)}	-6.83	-5.60	0.11
	UPSIT ^{注32)}	プラセボ群との差	-6.94	-5.71	
		[95%信頼区間] ^{注28)}	[-7.87, -6.01]	[-6.64, -4.77]	
		投与前 ^{注30)}	13.46	13.60	13.78
		変化量 ^{注27)}	9.53	9.99	-0.77
		プラセボ群との差	10.30	10.76	
		[95%信頼区間] ^{注28)}	[8.50, 12.10]	[8.95, 12.57]	

注 24) 両側鼻茸スコアが5以上(各鼻孔スコアは2以上)、鼻閉重症度スコアが2以上で週平均が1を超える、嗅覚障害や鼻漏(前鼻漏/後鼻漏)といったその他の症状を有する患者

注 25) 鼻茸スコア (0-8 点): 鼻閉重症度 (0-3 点); LMK (sinus opacification on the Lund-MacKay total CT) スコア (0-24 点); UPSIT (University of Pennsylvania smell identification test) (0-40 点)
鼻茸スコア、鼻閉重症度スコア、LMK スコアはスコアの減少が、UPSIT はスコアの増加が改善を意味する。

注 26) 平均値

注 27) 調整平均

注 28) WOCF 法及び多重代入法を合わせた混成手法により、投与前、喘息の状態、手術歴及び地域を要因とし、ベースライン値を共変量とした共分散分析で解析した。

注 29) Q2W 群と Q2W-Q4W 群の併合

本剤 Q2W 投与前での副作用は 24.2% (36/149 例)、Q2W-Q4W 群では 27.7% (41/148 例)、プラセボ群では 22.0% (33/150 例) に認められ、本剤 Q2W 投与前群及び Q2W-Q4W 群の主な副作用は注射部位紅斑 7.4%及び 6.8%、及び注射部位反応 3.4%及び 5.4%であった。

18. 薬効薬理

18.1 作用機序

デュピルマブは、ヒトインターロイキン-4 及びインターロイキン-13 受容体の複合体が共有している IL-4 受容体 α サブユニットに特異的に結合することにより、IL-4 及び IL-13 の両シグナル伝達を阻害する遺伝子組換えヒト IgG4 モノクローナル抗体である。IL-4 及び IL-13 はアトピー性皮膚炎、気管支喘息及び鼻茸を伴う慢性副鼻腔炎の病態において重要な役割を担う Type 2 サイトカインである⁷⁾。

18.2 IL-4 及び IL-13 シグナル伝達に対する作用

デュピルマブは高親和性にヒト IL-4R α に結合し、IL-4 及び IL-13 を介したシグナル伝達を *in vitro* 及び *in vivo* で抑制した⁷⁾。

18.3 2 型炎症モデルにおける炎症抑制作用

内因性マウス IL-4 及び IL-4R α の外部領域の両方を、相当するヒト配列で置換した遺伝子改変マウスを用いたチリダニアレルゲン誘発性 Type 2 炎症モデルにおいて、デュピルマブは、血清中 IgE 濃度、アレレルゲン特異的 IgG1 濃度等を低下させるとともに、肺好酸球浸潤、杯細胞化生並びに肺機能障害を抑制した⁷⁾。

19. 有効成分に関する理化学的知見

一般の名称: デュピルマブ (遺伝子組換え)

Dupilumab (Genetical Recombination)

本質: デュピルマブは、ヒトインターロイキン-4 受容体の α サブユニットに対する遺伝子組換えヒト IgG4 モノクローナル抗体であり、H 鎖 233 番目のアミノ酸残基が Pro に置換されている。デュピルマブは、チャイニーズハムスター卵巣細胞により産生される。デュピルマブは、452 個のアミノ酸残基からなる H 鎖 (γ 4 鎖) 2 本及び 219 個のアミノ酸残基からなる L 鎖 (κ 鎖) 2 本で構成される糖タンパク質 (分子量: 約 152,000) である。

20. 取扱い上の注意

20.1 外箱開封後は遮光して保存すること。

20.2 本剤を温めたり、直射日光に晒さないこと。また、本剤を振とうしないこと。

21. 承認条件

医薬品リスク管理計画を策定の上、適切に実施すること。

22. 包装

2mL × 1 本

23. 主要文献

- 社内資料: 国内第 I 相単回投与試験 (2018 年 1 月 19 日承認、CTD2.7.2.2)
- 社内資料: アトピー性皮膚炎患者を対象とした国際共同第 III 相単独療法試験 (2018 年 1 月 19 日承認、CTD2.7.2.2)
- 社内資料: アトピー性皮膚炎患者を対象とした国際共同第 III 相併用療法試験 (2018 年 1 月 19 日承認、審査報告書 p. 33-34)
- Simpson, E. L., et al.: N. Engl. J. Med. 2016; 375 (24), 2335-2348
- 社内資料: 気管支喘息患者を対象とした国際共同第 III 相試験 (2019 年 3 月 26 日承認、審査報告書 p. 15)
- Bachert, C., et al.: Lancet. 2019; 394 (10209), 1638-1650
- 社内資料: 非臨床薬効薬理試験 (2018 年 1 月 19 日承認、CTD2.6.2.1)

24. 文献請求先及び問い合わせ先

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26. 製造販売業者等

26.1 製造販売元

サノフィ株式会社

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26.2 提携先

リジェネロン社

添付文書（案）の「効能又は効果」、「用法及び用量」の設定根拠

1 「効能又は効果」（案）

鼻茸を伴う慢性副鼻腔炎（既存治療で効果不十分な患者に限る）

[設定根拠]

本申請におけるデュピルマブの「効能又は効果」（案）は、以下の既存の薬物療法や手術ではコントロール不十分な鼻茸を伴う慢性副鼻腔炎（CRSwNP）の成人（18歳以上）患者を対象に、基礎治療とした鼻噴霧用ステロイド薬にデュピルマブを追加投与したときの有効性及び安全性を検討した第3相試験2試験（EFC14280試験及びEFC14146試験）の成績に基づき設定した。

- EFC14280試験:既存の薬物療法や手術によってもコントロール不十分な18歳以上のCRSwNP患者を対象として、鼻噴霧用ステロイド薬による基礎治療下で、デュピルマブの有効性及び安全性を評価するランダム化、二重盲検、52週間投与、プラセボ対照試験。デュピルマブの投与方法は、52週間を通して300mgを隔週1回（q2w）投与、又は最初の24週間は300mg q2wを投与し、その後4週毎に1回（q4w）投与に切り替えて52週目まで投与した。
- EFC14146試験:既存の薬物療法や手術によってもコントロール不十分な18歳以上のCRSwNP患者を対象として、鼻噴霧用ステロイド薬による基礎治療下で、デュピルマブ300mg q2wの有効性及び安全性を評価するランダム化、二重盲検、24週間投与、プラセボ対照試験。

いずれの試験も国際共同試験として実施し、日本人患者はEFC14280試験に参加した。EFC14280試験の全ての主要有効性評価項目で、日本人部分集団の結果は全体集団と一貫性が認められた。上記2試験の併合解析の結果から、人種、民族、実施地域などでデュピルマブ300mg q2w投与の有効性に大きな影響を及ぼす部分集団は特定されなかった。また、安全性においても、人種、民族、実施地域などの部分集団による大きな差異は認められなかった。母集団薬物動態（Pop PK）解析から、人種及び民族はデュピルマブの薬物動態（PK）に明らかな影響を及ぼさなかった。したがって、国際共同試験を主体とした本申請の臨床データパッケージ全体に基づいて設定した用法及び用量は、日本人CRSwNP患者にも適用できると判断した。

以下に、効能又は効果（案）の設定根拠を示す（Module 2.5の6.4項）。

CRSwNPは、鼻腔及び副鼻腔粘膜の複雑なType2炎症性疾患であり、多様な症状を伴う。コントロール不十分なCRSwNP患者は、疾病負荷が大きく再発率も高い。また、Type2炎症を介した下気道疾患（喘息や非ステロイド性抗炎症薬過敏喘息〔NSAID-ERD〕など）を併発する患者が多く、さらにこ

これらの疾患はコントロールが困難である。患者の生活の質（QoL）は損なわれ、その結果、経済的影響も重大となっている。既存の治療選択肢は、局所又は全身性ステロイド薬の使用から内視鏡下鼻副鼻腔手術を含む様々な手術まで多岐に渡るが、治療後の再発率が高い。これらの治療法では疾患の一部である鼻茸しか治療することができず、CRSwNPを引き起こす副鼻腔での根本的な炎症過程を長期的に対処することはできない。

CRSwNP の治療目標は、全身性ステロイド薬療法に伴う副作用のリスクや侵襲性手術のリスクを回避しつつ、良好で持続的な症状コントロールを達成し、将来的な再発リスクを最小限にするとともに、下気道の併存疾患も良好にコントロールすることである。デュピルマブは、Type 2 炎症の主要なメディエーターであるサイトカインのインターロイキン-4（IL-4）及びインターロイキン-13（IL-13）のシグナル伝達経路を選択的に阻害することによって、既存治療でコントロール不十分な成人 CRSwNP 患者において、良好な安全性プロファイルとともに、頑健な臨床的に意味のあるベネフィットを示した。

上述した第3相試験では、既存治療でコントロール不十分な成人 CRSwNP 患者を対象に、鼻噴霧用ステロイド薬による基礎治療下でデュピルマブを追加投与することにより、プラセボと比べて、鼻茸スコア（NPS）を低下させ、副鼻腔炎の主要症状（鼻閉、嗅覚障害、鼻漏）の重症度を改善し、全体的な副鼻腔混濁度（CT 画像の評価による Lund-Mackay [LMK] スコア）を低下させることが証明された。その結果、CRSwNP の全ての疾患要素に対するデュピルマブの幅広い効果のエビデンスが十分に示された。

既存治療でコントロール不十分な CRSwNP 患者では、全身性ステロイド薬や副鼻腔手術を要する患者の割合が高い。デュピルマブの投与は結果として、臨床的意義のある重要なアウトカムである全身性ステロイド薬及び副鼻腔手術の必要性を、こうした患者集団で大きく低下させた。多くの患者にとって最も問題となる症状である嗅覚障害や味覚障害をほとんど又は全く改善させない手術や全身性ステロイド薬とは異なり、デュピルマブは CRSwNP 患者の嗅覚及び味覚を回復させた。

重要な点は、全体集団に加え、疾病負荷の高い部分集団でもデュピルマブの有効性が証明されたことである。有効性は、喘息又は NSAID-ERD の合併患者、手術歴のある患者といった疾患コントロールが困難な部分集団でも示された。具体的には、喘息を合併した CRSwNP 患者における事前に規定し多重性を調整した併合解析では、デュピルマブが肺機能及び喘息コントロールを改善した一方で、プラセボ群での吸入薬による局所治療では、コントロール不良の喘息をほとんど又は全く改善しなかった。

さらに、上気道及び下気道感染、副鼻腔及び耳の障害の発現頻度はプラセボ群に比べデュピルマブ群で低く、CRSwNP でよく見られる合併症に対するデュピルマブの全体的な保護作用が明らかとなった。これらのベネフィットはいずれも、疾患特異的な健康関連 QoL の改善と同時に認められた。

デュピルマブは、高齢の CRSwNP 患者においても、良好なベネフィット・リスクのプロファイルを示した。第3相試験でデュピルマブの投与を受けた CRSwNP 患者 440 名のうち、79 名は 65 歳以上、11 名は 75 歳以上であった。この年齢層におけるデュピルマブの有効性と安全性は、試験集団全体で見られたものと同様であった。

1.8 添付文書案

SAR231893 - デュピルマブ（遺伝子組換え）

デュピルマブは、CRSwNP 患者において良好な忍容性ととも持続的な有効性を示した初めての選択的全身性治療薬である。デュピルマブは IL-4 及び IL-13 により惹起される Type 2 炎症を抑制することによって、鼻茸、鼻炎、副鼻腔炎、併存疾患である喘息を含む全ての臨床症状の治療における実質的な有効性が証明され、ベネフィット・リスクのプロファイルも良好であった。CRSwNP 患者の治療において、鼻噴霧用ステロイド薬による基礎治療下でデュピルマブを追加投与したときの忍容性は概ね良好であり、安全性プロファイルは許容可能であった。CRSwNP 臨床開発プログラムで新たに特定された安全性の懸念はなかった。以上のことから、デュピルマブの効能又は効果（案）を「鼻茸を伴う慢性副鼻腔炎（既存治療で効果不十分な患者に限る）」とした。

2 「用法及び用量」（案）

通常、成人にはデュピルマブ（遺伝子組換え）として 1 回 300mg を 2 週間隔で皮下投与する。
なお、症状安定後には、1 回 300mg を 4 週間隔で皮下投与できる。

[設定根拠]

CRSwNP 患者に推奨されるデュピルマブの用法及び用量は、300 mg を隔週 1 回（q2w）皮下投与することである。この用法及び用量は、これまでのデュピルマブの全ての適応症の臨床開発プログラム全体に含まれる試験データから選択され、上述の CRSwNP 患者を対象とした 2 つの第 3 相試験（EFC14280 試験及び EFC14146 試験）で評価された。

以下に臨床試験の結果に基づく用法及び用量（案）の設定根拠を示す。

2.1 第 3 相試験での評価のための用法及び用量の選択

CRSwNP 患者を対象とした第 3 相試験の用法・用量は、CRSwNP 患者を対象とした第 2 相試験（ACT12340 試験）、中等症から重症の喘息患者を対象とした第 2b 相用量検討試験（DRI12544 試験）、中等症から重症のアトピー性皮膚炎（AD）患者を対象とした第 2b 相用量検討試験（R668-AD-1021 試験）及び第 3 相試験（R668-AD-1334 試験及び R668-AD-1416 試験）、PK/PD の補助的解析から得られたデータを含むデュピルマブの臨床開発プログラムから得られた臨床エビデンス全体に基づき選択された（Module 2.5 の 4.2.2 項及び Module 2.7.2 の 1.2.6 項）。

CRSwNP 患者を対象とした第 2 相試験（ACT12340 試験）では、Day 1 の初回用量（600 mg）を含む 300 mg 毎週 1 回（qw）投与を評価し、16 週間の治験薬投与期間終了時に主要及び副次有効性評価項目において、頑健かつ臨床的及び統計的に有意な投与効果が示された。ACT12340 試験では 300 mg qw の用法・用量のみを評価したが、有効性評価項目の PK/PD 解析から、300 mg q2w 投与及び 300 mg qw 投与はプラセボと比較して、NPS の臨床的に有意な改善（ベースラインから 1 を超える低下）、鼻閉症状及び嗅覚障害の改善といった投与効果が優れていることが予測された。ACT12340 試験の CRSwNP 患者データ及び DRI12544 試験の鼻茸を合併する喘息患者の用量検討データを利用した 22 項目の副鼻腔に関する評価質問票（SNOT-22）の曝露反応解析は、全て 300 mg q2w 投与で予測される有意な臨床効果を支持していた。また、AD 臨床開発プログラムの第 3 相試験では、300 mg qw 投与と 300 mg q2w 投与で有効性に差は認められなかった。したがって、喘息、AD 及び CRSwNP 患者を対象とした臨床試験から得られた有効性のデータは、CRSwNP 患者において 300 mg q2w 投与で最適な投与効果を達成する可能性が高いことを示した。

ACT12340 試験では、両側の NPS、鼻閉症状及び嗅覚に対する投与効果は時間経過とともに認められた。治験薬投与終了の Week 16 時点で上記評価項目が PD 定常状態に達しなかったことから、より

長い投与期間で更なる効果を得られることが示唆された。したがって、第3相試験ではより長い投与期間とし、Week 24 及び Week 52 時点で有効性を評価した。なお、ACT12340 試験では投与終了後観察期間の4ヵ月間にもデュピルマブの持続的な効果が認められたことから、EFC14280 試験では、最初の24週間の投与期間を300 mg q2w で投与し、その後投与頻度の低い300 mg q4w 投与に切り替えたときの投与効果の持続についても評価した。

2.2 第3相試験の用法及び用量の選択

CRSwNP 患者を対象とした第3相試験（EFC14146 試験及び EFC14280 試験）の有効性の結果から、鼻噴霧用ステロイド薬でコントロール不十分な成人 CRSwNP 患者において、デュピルマブ 300 mg q2w 投与により、Week 24（EFC14146 試験及び EFC14280 試験）及び Week 52（EFC14280 試験）の両時点の NPS 及び鼻閉重症度スコアは、プラセボと比べて統計的に有意かつ臨床的に意味のある改善を示した。いずれの試験もデュピルマブ 300 mg q2w 投与により、Week 24 時点の全ての有効性評価項目に対し有意かつ臨床的に意味のある効果が認められた（Module 2.5 の 4.6 項及び Module 2.7.3 の 4 項）。

EFC14146 試験及び EFC14280 試験で、デュピルマブ 300 mg q2w の投与は、全ての主要評価項目及び多重性を調整した副次評価項目の統計的に有意かつ臨床的に意味のある改善をもたらした。投与効果の発現は早期に認められ、ベースライン後の最初の評価時点（Week 2 又は Week 4）でプラセボとの差が認められ、Week 52 まで投与継続に伴い更に改善し続けた。

EFC14146 試験では、24週間のデュピルマブ投与終了後の後観察期間に、NPS、鼻閉重症度スコア、副鼻腔混濁度（LMK スコア）、全症状スコア、ペンシルベニア大学嗅覚識別検査（UPSIT）、患者が毎日評価する嗅覚障害の重症度及び SNOT-22 合計スコア、並びに肺機能（1秒量）及び喘息コントロール（喘息の管理に関するアンケート6項目）を含む全ての評価項目で、反跳効果は伴わなかったものの、効果の減弱が認められた。これらのデータは、後観察期間に症状が再発したことから明らかのように、CRSwNP（及び併存する喘息）の長期コントロールのために Type 2 炎症の持続的な抑制が必要であることを示している。

EFC14280 試験では、Week 24 から Week 52 までの投与継続により、デュピルマブ 300 mg q2w 群及び 300 mg q2w-q4w 群のいずれも、ほとんどの評価項目で Week 52 時点でプラトーに達することなく更なる改善が認められた。Week 24 から Week 52 の間に、q2w から q4w へと切り替えた患者と比べ q2w 投与を維持した患者では、NPS 及び LMK スコアの更なる改善が認められた。このことから、最大の投与効果にはまだ達しておらず、デュピルマブ 300 mg q2w を継続して投与することで患者に更なるベネフィットをもたらす可能性が高くなると考えられる。

デュピルマブの PK/PD 解析の結果は、CRSwNP 患者の有効性評価と一致した。Week 24 時点での 300 mg q2w 投与による狭い曝露量範囲では、濃度に関連した NPS 及び鼻閉反応の増加は示されなかった。52週間投与終了時の定常状態トラフ濃度は、300 mg q2w 投与（1.8%）と比較して 300 mg q2w-q4w 投与ではより多くの患者（8.7%）が定量下限（0.078 mg/L）未満であった。さらに、NPS の 50%効果

濃度（1.75 mg/L）を超える定常状態トラフ濃度を維持した患者の割合は、300 mg q2w 投与（97%）と比べて 300 mg q2w-q4w 投与（86%）で低かった（Module 2.5 の 3.3 項及び Module 2.7.2 の 3.3.4 項）。

EFC14146 試験及び EFC14280 試験の 24 週間の併合安全性解析において、CRSwNP 患者に鼻噴霧用ステロイド薬による基礎治療下でデュピルマブを投与したときの忍容性は概ね良好で、安全性プロファイルも良好であることが示された。有害事象、重篤な有害事象、又は治験薬の投与中止に至った有害事象の発現頻度はプラセボ群に比べデュピルマブ群で低かった（Module 2.5 の 5.19 項及び Module 2.7.4 の 3.1 項）。

EFC14280 試験では、52 週間のデュピルマブ投与による忍容性は良好で、安全性プロファイルは Week 24 時点で観察されたものと一致し、全体的にプラセボとも類似していた。安全性の全体的な結果から、新たな又は予期せぬ重大な有害事象は認められなかった。さらに、CRSwNPに関連した副鼻腔炎、喘息及び鼻茸の有害事象は、デュピルマブ群よりプラセボ群に多く認められ、また、デュピルマブを q2w 投与で維持された患者より q4w 投与に切り替えた患者で多く認められた（Module 2.5 の 5.14 項及び Module 2.7.4 の 2.5.2.9 項）。

以上のことから、既存治療でコントロール不十分な成人 CRSwNP 患者における推奨用法・用量は、デュピルマブ 300 mg q2w である。このことは、この用法・用量を用いた第 3 相試験全体で顕著な有効性が認められたこと、及び Week 52 までプラトーに達することなく改善し続けたことによって裏付けられる。

添付文書（案）の「使用上の注意」（案）の設定根拠

1. 警告

本剤の投与は、適応疾患の治療に精通している医師のもとで行うこと。

[設定根拠]

本剤の適正使用を推進するため、適応疾患の治療に精通している医師により本剤が投与されるように設定した。

2. 禁忌（次の患者には投与しないこと）

本剤の成分に対し過敏症の既往歴のある患者

[設定根拠]

前回の承認から変更なし。

5. 効能又は効果に関連する注意

〈アトピー性皮膚炎〉

5.1 ステロイド外用剤やタクロリムス外用剤等の抗炎症外用剤による適切な治療を一定期間施行しても、十分な効果が得られず、強い炎症を伴う皮疹が広範囲に及ぶ患者に用いること。

[17.1.1、17.1.2 参照]

5.2 原則として、本剤投与時にはアトピー性皮膚炎の病変部位の状態に応じて抗炎症外用剤を併用すること。

5.3 本剤投与時も保湿外用剤を継続使用すること。

〈気管支喘息〉

5.4 最新のガイドライン等を参考に、中用量又は高用量の吸入ステロイド薬とその他の長期管理薬を併用しても、全身性ステロイド薬の投与等が必要な喘息増悪をきたす患者に本剤を追加して投与すること。

5.5 本剤は IL-4 及び IL-13 シグナル伝達を阻害することにより、喘息の病態に関与する 2 型炎症反応を抑制することから、臨床試験で認められた本剤投与前の 2 型炎症に関連するバイオマ

ーカー（血中好酸球数、FeNO、IgE 等）の値と有効性の関係を十分に理解し、患者の当該バイオマーカーの値を考慮した上で、適応患者の選択を行うこと。[17.1.3 参照]

5.6 本剤は既に起きている気管支喘息の発作や症状を速やかに軽減する薬剤ではないので、急性の発作に対しては使用しないこと。

〈鼻茸を伴う慢性副鼻腔炎〉

5.7 本剤は全身性ステロイド薬、手術等ではコントロールが不十分な患者に用いること。

[設定根拠]

5.1～5.5 前回の承認から変更なし。

5.6 内容については前回の承認から変更なし。記載項について新記載要領に対応した整備を行った。

5.7 追加となる鼻茸を伴う慢性副鼻腔炎の対象となる患者を記載した。

7. 用法及び用量に関連する注意

〈アトピー性皮膚炎〉

7.1 本剤による治療反応は、通常投与開始から 16 週までには得られる。16 週までに治療反応が得られない場合は、投与中止を考慮すること。

[設定根拠]

前回の承認から変更なし。

8. 重要な基本的注意

〈効能共通〉

8.1 本剤の投与によって合併する他のアレルギー性疾患の症状が変化する可能性があり、当該アレルギー性疾患に対する適切な治療を怠った場合、症状が急激に悪化し、喘息等では死亡に至るおそれもある。本剤の投与間隔変更後及び投与中止後の疾患管理も含めて、本剤投与中から、合併するアレルギー性疾患を担当する医師と適切に連携すること。患者に対して、医師の指示なく、それらの疾患に対する治療内容を変更しないよう指導すること。

8.2 ショック、アナフィラキシーがあらわれることがあるので、観察を十分に行い、適切に対処できるようにしておくこと。[11.1.1 参照]

8.3 長期ステロイド療法を受けている患者において、本剤投与開始後にステロイド薬を急に中止しないこと。ステロイド薬の減量が必要な場合には、医師の管理下で徐々に行うこと。

8.4 本剤の臨床試験において、好酸球性肺炎及び好酸球性多発血管炎性肉芽腫症の発現が認められている。本剤投与中は、好酸球数の推移、並びに血管炎性皮疹、肺症状の悪化、心臓合併症及びニューロパチー等に注意すること。

8.5 本剤は IL-4 及び IL-13 の阻害作用により 2 型免疫応答を抑制する。2 型免疫応答は寄生虫感染に対する生体防御機能に関与している可能性がある。患者が本剤投与中に寄生虫感染を起こし、抗寄生虫薬による治療が無効な場合には、寄生虫感染が治癒するまで本剤の投与を一時中止すること。[9.1.1 参照]

8.6 本剤投与中の生ワクチンの接種は、安全性が確認されていないので避けること。

8.7 本剤の投与開始にあたっては、医療施設において、必ず医師によるか、医師の直接の監督のもとで投与を行うこと。自己投与の適用については、医師がその妥当性を慎重に検討し、十分な教育訓練を実施した後、本剤投与による危険性と対処法について患者が理解し、患者自ら確実に投与できることを確認した上で、医師の管理指導のもとで実施すること。また、適用後、本剤による副作用が疑われる場合や自己投与の継続が困難な状況となる可能性がある場合には、直ちに自己投与を中止させ、医師の管理下で慎重に観察するなど適切な処置を行うこと。また、本剤投与後に副作用の発現が疑われる場合は、医療機関へ連絡するよう患者に指導を行うこと。使用済みの注射器を再使用しないよう患者に注意を促し、すべての器具の安全な廃棄方法に関する指導の徹底を行うとともに、使用済みの注射器を廃棄する容器を提供すること。

〈アトピー性皮膚炎〉

8.8 本剤が疾病を完治させる薬剤でなく、本剤投与中も保湿外用剤等を併用する必要があることを患者に対して説明し、患者が理解したことを確認したうえで投与すること。

〈気管支喘息〉

8.9 本剤の投与開始後に喘息症状がコントロール不良であったり、悪化した場合には、医師の診療を受けるよう患者に指導すること。

[設定根拠]

8.1 追加となる鼻茸を伴う慢性副鼻腔炎の内容を反映させた。

8.2～8.9 内容については前回の承認から変更なし。記載項について新記載要領に対応した整備を行った。

9. 特定の背景を有する患者に関する注意

9.1 合併症・既往歴等のある患者

9.1.1 寄生虫感染患者

本剤を投与する前に寄生虫感染の治療を行うこと。[8.5 参照]

9.5 妊婦

妊婦又は妊娠している可能性のある女性には、治療上の有益性が危険性を上回ると判断される場合にのみ投与すること。本剤はヒト IgG4 モノクローナル抗体であり、ヒト IgG は胎盤関門を通過することが知られている。また、本剤のサル相同抗体を妊娠カニクイザルへ投与した場合、胎盤を通過して胎児に移行することが確認されている。

9.6 授乳婦

治療上の有益性及び母乳栄養の有益性を考慮し、授乳の継続又は中止を検討すること。本剤の

ヒト乳汁への移行は不明であるが、本剤はヒト IgG4 モノクローナル抗体であり、ヒト IgG は乳汁中に移行することが知られている。

9.7 小児等

〈アトピー性皮膚炎〉

小児等を対象とした臨床試験は実施していない。

〈気管支喘息〉

12 歳未満の小児等を対象とした臨床試験は実施していない。

〈鼻茸を伴う慢性副鼻腔炎〉

小児等を対象とした臨床試験は実施していない。

9.8 高齢者

一般的に生理機能（免疫機能等）が低下している。

[設定根拠]

9.1, 9.5 及び 9.6 内容については前回の承認から変更なし。記載項について新記載要領に対応した整備を行った。

9.7 鼻茸を伴う慢性副鼻腔炎では小児に対する臨床試験は行われていないことを追記した。

9.8 内容については前回の承認から変更なし。記載項について新記載要領に対応した整備を行った。

11. 副作用

次の副作用があらわれることがあるので、観察を十分に行い、異常が認められた場合には投与を中止するなど適切な処置を行うこと。

11.1 重大な副作用

11.1.1 重篤な過敏症

アナフィラキシー（0.1%未満）が報告されている。血圧低下、呼吸困難、意識消失、めまい、嘔気、嘔吐、そう痒感、潮紅等があらわれる可能性がある。〔8.2 参照〕

[設定根拠]

内容については前回の承認から変更なし。記載項について新記載要領に対応した整備を行った。

11.2 その他の副作用

	5%以上	5%未満	頻度不明
感染症および寄生虫症		結膜炎、細菌性結膜炎、口腔ヘルペス、単	

		純ヘルペス	
眼障害		アレルギー性結膜炎、 眼瞼炎、眼乾燥	眼そう痒症
血液およびリンパ系障害		好酸球増加症	
注射部位	注射部位紅斑	注射部位反応、注射部位 そう痒感、注射部位 浮腫	
神経系障害		頭痛	
その他		発熱	血清病、血清病様反 応

[設定根拠]

前回の承認から変更なし。

14. 適用上の注意

14.1 薬剤投与前の注意

14.1.1 投与前に 45 分以上かけて室温に戻しておくことが望ましい。

14.1.2 溶液が白濁したり、着色したり、微粒子がみられた場合及びシリンジに損傷がみられた場合には本剤は使用しないこと。

14.1.3 投与直前まで本剤の注射針のキャップを外さないこと。キャップを外したら直ちに投与すること。

14.2 薬剤投与時の注意

14.2.1 皮下注射は腹部、大腿部又は上腕部に行うこと。腹部へ投与する場合は、へその周り 5cm を外して投与すること。注射部位反応が報告されているので、同一箇所へ繰り返し注射することは避けること。

14.2.2 正常な皮膚の部位に注射すること。皮膚が敏感な部位、皮膚に損傷、打撲や傷のある部位、アトピー性皮膚炎の強い炎症を伴う部位には注射しないこと。

14.2.3 他の薬剤と混合しないこと。

14.2.4 本剤は 1 回使用の製剤であり、再使用しないこと。

[設定根拠]

内容については前回の承認から変更なし。記載項について新記載要領に対応した整備を行った。

15. その他の注意

15.1 臨床使用に基づく情報

デュピルマブ 300mg 隔週投与の 52 週間投与後のアトピー性皮膚炎患者、気管支喘息患者、又は鼻茸を伴う慢性副鼻腔炎患者の約 5%が抗薬物抗体（ADA）陽性反応を示し、約 2%が持続する ADA 陽性反応を示し、約 2%が中和抗体陽性であった。プラセボ群では約 4%が ADA 陽性反応を示し、約 2%が持続する ADA 陽性反応を示し、約 1%が中和抗体陽性であった。高抗体価（10,000 超）の ADA の発現例（発現頻度 0.6%未満）では、本剤の薬物動態及び有効性への影響が示唆された。加えて、高抗体価の ADA に関連した血清病及び血清病様反応が認められた。

[設定根拠]

鼻茸を伴う慢性副鼻腔炎患者も加えた集計結果に基づき記載した。



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デュピルマブ（遺伝子組換え）

1.12 添付資料一覧（鼻茸）

第4部の添付資料

4.2 試験報告書

4.2.1 薬理試験

4.2.1.1 効力を裏付ける試験

該当資料なし

4.2.1.2 副次的薬理試験

該当資料なし

4.2.1.3 安全性薬理試験

該当資料なし

4.2.1.4 薬力学的薬物相互作用試験

該当資料なし

4.2.2 薬物動態試験

4.2.2.1 分析法及びバリデーション報告書

該当資料なし

4.2.2.2 吸収

該当資料なし

4.2.2.3 分布

該当資料なし

4.2.2.4 代謝

該当資料なし

4.2.2.5 排泄

該当資料なし

4.2.2.6 薬物動態学的薬物相互作用（非臨床）

該当資料なし

4.2.2.7 その他の薬物動態試験

該当資料なし

4.2.3 毒性試験

4.2.3.1 単回投与毒性試験

該当資料なし

4.2.3.2 反復投与毒性試験

該当資料なし

4.2.3.3 遺伝毒性試験

4.2.3.3.1 In Vitro 試験

該当資料なし

4.2.3.3.2 In Vivo 試験

該当資料なし

4.2.3.4 がん原性試験

該当資料なし

4.2.3.4.1 長期がん原性試験

該当資料なし

4.2.3.4.2 短期又は中期がん原性試験

該当資料なし

4.2.3.4.3 その他の試験
該当資料なし

4.2.3.5 生殖発生毒性試験
4.2.3.5.1 受胎能及び着床までの初期胚発生に関する試験
該当資料なし

4.2.3.5.2 胚・胎児発生に関する試験
該当資料なし

4.2.3.5.3 出生前及び出生後の発生並びに母体の機能に関する試験
該当資料なし

4.2.3.5.4 新生児を用いた試験
該当資料なし

4.2.3.6 局所刺激性試験
該当資料なし

4.2.3.7 その他の毒性試験
4.2.3.7.1 抗原性試験
該当資料なし

4.2.3.7.2 免疫毒性試験
該当資料なし

4.2.3.7.3 毒性発現の機序に関する試験
該当資料なし

4.2.3.7.4 依存性試験
該当資料なし

4.2.3.7.5 代謝物の毒性試験
該当資料なし

4.2.3.7.6 不純物の毒性試験
該当資料なし

4.2.3.7.7 その他の試験
該当資料なし

4.3 参考文献

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4.3-3	Batra PS, Tong L, Citardi MJ. Analysis of Comorbidities and Objective Parameters in Refractory Chronic Rhinosinusitis. Laryngoscope. 2013; 123(Suppl 7): S1-11.
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1.12 添付資料一覧

SAR231893 - デュピルマブ(遺伝子組換え)

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第5部の添付資料

5.2 臨床試験一覧表

資料番号	標題	試験実施期間	電子データの有無	評価資料／参考資料
5.2	臨床試験一覧表	—	—	—

5.3 試験報告書及び関連情報

5.3.1 生物薬剤学試験報告書

5.3.1.1 バイオアベイラビリティ (BA) 試験報告書

該当資料なし

5.3.1.2 比較BA試験及び生物学的同等性 (BE) 試験報告書

該当資料なし

5.3.1.3 In Vitro-In Vivo の関連を検討した試験報告書

該当資料なし

5.3.1.4 生物学的及び理化学的分析法検討報告書

資料番号	標題	試験実施期間	電子データの有無	評価資料／参考資料
5.3.1.4-1	REGN668-MX-14119-SR-01V3 Determination of Study-specific Screening, Confirmation and Titer Cut Points for Dupilumab (REGN668) Anti-Drug Antibody (ADA) Assay	-20■■■■	無	参考資料
5.3.1.4-2	ACT12340-BA-01 V2 Determination of Functional Dupilumab Antibodies in Samples from Clinical Study ACT12340	-20■■■■	無	参考資料

5.3.2 ヒト生体試料を用いた薬物動態関連の試験報告書

5.3.2.1 血漿蛋白結合試験報告書

該当資料なし

5.3.2.2 肝代謝及び薬物相互作用試験報告書

該当資料なし

5.3.2.3 他のヒト生体試料を用いた試験報告書

該当資料なし

5.3.3 臨床薬物動態 (PK) 試験報告書

5.3.3.1 健康被験者におけるPK及び初期忍容性試験報告書

該当資料なし

5.3.3.2 患者におけるPK及び初期忍容性試験報告書

該当資料なし

5.3.3.3 内因性要因を検討したPK試験報告書

該当資料なし

5.3.3.4 外因性要因を検討したPK試験報告書

該当資料なし

5.3.3.5 ポピュレーションPK試験報告書

資料番号	標題	試験実施期間	電子データの有無	評価資料／参考資料
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1.12 添付資料一覧
SAR231893 - デュピルマブ(遺伝子組換え)

5.3.3.5-1	POH0668 Dupilumab Global Population Pharmacokinetic Base Model Development Using Pooled Data from Atopic Dermatitis Patients, Asthma Patients, and Healthy Subjects	-20■■■■	無	参考資料
5.3.3.5-2	POH0611 Population Pharmacokinetic Analysis of Dupilumab Using Pooled Data from One Phase 2 and Two Phase 3 Studies in Patients with Nasal Polyposis	-20■■■■	無	参考資料
5.3.3.5-3	POH0687 Empirical Exposure-Response Analysis of Nasal Polyps Score, Nasal Congestion, Loss of Sense of Smell and 22-Item Sino-nasal Outcome Test for Dupilumab Nasal Polyposis Phase 3 Studies	-20■■■■	無	参考資料

5.3.4 臨床薬力学 (PD) 試験報告書

5.3.4.1 健康被験者におけるPD試験及びPK/PD試験報告書
該当資料なし

5.3.4.2 患者におけるPD試験及びPK/PD試験報告書
該当資料なし

5.3.5 有効性及び安全性試験報告書

5.3.5.1 申請する適応症に関する比較対照試験報告書

資料番号	標題	試験実施期間	電子データの有無	評価資料／参考資料
5.3.5.1-1	両側性鼻茸患者を対象に鼻噴霧用ステロイド薬による基礎治療下でデュピルマブ300mgを隔週1回投与したときの有効性と安全性を評価するランダム化、二重盲検、24週間、プラセボ対照試験 <EFC14146試験>	2016/12/5 - 2018/7/5	無	参考資料
5.3.5.1-2	両側性鼻茸患者を対象に鼻噴霧用ステロイド薬による基礎治療下でデュピルマブの有効性と安全性を評価するランダム化、二重盲検、52週間、プラセボ対照試験 <EFC14280試験>	2016/11/28 - 20■■■■	有	評価資料

5.3.5.2 非対照試験報告書
該当資料なし

5.3.5.3 複数の試験成績を併せて解析した報告書

資料番号	標題	試験実施期間	電子データの有無	評価資料／参考資料
5.3.5.3-1	Integrated Summary of Efficacy	-	無	参考資料
5.3.5.3-2	Integrated Summary of Safety	-	無	参考資料
5.3.5.3-3	Responder analyses for PRO questionnaires (symptoms e-diary, SNOT-22 and ACQ-6)	-	無	参考資料
5.3.5.3-4	Compilation of serious infection data from the dupilumab program	-	無	参考資料
5.3.5.3-5	Cardiovascular classification process manual	-	無	参考資料

5.3.5.4 その他の臨床試験報告書

資料番号	標題	試験実施期間	電子データの有無	評価資料／参考資料
5.3.5.4-1	EFC14280 - Japanese data	-	無	参考資料

1.12 添付資料一覧
SAR231893 - デュピルマブ(遺伝子組換え)

5.3.5.4-2	EFC14280 - Dupilumab combined data	-	無	参考資料
5.3.5.4-3	Patient Reported Outcomes Assessment - CRSwNP	-	無	参考資料

5.3.6 市販後の使用経験に関する報告書

資料番号	標題	試験実施期間	電子データの有無	評価資料／参考資料
5.3.6-1	PERIODIC BENEFIT RISK EVALUATION REPORT - GPE-BW-2018-00970 - ■■■■-20■■■	20■■■■ - 20■■■■	無	参考資料
5.3.6-2	市販直後調査実施報告書 20■■年■■月■■日	2018/4/23 - 2018/10/22	無	参考資料

5.3.7 患者データ一覧表及び症例記録

資料番号	症例一覧表
5.3.7-1	試験症例一覧表
5.3.7-2	副作用症例一覧表
5.3.7-3	重篤な有害事象発現症例一覧表

5.4 参考文献

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SAR231893 - デュピルマブ(遺伝子組換え)

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