デュピクセント皮下注 300mg シリンジ、
デュピクセント皮下注 300mg ペン、
デュピクセント皮下注 200mg シリンジ、
デュピクセント皮下注 200mg ペン
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（小児気管支喘息）

Total number of pages: 6

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1.5 起原又は発見の経緯及び開発の経緯（小児気管支喘息） **1**

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図 1　デュピルマブの 6 歳以上 12 歳未満の小児喘息に係る開発の経緯図 6

1　起原又は発見の経緯及び開発の経緯

1.1　序文

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 シグナル伝達を阻害するヒト IgG4 モノクローナル抗体である。日本では 2018 年 1 月に 300 mg シリンジ製剤がアトピー性皮膚炎に係る効能・効果で承認されて以降、気管支喘息（以下、喘息）、鼻茸を伴う慢性副鼻腔炎、結節性痒疹、特発性の慢性蕁麻疹及び慢性閉塞性肺疾患（COPD）に係る効能・効果で承認されており、2020 年 9 月に 300 mg ペン製剤、2023 年 9 月に 200 mg シリンジ製剤、2025 年 7 月に 200 mg ペン製剤も承認されている。

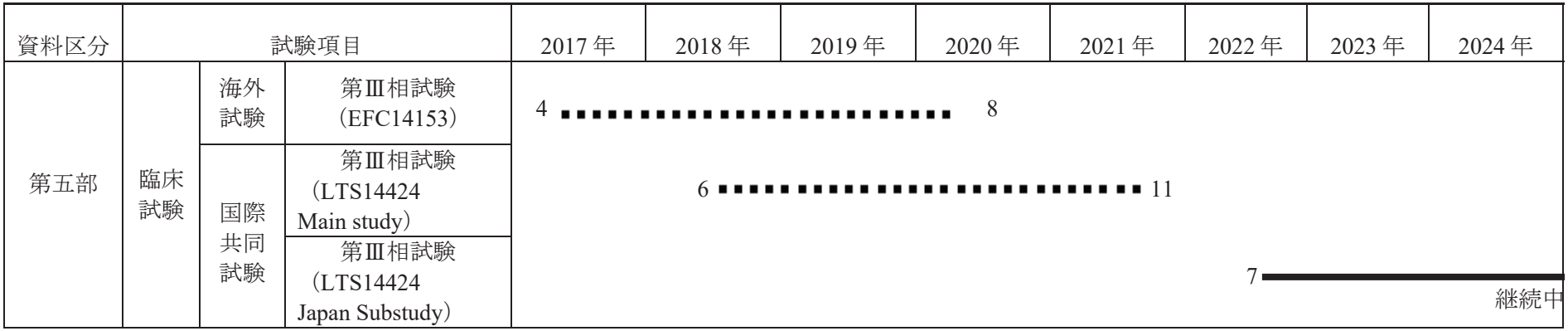
喘息は慢性気道炎症と多くの場合は可逆性の気流制限を特徴とする複雑で多様な疾患である。症状には喘鳴、息切れ、胸苦しさ及び咳などがあり、これらの症状は時間とともに変化し、その強度も変化する。喘息増悪は喘息に関連する罹患率／死亡率上昇の主な原因であり、急性気管支収縮の発作を特徴とする。小児期の肺機能異常は、肺の成長低下、成人期における肺機能の進行性の低下及び COPD 早期発症のリスク要因である。小児喘息に対する薬物治療は成人と同様で、主要な長期管理薬は吸入ステロイド薬（ICS）であり、追加の長期管理薬としては長時間作用性 β2 刺激薬（LABA）、ロイコトリエン受容体拮抗薬（LTRA）又は長時間作用性抗コリン薬（LAMA）が使用される。これらの治療を行っても喘息のコントロール不良が続く場合は、全身性ステロイド薬、抗 IgE 抗体薬及び抗 IL-5 抗体薬等の使用を考慮する。抗 IgE 抗体薬及び抗 IL-5 抗体薬は 6 歳以上 12 歳未満の小児喘息に対する治療薬として承認されているものの、いずれも小児集団において肺機能を改善させる持続的な効果は確認されていない。小児喘息患者は他の併存疾患を抱えていることが多く、それが生活の質に影響を与えることがある。したがって、標準治療を受けてもコントロール不良の中等症から重症の小児喘息患者に対しては、喘息増悪の発生頻度を減らし、肺機能を改善できる安全で効果的な治療法に対するアンメットニーズが依然として存在する。また、一般的には、小児期の喘息はアトピー性皮膚炎、アレルギー性鼻炎、食物アレルギー及びアレルギー感作など他のアトピー性疾患と最も関連している。

今般、海外試験である EFC14153 試験及び国際共同試験である LTS14424 試験（海外で実施された Main study 及び日本人で実施された Japan substudy）において、既存治療によっても喘息症状をコントロールできない 6 歳以上 12 歳未満の喘息患者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、デュピルマブの適応を 6 歳以上 12 歳未満の小児喘息患者に拡大するため、一部変更承認申請を行うこととした。

1.2　開発の経緯

デュピルマブの 6 歳以上 12 歳未満の小児喘息に係る開発の経緯を図 1 に示す。小児喘息に対するデュピルマブの臨床開発プログラムの概要を Module 2.5 の 1.4 項に示す。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。

図 1　デュピルマブの 6 歳以上 12 歳未満の小児喘息に係る開発の経緯図



：国際共同試験（日本が参加している試験）

■■■■■ ：国際共同試験及び海外試験（日本が参加していない試験）

数字は開始(First Visit First Subject)及び終了(Last Visit Last Subject)月を示す。

サノフィ株式会社

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（小児気管支喘息）

Total number of pages: 2

1　外国での承認(許可)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（AD）の適応で承認されて以降、AD、喘息、鼻茸を伴う慢性副鼻腔炎、好酸球性食道炎、結節性痒疹、慢性閉塞性肺疾患等の 2 型炎症性疾患に対する治療薬として 60 以上の国・地域で承認されている。

本申請で追加する気管支喘息に対する 6 歳以上 12 歳未満の小児用量は、米国で 2021 年 10 月、欧州で 2022 年 4 月に承認されている。

本剤の企業中核データシート（CCDS）、米国及び欧州の添付文書を添付する。

DUPILUMAB

Solution for SC injection in pre-filled syringe or pre-filled pen

COMPANY CORE DATA SHEET

[redacted]

以下、2～181頁を省略（削除）。

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, Chronic Rhinosinusitis with Nasal Polyps (1.3)	09/2024
Indications and Usage, Eosinophilic Esophagitis (1.4)	01/2024
Indications and Usage, Chronic Obstructive Pulmonary Disease (1.6)	09/2024
Dosage and Administration, 100 mg Q2W in pediatric patients 6 to 11 years of age with asthma (2.4)	Removed 04/2024
Dosage and Administration, Chronic Rhinosinusitis with Nasal Polyps (2.5)	09/2024
Dosage and Administration, Eosinophilic Esophagitis (2.6)	01/2024
Dosage and Administration, Chronic Obstructive Pulmonary Disease (2.8)	09/2024
Warnings and Precautions (5.2, 5.4)	09/2024

INDICATIONS AND USAGE

DUPIXENT is an interleukin-4 receptor alpha antagonist indicated:

Atopic Dermatitis
- for the treatment of adult and pediatric patients aged 6 months and older with moderate-to-severe AD 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)

Asthma
- as an add-on maintenance treatment of adult and pediatric patients aged 6 years and older with moderate-to-severe asthma characterized by an eosinophilic phenotype or with oral corticosteroid dependent asthma. (1.2)
- *Limitations of Use:* Not for the relief of acute bronchospasm or status asthmaticus. (1.2)

Chronic Rhinosinusitis with Nasal Polyps
- as an add-on maintenance treatment in adult and pediatric patients aged 12 years and older with inadequately controlled chronic rhinosinusitis with nasal polyps (CRSwNP). (1.3)

Eosinophilic Esophagitis
- for the treatment of adult and pediatric patients aged 1 year and older, weighing at least 15 kg, with eosinophilic esophagitis (EoE). (1.4)

Prurigo Nodularis
- for the treatment of adult patients with prurigo nodularis (PN). (1.5)

Chronic Obstructive Pulmonary Disease
- as an add-on maintenance treatment of adult patients with inadequately controlled chronic obstructive pulmonary disease (COPD) and an eosinophilic phenotype. (1.6)
- *Limitations of Use:* Not for the relief of acute bronchospasm. (1.6)

DOSAGE AND ADMINISTRATION

Atopic Dermatitis

Dosage in Adults (2.3):

Recommended dosage is an initial dose of 600 mg (two 300 mg injections), followed by 300 mg given every other week (Q2W).

Dosage in Pediatric Patients 6 Months to 5 Years of Age (2.3):

Body Weight	Initial and Subsequent Dosage
5 to less than 15 kg	200 mg (one 200 mg injection) every 4 weeks (Q4W)
15 to less than 30 kg	300 mg (one 300 mg injection) every 4 weeks (Q4W)

Dosage in Pediatric Patients 6 Years to 17 Years of Age (2.3):

Body Weight	Initial Loading Dose	Subsequent Dosage[a]
15 to less than 30 kg	600 mg (two 300 mg injections)	300 mg Q4W
30 to less than 60 kg	400 mg (two 200 mg injections)	200 mg Q2W
60 kg or more	600 mg (two 300 mg injections)	300 mg Q2W

[a] Q2W – every other week; Q4W – every 4 weeks

Asthma

Dosage in Adult and Pediatric Patients 12 Years and Older (2.4):

Initial Loading Dose	Subsequent Dosage
400 mg (two 200 mg injections)	200 mg every 2 weeks (Q2W)
Or	
600 mg (two 300 mg injections)	300 mg every 2 weeks (Q2W)
Dosage for patients with oral corticosteroid-dependent asthma or with co-morbid moderate-to-severe atopic dermatitis or adults with co-morbid chronic rhinosinusitis with nasal polyps	
600 mg (two 300 mg injections)	300 mg every 2 weeks (Q2W)

Dosage in Pediatric Patients 6 to 11 Years of Age (2.4):

Body Weight	Initial Dose and Subsequent Dosage
15 to less than 30 kg	300 mg every four weeks (Q4W)
≥30 kg	200 mg every other week (Q2W)

For pediatric patients 6 to 11 years old with asthma and co-morbid moderate-to-severe atopic dermatitis, follow the recommended dosage as per Table 2 which includes an initial loading dose. (2.3)

Chronic Rhinosinusitis with Nasal Polyps (2.5):

Recommended dosage for adult and pediatric patients 12 years of age and older is 300 mg given every other week (Q2W).

Eosinophilic Esophagitis (2.6):

Body Weight	Recommended Dosage in Adult and Pediatric Patients 1 Year and Older, Weighing At Least 15 kg
15 to less than 30 kg	200 mg every other week (Q2W)
30 to less than 40 kg	300 mg every other week (Q2W)
40 kg or more	300 mg every week (QW)

Prurigo Nodularis (2.7):

Recommended dosage for adult patients is an initial dose of 600 mg (two 300 mg injections), followed by 300 mg given every other week (Q2W).

Chronic Obstructive Pulmonary Disease (2.8):

Recommended dosage for adult patients is 300 mg given every other week (Q2W).

DOSAGE FORMS AND STRENGTHS

Single-Dose Pre-Filled Syringe with Needle Shield (3):
- Injection: 300 mg/2 mL
- Injection: 200 mg/1.14 mL

Single-Dose Pre-Filled Pen (3):
- Injection: 300 mg/2 mL
- Injection: 200 mg/1.14 mL

CONTRAINDICATIONS

Known hypersensitivity to dupilumab or any excipients in DUPIXENT. (4)

WARNINGS AND PRECAUTIONS

- Hypersensitivity: Hypersensitivity reactions including anaphylaxis, serum sickness, angioedema, urticaria, rash, erythema nodosum, and erythema multiforme have occurred. Discontinue DUPIXENT in the event of a hypersensitivity reaction. (5.1)
- Conjunctivitis and Keratitis: Advise patients to report new onset or worsening eye symptoms to their healthcare provider. Consider ophthalmological examination, as appropriate. (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 DUPIXENT. Decrease steroids gradually, if appropriate. (5.5)
- Arthralgia: Advise patients to report new onset or worsening joint symptoms to their healthcare provider. If symptoms persist or worsen, consider rheumatological evaluation and/or discontinuation of DUPIXENT. (5.7)
- Parasitic (Helminth) Infections: Treat pre-existing helminth infections before initiating DUPIXENT. If patients become infected while receiving DUPIXENT and do not respond to anti-helminth treatment, discontinue DUPIXENT until the infection resolves. (5.8)
- Vaccinations: Avoid use of live vaccines. (5.9)

ADVERSE REACTIONS

Most common adverse reactions are:

- Atopic Dermatitis incidence ≥1%): injection site reactions, conjunctivitis, blepharitis, oral herpes, keratitis, eye pruritus, other herpes simplex virus infection, dry eye, and eosinophilia. (6.1)
- Asthma incidence ≥1%): injection site reactions, oropharyngeal pain, and eosinophilia. (6.1)
- Chronic Rhinosinusitis with Nasal Polyps incidence ≥1%): injection site reactions, eosinophilia, insomnia, toothache, gastritis, arthralgia, and conjunctivitis. (6.1)
- Eosinophilic Esophagitis incidence ≥2%): injection site reactions, upper respiratory tract infections, arthralgia, and herpes viral infections. (6.1)
- Prurigo Nodularis incidence ≥2%): nasopharyngitis, conjunctivitis, herpes infection, dizziness, myalgia, and diarrhea. (6.1)
- Chronic Obstructive Pulmonary Disease (incidence ≥2%): viral infection, headache, nasopharyngitis, back pain, diarrhea, arthralgia, urinary tract infection, local administration reactions, rhinitis, eosinophilia, toothache, and gastritis. (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.

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

Revised: 09/2024

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- 1.4 Eosinophilic Esophagitis
- 1.5 Prurigo Nodularis
- 1.6 Chronic Obstructive Pulmonary Disease

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***Sections or subsections omitted from the full prescribing information are not listed.**

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 Atopic Dermatitis

DUPIXENT is indicated for the treatment of adult and pediatric patients aged 6 months and older with moderate-to-severe atopic dermatitis (AD) 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 of adult and pediatric patients aged 6 years and older with moderate-to-severe asthma characterized by an eosinophilic phenotype or with oral corticosteroid dependent asthma *[see Clinical Studies (14)]*.

Limitations of Use

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

1.3 Chronic Rhinosinusitis with Nasal Polyps

DUPIXENT is indicated as an add-on maintenance treatment in adult and pediatric patients aged 12 years and older with inadequately controlled chronic rhinosinusitis with nasal polyps (CRSwNP).

1.4 Eosinophilic Esophagitis

DUPIXENT is indicated for the treatment of adult and pediatric patients aged 1 year and older, weighing at least 15 kg, with eosinophilic esophagitis (EoE).

1.5 Prurigo Nodularis

DUPIXENT is indicated for the treatment of adult patients with prurigo nodularis (PN).

1.6 Chronic Obstructive Pulmonary Disease

DUPIXENT is indicated as an add-on maintenance treatment of adult patients with inadequately controlled chronic obstructive pulmonary disease (COPD) and an eosinophilic phenotype.

Limitations of Use

DUPIXENT is not indicated for the relief of acute bronchospasm.

2 DOSAGE AND ADMINISTRATION

2.1 Important Administration Instructions

DUPIXENT is administered by subcutaneous injection.

DUPIXENT is intended for use under the guidance of a healthcare provider. Provide proper training to patients and/or caregivers on the preparation and administration of DUPIXENT prior to use according to the "Instructions for Use".

Use of Pre-filled Pen or Pre-filled Syringe

The DUPIXENT pre-filled pen is for use in adult and pediatric patients aged 2 years and older.

The DUPIXENT pre-filled syringe is for use in adult and pediatric patients aged 6 months and older.

A caregiver or patient 12 years of age and older may inject DUPIXENT using the pre-filled syringe or pre-filled pen. In pediatric patients 12 to 17 years of age, administer DUPIXENT under the supervision of an adult. In pediatric patients 6 months to less than 12 years of age, administer DUPIXENT by a caregiver.

Administration Instructions

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

For AD and 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.

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

2.2 Vaccination Prior to Treatment

Consider completing all age-appropriate vaccinations as recommended by current immunization guidelines prior to initiating treatment with DUPIXENT *[see Warnings and Precautions (5.9)]*.

2.3 Recommended Dosage for Atopic Dermatitis

Dosage in Adults

The recommended dosage of DUPIXENT for adult patients is an initial dose of 600 mg (two 300 mg injections), followed by 300 mg given every other week (Q2W).

Dosage in Pediatric Patients 6 Months to 5 Years of Age

The recommended dosage of DUPIXENT for pediatric patients 6 months to 5 years of age is specified in Table 1.

Table 1: Dosage of DUPIXENT in Pediatric Patients 6 Months to 5 Years of Age with Atopic Dermatitis

Body Weight	Initial[a] and Subsequent Dosage
5 to less than 15 kg	200 mg (one 200 mg injection) every 4 weeks (Q4W)
15 to less than 30 kg	300 mg (one 300 mg injection) every 4 weeks (Q4W)

[a] For pediatric patients 6 months to 5 years of age with AD, no initial loading dose is recommended.

Dosage in Pediatric Patients 6 Years to 17 Years of Age

The recommended dosage of DUPIXENT for pediatric patients 6 years to 17 years of age is specified in Table 2.

Table 2: Dosage of DUPIXENT in Pediatric Patients 6 Years to 17 Years of Age with Atopic Dermatitis

Body Weight	Initial Loading Dose	Subsequent Dosage
15 to less than 30 kg	600 mg (two 300 mg injections)	300 mg every 4 weeks (Q4W)
30 to less than 60 kg	400 mg (two 200 mg injections)	200 mg every other week (Q2W)
60 kg or more	600 mg (two 300 mg injections)	300 mg every other week (Q2W)

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.

2.4 Recommended Dosage for Asthma

Dosage in Adult and Pediatric Patients 12 Years and Older

The recommended dosage of DUPIXENT for adult and pediatric patients 12 years of age and older is specified in Table 3.

Table 3: Dosage of DUPIXENT in Adult and Pediatric Patients 12 Years and Older with Asthma

Initial Loading Dose	Subsequent Dosage
400 mg (two 200 mg injections)	200 mg every 2 weeks (Q2W)
Or	
600 mg (two 300 mg injections)	300 mg every 2 weeks (Q2W)
Dosage for patients with oral corticosteroid-dependent asthma or with co-morbid moderate-to-severe atopic dermatitis or adults with co-morbid chronic rhinosinusitis with nasal polyps	
600 mg (two 300 mg injections)	300 mg every 2 weeks (Q2W)

Dosage in Pediatric Patients 6 to 11 Years of Age

The recommended dosage of DUPIXENT for pediatric patients 6 to 11 years of age is specified in Table 4.

Table 4: Dosage of DUPIXENT in Pediatric Patients 6 to 11 Years of Age with Asthma

Body Weight	Initial[a] and Subsequent Dosage
15 to less than 30 kg	300 mg every four weeks (Q4W)
≥30 kg	200 mg every other week (Q2W)

[a] For pediatric patients 6 to 11 years of age with asthma, no initial loading dose is recommended.

For pediatric patients 6 to 11 years of age with asthma and co-morbid moderate-to-severe AD, follow the recommended dosage as per Table 2 which includes an initial loading dose *[see Dosage and Administration (2.3)]*.

2.5 Recommended Dosage for Chronic Rhinosinusitis with Nasal Polyps

The recommended dosage of DUPIXENT for adult and pediatric patients 12 years of age and older is 300 mg given every other week (Q2W).

2.6 Recommended Dosage for Eosinophilic Esophagitis

The recommended dosage of DUPIXENT for adult and pediatric patients 1 year of age and older, weighing at least 15 kg, is specified in Table 5.

Table 5: Dosage of DUPIXENT in Adult and Pediatric Patients 1 Year of Age and Older with Eosinophilic Esophagitis

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

2.7 Recommended Dosage for Prurigo Nodularis

The recommended dosage of DUPIXENT for adult patients is an initial dose of 600 mg (two 300 mg injections) followed by 300 mg given every other week (Q2W).

2.8 Recommended Dosage for Chronic Obstructive Pulmonary Disease

The recommended dosage of DUPIXENT for adult patients is 300 mg given every other week (Q2W).

2.9 Missed Doses

If a weekly dose is missed, administer the dose as soon as possible, and start a new weekly schedule from the date of the last administered dose.

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

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

2.10 Preparation for Use

Before injection, remove DUPIXENT from the refrigerator and allow DUPIXENT to reach room temperature (45 minutes for the 300 mg/2 mL pre-filled syringe or pre-filled pen, and 30 minutes for the 200 mg/1.14 mL pre-filled syringe or pre-filled pen) without removing the needle cap. After removal from the refrigerator, DUPIXENT must be used within 14 days or discarded.

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 or pre-filled pen.

3 DOSAGE FORMS AND STRENGTHS

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

Single-dose pre-filled syringe with needle shield as:

- Injection: 300 mg/2 mL
- Injection: 200 mg/1.14 mL

Single-dose pre-filled pen as:

- Injection: 300 mg/2 mL
- Injection: 200 mg/1.14 mL

4 CONTRAINDICATIONS

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

5 WARNINGS AND PRECAUTIONS

5.1 Hypersensitivity

Hypersensitivity reactions, including anaphylaxis, serum sickness or serum sickness-like reactions, angioedema, generalized urticaria, rash, erythema nodosum, and erythema multiforme have been reported. If a clinically significant hypersensitivity reaction occurs, institute appropriate therapy and discontinue DUPIXENT *[see Adverse Reactions (6.1, 6.2) and Clinical Pharmacology (12.6)]*.

5.2 Conjunctivitis and Keratitis

Conjunctivitis and keratitis adverse reactions have been reported in clinical trials.

Conjunctivitis and keratitis occurred more frequently in AD subjects who received DUPIXENT compared to those who received placebo. Conjunctivitis was the most frequently reported eye disorder. Most subjects with conjunctivitis or keratitis recovered or were recovering during the treatment period *[see Adverse Reactions (6.1)]*.

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

In adult 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)]*.

Among subjects with EoE, there were no reports of conjunctivitis and keratitis in the DUPIXENT group in placebo-controlled trials *[see Adverse Reactions (6.1)]*.

In subjects with PN, the frequency of conjunctivitis was 4% in the DUPIXENT group compared to 1% in the placebo group; these subjects recovered or were recovering during the treatment period. There were no cases of keratitis reported in the PN development program *[see Adverse Reactions (6.1)]*.

Among subjects with COPD, the frequency of conjunctivitis and keratitis was 1.4% and 0.1% in the DUPIXENT group and 1% and 0% in the placebo group, respectively *[see Adverse Reactions (6.1)]*.

Conjunctivitis and keratitis adverse events have also been reported with DUPIXENT in postmarketing settings, predominantly in AD patients. Some patients reported visual disturbances (e.g., blurred vision) associated with conjunctivitis or keratitis.

Advise patients or their caregivers to report new onset or worsening eye symptoms to their healthcare provider. Consider ophthalmological examination for patients who develop conjunctivitis that does not resolve following standard treatment or signs and symptoms suggestive of keratitis, as appropriate *[see Adverse Reactions (6.1)]*.

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. Healthcare providers 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 subjects who participated in the asthma development program and cases of vasculitis consistent with eosinophilic granulomatosis with polyangiitis have been reported with DUPIXENT in adult subjects who participated in the asthma development program as well as in adult subjects with co-morbid asthma in the CRSwNP development program. A causal association between DUPIXENT and these conditions has not been established.

5.4 Acute Symptoms of Asthma or Chronic Obstructive Pulmonary Disease or Acute Deteriorating Disease

DUPIXENT should not be used to treat acute symptoms or acute exacerbations of asthma or COPD. Do not use DUPIXENT to treat acute bronchospasm or status asthmaticus. Patients

should seek medical advice if their asthma or COPD remains uncontrolled or worsens after initiation of treatment with DUPIXENT.

5.5 Risk Associated with Abrupt 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 healthcare provider. 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 co-morbid asthma not to adjust or stop their asthma treatments without consultation with their physicians.

5.7 Arthralgia

Arthralgia has been reported with the use of DUPIXENT with some patients reporting gait disturbances or decreased mobility associated with joint symptoms; some cases resulted in hospitalization *[see Adverse Reactions (6.1)]*. In postmarketing reports, onset of arthralgia was variable, ranging from days to months after the first dose of DUPIXENT. Some patients' symptoms resolved while continuing treatment with DUPIXENT and other patients recovered or were recovering following discontinuation of DUPIXENT.

Advise patients to report new onset or worsening joint symptoms to their healthcare provider. If symptoms persist or worsen, consider rheumatological evaluation and/or discontinuation of DUPIXENT.

5.8 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. Adverse reactions of helminth infections (5 cases of enterobiasis and 1 case of ascariasis) were reported in pediatric subjects 6 to 11 years old who participated in the pediatric asthma development program *[see Adverse Reactions (6.1)]*.

5.9 Vaccinations

Consider completing all age-appropriate vaccinations as recommended by current immunization guidelines prior to initiating treatment with DUPIXENT. Avoid use of live vaccines during treatment with DUPIXENT. It is unknown if administration of live vaccines during DUPIXENT treatment will impact the safety or effectiveness of these vaccines. Limited data are available regarding coadministration of DUPIXENT with non-live vaccines *[see Clinical Pharmacology (12.2)]*.

6 ADVERSE REACTIONS

The following clinically significant adverse reactions are described elsewhere in the labeling:

- Hypersensitivity *[see Warnings and Precautions (5.1)]*
- Conjunctivitis and Keratitis *[see Warnings and Precautions (5.2)]*
- Arthralgia *[see Warnings and Precautions (5.7)]*
- Parasitic (Helminth) Infections *[see Warnings and Precautions (5.8)]*

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 (SOLO 1, SOLO 2, and CHRONOS) and one dose-ranging trial (AD-1021) evaluated the safety of DUPIXENT in subjects with moderate-to-severe AD. 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 AD.

SOLO 1, SOLO 2, and AD-1021 compared the safety of DUPIXENT monotherapy to placebo through Week 16. CHRONOS compared the safety of DUPIXENT + TCS to placebo + TCS through Week 52.

AD-1225 is a multicenter, open-label extension (OLE) trial which assessed the long-term safety of repeat doses of DUPIXENT through 260 weeks of treatment in adults with moderate-to-severe AD who had previously participated in controlled trials of DUPIXENT or had been screened for SOLO 1 or SOLO 2. The safety data in AD-1225 reflect exposure to DUPIXENT 200 mg QW, 300 mg QW and 300 mg Q2W in 2677 subjects, including 2254 exposed for at least 52 weeks, 1224 exposed for at least 100 weeks, 561 exposed for at least 148 weeks and 179 exposed for at least 260 weeks.

Weeks 0 to 16 (SOLO 1, SOLO 2, CHRONOS, and AD-1021)

In DUPIXENT monotherapy trials (SOLO 1, SOLO 2, and AD-1021) 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 6 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 6: Adverse Reactions Occurring in ≥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 SOLO 1, SOLO 2, and AD-1021.
[b] Analysis of CHRONOS 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 (CHRONOS)

In the DUPIXENT with concomitant TCS trial (CHRONOS) 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.

Safety through 260 Weeks (AD-1225)

The long-term safety profile observed in this trial through 260 weeks was generally consistent with the safety profile of DUPIXENT observed in controlled studies.

Pediatric Subjects 12 to 17 Years of Age with Atopic Dermatitis

The safety of DUPIXENT was assessed in a trial of 250 pediatric subjects 12 to 17 years of age with moderate-to-severe AD (AD-1526). The safety profile of DUPIXENT in these subjects through Week 16 was similar to the safety profile seen in adults with AD.

The long-term safety of DUPIXENT was assessed in an open-label extension study in pediatric subjects 12 to 17 years of age with moderate-to-severe AD (AD-1434). The safety profile of DUPIXENT in subjects followed through Week 52 was similar to the safety profile observed at

Week 16 in AD-1526. The long-term safety profile of DUPIXENT observed in pediatric subjects 12 to 17 years of age was consistent with that seen in adults with AD.

Pediatric Subjects 6 to 11 Years of Age with Atopic Dermatitis

The safety of DUPIXENT with concomitant TCS was assessed in a trial of 367 pediatric subjects 6 to 11 years of age with severe AD (AD-1652). The safety profile of DUPIXENT + TCS in these subjects through Week 16 was similar to the safety profile from trials in adult and pediatric subjects 12 to 17 years of age with AD.

The long-term safety of DUPIXENT ± TCS was assessed in an open-label extension study of 368 pediatric subjects 6 to 11 years of age with AD (AD-1434). Among subjects who entered this study, 110 (30%) had moderate and 72 (20%) had severe AD at the time of enrollment in AD-1434. The safety profile of DUPIXENT ± TCS in subjects followed through Week 52 was similar to the safety profile observed through Week 16 in AD-1652. The long-term safety profile of DUPIXENT ± TCS observed in pediatric subjects 6 to 11 years of age was consistent with that seen in adult and pediatric subjects 12 to 17 years of age with AD *[see Use in Specific Populations (8.4)]*.

Pediatric Subjects 6 Months to 5 Years of Age with Atopic Dermatitis

The safety of DUPIXENT with concomitant TCS was assessed in a trial of 161 pediatric subjects 6 months to 5 years of age with moderate-to-severe AD (AD-1539). The safety profile of DUPIXENT + TCS in these subjects through Week 16 was similar to the safety profile from trials in adults and pediatric subjects 6 to 17 years of age with AD.

The long-term safety of DUPIXENT ± TCS was assessed in an open-label extension study of 180 pediatric subjects 6 months to 5 years of age with AD (AD-1434). The majority of subjects were treated with DUPIXENT 300 mg every 4 weeks. The safety profile of DUPIXENT ± TCS in subjects followed through Week 52 was similar to the safety profile observed through Week 16 in AD-1539. The long-term safety profile of DUPIXENT ± TCS observed in pediatric subjects 6 months to 5 years of age was consistent with that seen in adults and pediatric subjects 6 to 17 years old with AD. In addition, hand-foot-and-mouth disease was reported in 9 (5%) pediatric subjects and skin papilloma was reported in 4 (2%) pediatric subjects treated with DUPIXENT ± TCS. These cases did not lead to study drug discontinuation *[see Use in Specific Populations (8.4)]*.

Atopic Dermatitis with Hand and/or Foot Involvement

The safety of DUPIXENT was assessed in a 16-week, multicenter, randomized, double-blind, parallel-group, placebo-controlled trial (Liberty-AD-HAFT) in 133 adult and pediatric subjects 12 to 17 years of age with atopic dermatitis with moderate-to-severe hand and/or foot involvement *[see Clinical Studies (14)]*. In this trial 67 subjects received DUPIXENT, and 66 subjects received placebo. DUPIXENT-treated subjects received the recommended dosage based on their age and body weight *[see Dosage and Administration (2.3)]*. The safety profile of DUPIXENT in these subjects through Week 16 was consistent with the safety profile from studies in adult and pediatric subjects 6 months of age and older with moderate-to-severe AD.

Asthma

Adults and Pediatric Subjects 12 Years of Age and Older with Asthma

A total of 2888 adult and pediatric subjects 12 to 17 years of age with moderate-to-severe asthma (AS) were evaluated in 3 randomized, placebo-controlled, multicenter trials of 24 to 52 weeks duration (DRI12544, QUEST, and VENTURE). 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) (DRI12544 and QUEST). A total of 210 subjects with oral corticosteroid-dependent asthma receiving high-dose inhaled corticosteroids plus up to two additional controllers were enrolled (VENTURE). The safety population (DRI12544 and QUEST) 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 DRI12544 and QUEST, 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 7 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 DRI12544 and QUEST.

Table 7: Adverse Reactions Occurring in ≥1% of Adult and Pediatric Subjects 12 Years of Age and Older with Asthma in the DUPIXENT Groups in DRI12544 and QUEST and Greater than Placebo (6 Month Safety Pool)

Adverse Reaction	DRI12544 and QUEST		
	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 ≥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.

Pediatric Subjects 6 to 11 Years of Age with Asthma

The safety of DUPIXENT was assessed in 405 pediatric subjects 6 to 11 years of age with moderate-to-severe asthma (VOYAGE). The safety profile of DUPIXENT in these subjects through Week 52 was similar to the safety profile from studies in adult and pediatric subjects 12 years of age and older with moderate-to-severe asthma with the addition of helminth infections. Helminth infections were reported in 2.2% (6 subjects) in the DUPIXENT group and 0.7% (1 subject) in the placebo group. The majority of cases were enterobiasis, reported in 1.8% (5

subjects) in the DUPIXENT group and none in the placebo group. There was one case of ascariasis in the DUPIXENT group. All helminth infection cases were mild to moderate and subjects recovered with anti-helminth treatment without DUPIXENT treatment discontinuation.

Chronic Rhinosinusitis with Nasal Polyps

A total of 722 adult subjects with chronic rhinosinusitis with nasal polyps (CRSwNP) were evaluated in 2 randomized, placebo-controlled, multicenter 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 from both studies.

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

Table 8 summarizes the adverse reactions that occurred at a rate of at least 1% in adult subjects treated with DUPIXENT and at a higher rate than in their respective comparator group in SINUS-24 and SINUS-52.

Table 8: Adverse Reactions Occurring in ≥1% of Adult Subjects with CRSwNP in the DUPIXENT Group in SINUS-24 and SINUS-52 and Greater than Placebo (24-Week Safety Pool)

Adverse Reaction	SINUS-24 and SINUS-52	
	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.

Eosinophilic Esophagitis

Adults and Pediatric Subjects 12 Years of Age and Older with EoE

A total of 239 adult and pediatric subjects 12 years of age and older, weighing at least 40 kg, with EoE were evaluated in a randomized, double-blind, parallel-group, multicenter, placebo-controlled trial, including two 24-week treatment periods (Study EoE-1 Parts A and B) and received either DUPIXENT 300 mg QW or placebo *[see Clinical Studies (14.4)]*.

The proportion of subjects who discontinued treatment due to adverse events was 2% of the placebo group and 2% of the DUPIXENT 300 mg QW group.

Table 9 summarizes the adverse reactions that occurred at a rate of at least 2% in subjects treated with DUPIXENT and at a higher rate than in their respective comparator group in Parts A and B.

Table 9: Adverse Reactions Occurring in ≥2% of Adult and Pediatric Subjects 12 Years of Age and Older with EoE Treated with DUPIXENT in a Placebo-Controlled Trial (Study EoE-1 Parts A and B; 24-Week Safety Pool)

	Study EoE-1 Parts A and B	
Adverse Reaction	**DUPIXENT 300 mg QW N=122 n %**	**Placebo N=117 n (%**
Injection site reactions[a]	46 (38%)	39 (33%)
Upper respiratory tract infections[b]	22 (18%)	12 (10%)
Arthralgia	3 2%	1 1%
Herpes viral infections[c]	3 (2%)	1 1%

[a] Injection site reactions are composed of several terms including, but not limited to, injection site swelling, pain, and bruising.
[b] Upper respiratory tract infections are composed of several terms including, but not limited to, COVID-19, sinusitis, and upper respiratory tract infection.
[c] Herpes viral infections are composed of oral herpes and herpes simplex.

The safety profile of DUPIXENT in 72 pediatric subjects 12 to 17 years of age, weighing at least 40 kg, and adults in Parts A and B was similar.

Pediatric Subjects 1 to 11 Years of Age, Weighing at least 15 kg, with EoE

A total of 61 pediatric subjects 1 to 11 years of age, weighing at least 15 kg, with EoE were evaluated in a randomized, blinded, parallel-group, multicenter trial, including an initial 16-week placebo-controlled treatment period (Study EoE-2 Part A) and a 36-week extended active treatment period (Study EoE-2 Part B). Subjects in Part A received a weight-based dosing regimen of DUPIXENT or placebo *[see Clinical Studies (14.4)]*. All subjects in Part B completed Part A and received active treatment with weight-based dosing regimens of DUPIXENT in Part B (N=47).

The safety profile of DUPIXENT through Week 16 of Study EoE-2 Part A was generally similar to the safety profile in adult and pediatric subjects 12 years of age and older with EoE. In Part B, a helminth infection was reported in one DUPIXENT-treated subject.

Prurigo Nodularis

A total of 309 adult subjects with prurigo nodularis (PN) were evaluated in two 24-week randomized, double-blind, placebo-controlled, multicenter trials (PRIME and PRIME2). The safety pool included data from the 24-week treatment and 12-week follow-up periods from both trials.

The proportion of subjects who discontinued treatment due to adverse events was 3% of the placebo group and 0% of the DUPIXENT 300 mg Q2W group.

The safety population had a mean age of 49 years; 65% of subjects were female, 56% were White, 34% were Asian, and 6% were Black or African American. Subjects with co-morbid conditions included 43% of subjects with a history of atopy (defined as having a medical history of AD, allergic rhinitis/rhino conjunctivitis, asthma, or food allergy), 8% of subjects with a history of hypothyroidism and 9% of subjects with a history of diabetes mellitus type 2.

Table 10 summarizes the adverse reactions that occurred at a rate of at least 2% in subjects treated with DUPIXENT and at a higher rate than in their respective comparator group in PRIME and PRIME2.

Table 10: Adverse Reactions Occurring in ≥2% of Adult Subjects with PN in the DUPIXENT Group in PRIME and PRIME2 and Greater than Placebo

Adverse Reaction	PRIME and PRIME2	
	DUPIXENT 300 mg Q2W N=152 n (%	Placebo N=157 n (%
Nasopharyngitis[a]	8 5%	3 2%
Conjunctivitis[b]	6 4%	2 1%
Herpes Infection[c]	5 3%	0%
Dizziness[d]	5 3%	2 1%
Myalgia[e]	5 3%	2 1%
Diarrhea	4 3%	1 1%

[a] Nasopharyngitis includes pharyngitis
[b] Conjunctivitis includes conjunctivitis and allergic conjunctivitis.
[c] Herpes infection includes oral herpes, genital herpes simplex, herpes zoster and ophthalmic herpes zoster
[d] Dizziness includes dizziness postural, vertigo and vertigo positional
[e] Myalgia includes musculoskeletal pain and musculoskeletal chest pain

Chronic Obstructive Pulmonary Disease

A total of 1874 adult subjects with inadequately controlled chronic obstructive pulmonary disease (COPD) and an eosinophilic phenotype were evaluated in two randomized, double-blind, multicenter, parallel group, placebo-controlled trials with a 52-week treatment period (BOREAS and NOTUS) *[see Clinical Studies (14.6)]*. Of those randomized, 1872 subjects received at least one dose of DUPIXENT 300 mg or placebo subcutaneously every 2 weeks (Q2W). The safety of DUPIXENT was assessed in the pooled safety population from BOREAS and NOTUS, which consisted of 938 adult subjects treated with DUPIXENT. Of the subjects treated with DUPIXENT, 98% utilized inhaled triple therapy at baseline (comprising of an inhaled corticosteroid, long-acting beta-agonist, and long-acting muscarinic antagonist), and 97% had chronic bronchitis.

Table 11 summarizes the adverse reactions that occurred in at least 2% of subjects treated with DUPIXENT and at a higher rate than placebo in BOREAS and NOTUS trials.

Table 11: Adverse Reactions That Occurred in ≥2% of Adult Subjects with COPD Treated with DUPIXENT in BOREAS and NOTUS Trials (Pooled Safety Population) and Greater than Placebo

Adverse Reaction	BOREAS and NOTUS	
	DUPIXENT 300 mg Q2W N=938 n (%	Placebo N=934 n (%
Viral Infection[a]	133 (14.2)	115 (12.3)
Headache	73 (7.8)	62 (6.6)
Nasopharyngitis	73 (7.8)	69 (7.4)
Back Pain	42 (4.5)	29 (3.1)
Diarrhea[a]	35 (3.7)	30 (3.2)
Arthralgia	29 (3.1)	25 (2.7)
Urinary Tract Infection	28 (3.0)	18 (1.9)
Local Administration Reaction[a]	26 (2.8)	6 (0.6)
Injection Site Reaction	11 (1.2)	2 (0.2)
Rhinitis	24 (2.6)	17 (1.8)
Eosinophilia[b]	22 (2.3)	7 (0.7)
Toothache	20 (2.1)	11 (1.2)
Gastritis	19 (2)	7 (0.7)

[a] Consists of multiple similar terms.
[b] Eosinophilia was defined as blood eosinophils ≥3,000 cells/mcL or deemed by the investigator to be an adverse event. None met the criteria for serious eosinophilic conditions.

Less Common Adverse Reaction in Subjects with COPD: Cholecystitis

In adult subjects with COPD, cholecystitis was reported in 6 subjects 0.6%) in the DUPIXENT group compared to 1 subject (0.1%) in the placebo group. Among these subjects, serious cholecystitis was reported in 4 (0.4%) of the DUPIXENT group compared with 0% of the placebo group.

Specific Adverse Reactions for AD, Asthma, CRSwNP, EoE, PN and COPD

Conjunctivitis and Keratitis

In adult subjects with AD, conjunctivitis was reported in 10% (34 per 100 subject-years) in the 300 mg Q2W dose group and in 2% of the placebo group (8 per 100 subject-years) during the 16-week treatment period of the monotherapy trials (SOLO 1, SOLO 2, and AD-1021). During the 52-week treatment period of concomitant therapy AD trial (CHRONOS), 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). During the long-term OLE trial with data through 260 weeks (AD-1225), conjunctivitis was reported in 21% of the DUPIXENT group (12 per 100 subject-years).

In DUPIXENT AD monotherapy trials (SOLO 1, SOLO 2, and AD-1021) through Week 16, 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 52-week DUPIXENT + topical corticosteroids (TCS) AD trial (CHRONOS), keratitis was reported in 4% of the DUPIXENT + TCS group (4 per 100 subject-years) and in 2% of the placebo + TCS group (2 per 100 subject-

years). Conjunctivitis and keratitis occurred more frequently in AD subjects who received DUPIXENT. Conjunctivitis was the most frequently reported eye disorder. During the long-term OLE trial with data through 260 weeks (AD-1225 , keratitis was reported in 3% of the DUPIXENT group (1 per 100 subject-years). Most subjects with conjunctivitis or keratitis recovered or were recovering during the treatment period.

Among subjects with asthma, the frequency of conjunctivitis and keratitis was similar between DUPIXENT and placebo.

In adult 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.

In the 52-week CRSwNP study (SINUS-52), the frequency of conjunctivitis was 3% in the DUPIXENT adult subjects and 1% in the placebo subjects; all of these subjects recovered. There were no cases of keratitis reported in the CRSwNP development program *[see Warnings and Precautions (5.2)]*.

Among subjects with EoE, there were no reports of conjunctivitis and keratitis in the DUPIXENT group in placebo-controlled trials *[see Warnings and Precautions (5.2)]*. In the 36-week active treatment extension period of Study EoE-2 Part B, conjunctivitis was reported in 4% of DUPIXENT-treated pediatric subjects with EoE.

Among subjects with PN, the frequency of conjunctivitis was 4% in the DUPIXENT group compared to 1% in the placebo group; all of these subjects recovered or were recovering during the treatment period. There were no cases of keratitis reported in the PN development program *[see Warnings and Precautions (5.2)]*.

Among subjects with COPD, the frequency of conjunctivitis and keratitis was 1.4% and 0.1% in the DUPIXENT group and 1% and 0% in the placebo group, respectively *[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 AD trials. The rates remained stable through 260 weeks in the long-term OLE trial (AD-1225).

Herpes zoster was reported in <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 AD monotherapy trials. In the 52-week DUPIXENT + TCS AD 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). During the long-term OLE trial with data through 260 weeks (AD-1225), 2.0% of DUPIXENT-treated subjects reported herpes zoster (0.94 per 100 subject-years of follow up). Among asthma subjects the frequency of herpes zoster was similar between DUPIXENT and placebo. Among subjects with CRSwNP or EoE there were no reported cases of herpes zoster or eczema herpeticum.

Among subjects with PN, herpes zoster and ophthalmic herpes zoster were each reported in <1% of the DUPIXENT group (1 per 100 subject-years) and 0% of the placebo group.

Among subjects with COPD, herpes zoster was reported in 0.9% of the DUPIXENT group and 0.2% of the placebo group. Ophthalmic herpes zoster was reported in 0.1% of the DUPIXENT group and 0.2% of the placebo group.

Hypersensitivity Reactions

Hypersensitivity reactions were reported in <1% of DUPIXENT-treated subjects. These included anaphylaxis, serum sickness or serum sickness-like reactions, generalized urticaria, rash, erythema nodosum, and erythema multiforme *[see Contraindications (4), Warnings and Precautions (5.1), and Clinical Pharmacology (12.6)]*.

Eosinophils

DUPIXENT-treated subjects with AD, asthma, CRSwNP, and COPD had a greater initial increase from baseline in blood eosinophil count compared to subjects treated with placebo. In adult subjects with AD (SOLO 1, SOLO 2, and AD-1021), the mean and median increases in blood eosinophils from baseline to Week 4 were 100 and 0 cells/mcL, respectively. In pediatric subjects <6 years old with AD, the mean and median increases from baseline to week 4 were 478 and 90 cells/mcL, respectively.

In adult and pediatric subjects 12 years of age and older with asthma (DRI12544 and QUEST), the mean and median increases in blood eosinophils from baseline to Week 4 were 130 and 10 cells/mcL, respectively. In subjects 6 to 11 years of age with asthma (VOYAGE), the mean and median increases in blood eosinophils from baseline to Week 12 were 124 and 0 cells/mcL, respectively.

In adult subjects with CRSwNP (SINUS-24 and SINUS-52), the mean and median increases in blood eosinophils from baseline to Week 16 were 150 and 50 cells/mcL, respectively.

In subjects with COPD (BOREAS and NOTUS), the mean and median increases in blood eosinophils from baseline to Week 8 were 60 and 0 cells/mcL, respectively.

An increase from baseline in blood eosinophil count was not observed in adult and pediatric subjects 12 years of age and older with EoE treated with DUPIXENT as compared to placebo (Study EoE-1). In pediatric subjects 1 to 11 years of age with EoE (Study EoE-2 Part A), blood eosinophil counts were generally consistent with those observed in Study EoE-1.

In subjects with PN (PRIME and PRIME2), the mean and median decrease in blood eosinophils from baseline to Week 4 were 9 and 10 cells/mcL, respectively.

In the trials for the COPD indication, treatment-emergent eosinophilia ≥500 cells/mcL) was higher in DUPIXENT (41.7%) than in the placebo group (39.4%); none of the cases were associated with clinical symptoms, and treatment-emergent eosinophilia ≥1000 cells/mcL) was higher in DUPIXENT (13.6%) than in the placebo group (8.1%).

Across the trials for AD, asthma, and CRSwNP indications, the incidence of treatment-emergent eosinophilia (≥500 cells/mcL) was similar in DUPIXENT and placebo groups.

In the trials for the PN indication, the incidence of treatment-emergent eosinophilia (≥500 cells/mcL) was lower in DUPIXENT than in the placebo group.

Treatment-emergent eosinophilia (≥5,000 cells/mcL) was reported in <3% of DUPIXENT-treated subjects and <0.5% in placebo-treated subjects (SOLO 1, SOLO 2, and AD-1021; DRI12544, QUEST, and VOYAGE; SINUS-24 and SINUS-52; PRIME and PRIME2; BOREAS and NOTUS). Blood eosinophil counts declined to near baseline or remained below baseline levels (PRIME and PRIME2; BOREAS and NOTUS) during study treatment. In study AD-1539,

treatment-emergent eosinophilia (≥5,000 cells/mcL) was reported in 8% of DUPIXENT-treated subjects and 0% in placebo-treated subjects *[see Warnings and Precautions (5.3)]*.

Cardiovascular Thromboembolic Events

In the 1-year placebo-controlled trial in adult and pediatric subjects 12 years of age and older with asthma (QUEST), 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 AD (CHRONOS), 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 adult subjects with CRSwNP (SINUS-24), 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 adult subjects with CRSwNP (SINUS-52), there were no cases of cardiovascular thromboembolic events (cardiovascular deaths, non-fatal myocardial infarctions, and non-fatal strokes) reported in any treatment arm.

In the 24-week placebo-controlled trial in subjects with EoE (Study EoE-1 Parts A and B), 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 Postmarketing Experience

The following adverse reactions have been identified during post-approval use of DUPIXENT. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Immune system disorders: angioedema *[see Warnings and Precautions (5.1)]*

Skin and subcutaneous tissue disorders: Facial skin reactions, including erythema, rash, scaling, edema, papules, pruritus, burning, and pain

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.

Healthcare providers and patients may call 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-4Rα) during organogenesis through parturition at doses up to 10-times the maximum recommended human dose (MRHD) (*see Data*).

The 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-4Rα 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 effectiveness of DUPIXENT have been established in pediatric patients 6 months of age and older with moderate-to-severe AD, whose disease is not adequately controlled with topical prescription therapies or when those therapies are not advisable *[see Clinical Studies (14.1)]*.

Use of DUPIXENT in this age group is supported by data from the following clinical trials:

- AD-1526 which included 251 pediatric subjects 12 to 17 years of age with moderate-to-severe AD. Of the 251 subjects, 82 were treated with DUPIXENT 200 mg Q2W (<60 kg) or 300 mg Q2W (≥60 kg) and 85 were treated with matching placebo
- AD-1652 which included 367 pediatric subjects 6 to 11 years of age with severe AD. Of the 367 subjects, 120 were treated with DUPIXENT 300 mg Q4W + TCS (15 to <30 kg) or 200 mg Q2W + TCS ≥30 kg) and 123 were treated with matching placebo + TCS
- AD-1539 which included 162 pediatric subjects 6 months to 5 years of age with moderate-to-severe AD. Of the 162 subjects, 83 were treated with DUPIXENT 200 mg Q4W + TCS (5 to <15 kg) or 300 mg Q4W + TCS (15 to <30 kg) and 79 subjects were assigned to be treated with matching placebo + TCS
- AD-1434, an open-label extension study that enrolled 275 pediatric subjects 12 to 17 years of age treated with DUPIXENT ± TCS, 368 pediatric subjects 6 to 11 years of age treated with DUPIXENT ± TCS, and 180 pediatric subjects 6 months to 5 years of age treated with DUPIXENT ± TCS
- Liberty-AD-HAFT which included 27 pediatric subjects 12 to 17 years of age with atopic dermatitis with moderate-to-severe hand and/or foot involvement treated with DUPIXENT (N=14) or matching placebo (N=13)

The safety and effectiveness were generally consistent between pediatric and adult patients *[see Adverse Reactions (6.1) and Clinical Studies (14.1)]*. In addition, hand-foot-and-mouth disease was reported in 9 (5%) pediatric subjects and skin papilloma was reported in 4 (2%) pediatric subjects 6 months to 5 years of age treated with DUPIXENT ± TCS in AD-1434. These cases did not lead to study drug discontinuation *[see Adverse Reactions (6.1)]*.

Safety and effectiveness in pediatric patients younger than 6 months of age with AD have not been established.

Asthma

The safety and effectiveness of DUPIXENT for an add-on maintenance treatment in patients with moderate-to-severe asthma characterized by an eosinophilic phenotype or with oral corticosteroid dependent asthma have been established in pediatric patients 6 years of age and older. Use of DUPIXENT for this indication is supported by evidence from adequate and well-controlled studies in adult and pediatric patients 6 years and older *[see Clinical Studies (14.2)]*.

Pediatric Subjects 12 to 17 Years of Age:

A total of 107 pediatric subjects 12 to 17 years of age with moderate-to-severe asthma were enrolled in QUEST 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 pediatric subjects 12 to 17 years of age and adults. For both the 200 mg and 300 mg Q2W doses, improvements in FEV_1 (LS mean change from baseline at Week 12) were observed (0.36 L and 0.27 L, respectively). For the 200 mg Q2W dose, subjects had a reduction in the rate of severe exacerbations that was consistent with adults. Dupilumab exposure was higher in pediatric subjects 12 to 17 years of age 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 pediatric subjects 12 to 17 years of age was generally similar to the adults *[see Adverse Reactions (6.1)]*.

Pediatric Subjects 6 to 11 Years of Age:

A total of 408 pediatric subjects 6 to 11 years of age with moderate-to-severe asthma were enrolled in VOYAGE, which evaluated doses of 100 mg Q2W or 200 mg Q2W. Improvement in asthma exacerbations and lung function were demonstrated *[see Clinical Studies (14.2)]*. The effectiveness of DUPIXENT 300 mg Q4W in subjects 6 to 11 years of age with body weight 15 to <30 kg was extrapolated from efficacy of 100 mg Q2W in VOYAGE with support from population pharmacokinetic analyses showing higher drug exposure levels with 300 mg Q4W *[see Clinical Pharmacology (12.3)]*. Subjects who completed the treatment period of the VOYAGE study could participate in the open-label extension study (LTS14424). Eighteen subjects (≥15 to <30 kg) out of 365 subjects were exposed to 300 mg Q4W in this study, and the safety profile in these eighteen subjects was consistent with that seen in VOYAGE. Additional safety for DUPIXENT 300 mg Q4W is based upon available safety information from the pediatric AD indication *[see Adverse Reactions (6.1) and Clinical Pharmacology (12.3)]*.

Safety and effectiveness in pediatric patients younger than 6 years of age with asthma have not been established.

CRSwNP

The safety and effectiveness of DUPIXENT for add-on maintenance treatment in patients with inadequately controlled chronic rhinosinusitis with nasal polyps (CRSwNP) have been established in pediatric patients aged 12 years and older. Use of DUPIXENT for this indication is supported by evidence from adequate and well-controlled studies of DUPIXENT as add-on maintenance treatment in adults with inadequately controlled CRSwNP (SINUS-24 and SINUS-52) with the following additional data:

- Pharmacokinetic (PK) data from adult and pediatric patients aged 12 years and older with moderate-to-severe asthma and adult patients with inadequately controlled CRSwNP
- Safety data in pediatric patients aged 12 years and older with moderate-to-severe asthma *[see Adverse Reactions (6.1), Clinical Pharmacology (12.3), and Clinical Studies (14.3)]*

Safety and effectiveness in pediatric patients younger than 12 years of age with CRSwNP have not been established.

EoE

The safety and effectiveness of DUPIXENT for the treatment of EoE have been established in pediatric subjects 1 year of age and older, weighing at least 15 kg. Use of DUPIXENT in this population is supported by an adequate well-controlled study in adults and 72 pediatric subjects 12 to 17 years of age (Study EoE-1), a clinical study in 61 pediatric subjects 1 to 11 years of age (Study EoE-2), and pharmacokinetic data in adult and pediatric subjects 1 to 17 years of age. The safety of DUPIXENT in pediatric subjects 1 to 17 years of age was similar to adults *[see Adverse Reactions (6.1), Clinical Pharmacology (12.3), and Clinical Studies (14.4)]*.

Safety and effectiveness in pediatric patients younger than 1 year of age, or weighing less than 15 kg, with EoE have not been established.

Prurigo Nodularis

Safety and effectiveness in pediatric patients younger than 18 years of age with PN have not been established.

Chronic Obstructive Pulmonary Disease

The safety and effectiveness in pediatric patients less than 18 years of age with COPD have not been established. COPD is largely a disease of adult patients.

8.5 Geriatric Use

Of the 1539 subjects with AD exposed to DUPIXENT in a dose-ranging study and placebo-controlled trials, 70 subjects were 65 years or older. Clinical trials of DUPIXENT in AD did not include sufficient numbers of subjects aged 65 years and over 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.

Clinical studies of DUPIXENT in EoE did not include sufficient numbers of subjects aged 65 years and over to determine whether they respond differently from younger adult subjects.

Of the 152 subjects with PN exposed to DUPIXENT, a total of 37 were 65 years or older including 8 subjects 75 years or older. Clinical trials did not include a sufficient number of subjects 65 years of age and older to determine whether they respond differently from younger adult subjects.

Of the 1874 subjects with COPD randomized in clinical trials of DUPIXENT, a total of 1072 were 65 years or older, while 244 subjects were 75 years or older. No overall differences in safety or effectiveness of DUPIXENT have been observed between subjects 65 years of age and older and younger adult subjects.

10 OVERDOSAGE

There is no specific treatment for DUPIXENT overdose. In the event of overdosage, contact Poison Control (1-800-222-1222) for the latest recommendations and 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-4Rα 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 either a single-dose pre-filled syringe with needle shield or a single-dose pre-filled pen in a siliconized Type-1 clear glass syringe. The needle cap is not made with natural rubber latex.

Each 300 mg pre-filled syringe or pre-filled pen 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 or pre-filled pen 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-4Rα 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 driven by IL-4 and IL-13 is an important component in the pathogenesis of asthma, AD, CRSwNP, EoE, PN, and COPD. Multiple cell types that express IL-4Rα (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-4Rα with dupilumab inhibits IL-4 and IL-13 cytokine-induced inflammatory responses, including the release of proinflammatory cytokines, chemokines, nitric oxide, and IgE. The mechanism of dupilumab action has not been definitively established.

12.2 Pharmacodynamics

Consistent with inhibition of IL-4 and IL-13 signaling, dupilumab treatment decreased certain biomarkers of inflammation. 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. Reductions in these 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 (DRI12544) and 70% at Week 52 (QUEST). For FeNO, the mean percent reduction from baseline at Week 2 was 35% and 24% in DRI12544 and QUEST, respectively, and in the overall safety population, the mean FeNO level decreased to 20 ppb.

Antibody Response to Non-Live Vaccines During DUPIXENT Treatment

In a clinical study, adult subjects with AD were treated once weekly for 16 weeks with 300 mg of DUPIXENT (twice the recommended dosing frequency). After 12 weeks of administration, subjects received a Tdap vaccine and a meningococcal polysaccharide vaccine. Antibody responses to tetanus toxoid and serogroup C meningococcal polysaccharide were assessed 4 weeks later. Antibody responses to both tetanus toxoid and serogroup C meningococcal polysaccharide were similar in DUPIXENT-treated and placebo-treated subjects. Antibody responses to the other active components of both vaccines were not assessed. Antibody responses to other non-live vaccines were also not assessed.

12.3 Pharmacokinetics

The pharmacokinetics of dupilumab is similar in subjects with AD, asthma, CRSwNP, EoE, PN, and COPD.

Absorption

Following an initial subcutaneous (SC) dose of 600 mg, 400 mg, or 300 mg, dupilumab reached peak mean ± 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 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 ± SD steady-state trough concentrations ranged from 55.3±34.3 mcg/mL to 80.2±35.3 mcg/mL for 300 mg administered Q2W, from 173±75.9 mcg/mL to 195±71.7 mcg/mL for 300 mg administered weekly, and from 29.2±18.7 to 36.5±22.2 mcg/mL for 200 mg administered Q2W.

The bioavailability of dupilumab following a SC dose is similar between AD, asthma, CRSwNP, EoE, PN, and COPD subjects, 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 QW, 300 mg Q2W, 200 mg Q2W, 300 mg Q4W, or 200 mg Q4W dupilumab, the median times to non-detectable concentration (<78 ng/mL) ranged from 9 to 13 weeks in adults and pediatric subjects 12 to 17 years of age. Population pharmacokinetic analyses indicate the median times to non-detectable concentration are approximately 1.5 times (up to 19 weeks) and 2.5 times (up to 32 weeks) longer in pediatric subjects 6 to 11 years of age and pediatric subjects 6 months to 5 years of age, 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.

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

Age

Based on population pharmacokinetic analysis, age did not affect dupilumab clearance in adults and in pediatric subjects 6 to 17 years of age. In pediatric subjects 6 months to 5 years of age, clearance increased with age.

Geriatric Patients

No overall differences in the pharmacokinetics of dupilumab were observed between elderly and younger adult subjects.

Pediatric Patients

Atopic Dermatitis

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

For pediatric subjects 6 to 11 years of age with AD receiving every other week dosing (Q2W) with 200 mg (≥30 kg) or every four week dosing (Q4W) with 300 mg (<30 kg), mean ± SD steady-state trough concentration was 86.0±34.6 mcg/mL and 98.7±33.2 mcg/mL, respectively.

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

Asthma

A total of 107 pediatric subjects 12 to 17 years of age with asthma were enrolled in QUEST. 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 Q2W.

In VOYAGE, dupilumab pharmacokinetics was investigated in 270 subjects with moderate-to-severe asthma following subcutaneous administration of either 100 mg Q2W (for 91 pediatric subjects weighing <30 kg) or 200 mg Q2W (for 179 pediatric subjects weighing ≥30 kg). The mean ± SD steady-state trough concentration was 58.4±28.0 mcg/mL and 85.1±44.9 mcg/mL,

respectively. Simulation of a 300 mg Q4W subcutaneous dose in pediatric subjects 6 to 11 years of age with body weight of ≥15 to <30 kg resulted in predicted steady-state trough concentrations (98.7±41.0 mcg/mL) and average concentrations higher than the observed trough concentrations and average concentrations of 100 mg Q2W (<30 kg).

CRSwNP

Clinical studies have not been conducted in pediatric patients aged 12 years and older with CRSwNP. Dupilumab exposures are expected to be comparable between adults and pediatric patients aged 12 years and older at the recommended dosage for CRSwNP (300 mg every 2 weeks).

Eosinophilic Esophagitis

In Study EoE-1, dupilumab pharmacokinetics were investigated in 35 pediatric subjects 12 to 17 years of age, weighing at least 40 kg, with EoE, receiving 300 mg QW. The mean ± SD steady-state trough concentration of dupilumab was 227±95.3 mcg/mL.

In Study EoE-2 Part A, dupilumab pharmacokinetics were investigated in 20 pediatric subjects 1 to 11 years of age with EoE receiving the following weight-based dosing regimens: ≥15 to <30 kg (200 mg Q2W) and ≥30 to <40 kg (300 mg Q2W). At Week 16, the mean ± SD steady-state trough concentration of dupilumab was 174±66.2 mcg/mL.

The systemic exposure in pediatric subjects 1 to 11 years of age with a body weight ≥40 kg receiving 300 mg QW is expected to be comparable to adult and pediatric subjects 12 years and older with a body weight ≥40 kg. The systemic exposure in pediatric subjects 12 to 17 years of age with a body weight <40 kg receiving 300 mg Q2W is expected to be comparable to pediatric subjects 6 to 11 years of age.

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 subjects 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 AD (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%.

12.6 Immunogenicity

The observed incidence of anti-drug antibodies is highly dependent on the sensitivity and specificity of the assay. Differences in assay methods preclude meaningful comparisons of the incidence of anti-drug antibodies in the studies described below with the incidence of anti-drug antibodies in other studies, including those of DUPIXENT or of other dupilumab products.

Atopic Dermatitis

Approximately 6% of subjects with AD who received DUPIXENT 300 mg Q2W for 52 weeks developed antibodies to DUPIXENT; approximately 2% exhibited persistent ADA responses, and approximately 1% had neutralizing antibodies. Similar results were observed in pediatric subjects 6 months to 11 years of age with AD who received either DUPIXENT 200 mg Q2W, 200 mg Q4W, or 300 mg Q4W.

Approximately 16% of pediatric subjects 12 to 17 years of age with AD who received DUPIXENT 300 mg or 200 mg Q2W for 16 weeks developed antibodies to DUPIXENT; approximately 3% exhibited persistent ADA responses, and approximately 5% had neutralizing antibodies.

Asthma

Approximately 5% of subjects with asthma who received DUPIXENT 300 mg Q2W for 52 weeks developed antibodies to DUPIXENT; approximately 2% exhibited persistent ADA responses, and approximately 2% had neutralizing antibodies. Similar results were observed in pediatric subjects 6 to 11 years of age with asthma who received either DUPIXENT 100 mg Q2W or 200 mg Q2W up to 52 weeks.

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

Chronic Rhinosinusitis with Nasal Polyps

Approximately 5% of adult subjects with CRSwNP who received DUPIXENT 300 mg Q2W for 52 weeks developed antibodies to DUPIXENT; approximately 2% exhibited persistent ADA responses, and approximately 3% had neutralizing antibodies.

Eosinophilic Esophagitis

Approximately 1% of subjects with EoE who received DUPIXENT 300 mg QW for 52 weeks developed antibodies to DUPIXENT; no subjects exhibited persistent ADA responses or had neutralizing antibodies. Similar results were observed in pediatric subjects 1 to 11 years of age with EoE administered either DUPIXENT 200 mg Q2W or 300 mg Q2W for 52 weeks.

Prurigo Nodularis

Approximately 8% of subjects with PN who received DUPIXENT 300 mg Q2W for 24 weeks developed antibodies to DUPIXENT; approximately 1% exhibited persistent ADA responses, and approximately 3% had neutralizing antibodies.

Chronic Obstructive Pulmonary Disease

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

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

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

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-4Rα 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 (SOLO 1 (NCT02277743), SOLO 2 (NCT02277769), and CHRONOS (NCT02260986)) enrolled a total of 2119 adult subjects 18 years of age and older with moderate-to-severe 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 ≥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 (SOLO 1 and SOLO 2), subjects received DUPIXENT or placebo for 16 weeks.

In the concomitant therapy trial (CHRONOS), 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 (SOLO 1, SOLO 2, and CHRONOS)

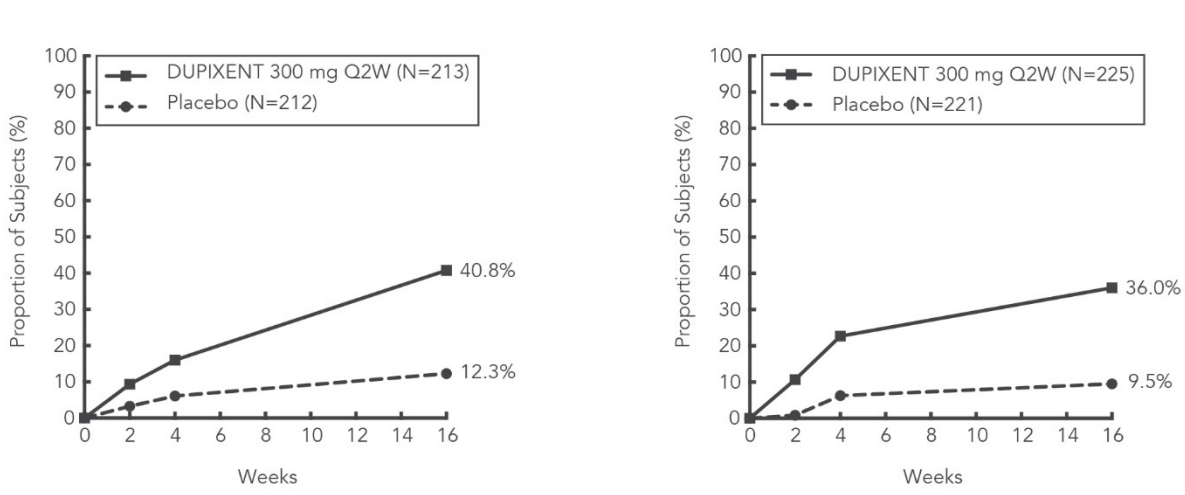
The results of the DUPIXENT monotherapy trials (SOLO 1 and SOLO 2) and the DUPIXENT with concomitant TCS trial (CHRONOS) are presented in Table 12.

Table 12: Efficacy Results of DUPIXENT with or without Concomitant TCS at Week 16 (FAS) in Adult Subjects 18 Years of Age and Older with Moderate-to-Severe AD

	SOLO 1		SOLO 2		CHRONOS	
	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 Adult Subjects 18 Years of Age and Older with Moderate-to-Severe AD with ≥4-point Improvement on the Peak Pruritus NRS in SOLO 1[a] and SOLO 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 CHRONOS, 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 (CHRONOS) are presented in Table 13.

Table 13: Efficacy Results (IGA 0 or 1) of DUPIXENT with Concomitant TCS at Week 16 and 52 in Adult Subjects 18 Years of Age and Older with Moderate-to-Severe AD

	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 CHRONOS, 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 SOLO 1, SOLO 2, and CHRONOS were generally consistent with the results in the overall study population.

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

Subjects in SOLO 1 and SOLO 2 who had an IGA 0 or 1 with a reduction of ≥2 points were re-randomized into SOLO CONTINUE (NCT02395133). SOLO CONTINUE 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.

Pediatric Subjects 12 to 17 Years of Age with Atopic Dermatitis

The efficacy of DUPIXENT monotherapy in pediatric subjects 12 to 17 years of age was evaluated in a multicenter, randomized, double-blind, placebo-controlled trial (AD-1526; NCT03054428) in 251 pediatric 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 ≥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 AD-1526, 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 AD-1526 are presented in Table 14.

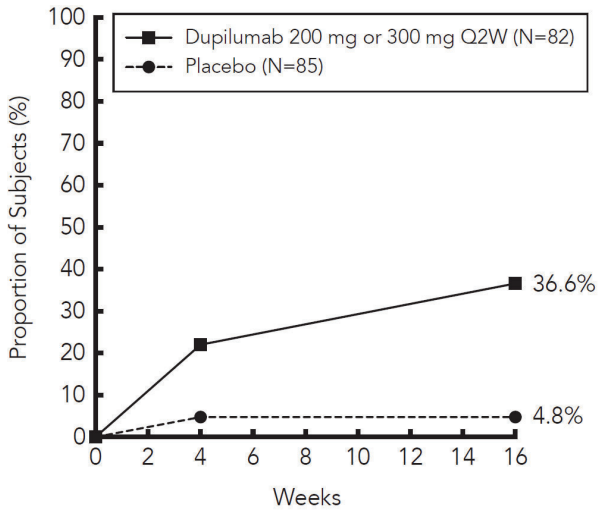
Table 14: Efficacy Results of DUPIXENT in AD-1526 at Week 16 (FAS)[a] in Pediatric Subjects 12 to 17 Years of Age with Moderate-to-Severe AD

	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 Pediatric Subjects 12 to 17 Years of Age with Moderate-to-Severe AD with ≥4-point Improvement on the Peak Pruritus NRS in AD-1526[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.

Pediatric Subjects 6 to 11 Years of Age with Atopic Dermatitis

The efficacy and safety of DUPIXENT use concomitantly with TCS in pediatric subjects was evaluated in a multicenter, randomized, double-blind, placebo-controlled trial (AD-1652; NCT03345914) in 367 subjects 6 to 11 years of age, with AD defined by an IGA score of 4 (scale of 0 to 4), an EASI score ≥21 (scale of 0 to 72), and a minimum BSA involvement of ≥15%. Eligible subjects enrolled into this trial had previous inadequate response to topical medication. Enrollment was stratified by baseline weight (<30 kg; ≥30 kg).

Subjects in the DUPIXENT Q4W + TCS group received an initial dose of 600 mg on Day 1, followed by 300 mg Q4W from Week 4 to Week 12, regardless of weight. Subjects in the DUPIXENT Q2W + TCS group with baseline weight of <30 kg received an initial dose of 200 mg on Day 1, followed by 100 mg Q2W from Week 2 to Week 14, and subjects with baseline weight of ≥30 kg received an initial dose of 400 mg on Day 1, followed by 200 mg Q2W from Week 2 to Week 14. Subjects were permitted to receive rescue treatment at the discretion of the investigator. Subjects who received rescue treatment were considered non-responders.

In AD-1652, the mean age was 8.5 years, the median weight was 29.8 kg, 50% of subjects were female, 69% were White, 17% were Black, and 8% were Asian. At baseline, the mean BSA involvement was 58%, and 17% had received prior systemic non-steroidal immunosuppressants. Also, at baseline the mean EASI score was 37.9, and the weekly average of daily worst itch score was 7.8 on a scale of 0-10. Overall, 92% of subjects had at least one co-morbid allergic condition; 64% had food allergies, 63% had other allergies, 60% had allergic rhinitis, and 47% had asthma.

The primary endpoint was the proportion of subjects with an IGA 0 (clear) or 1 (almost clear) at 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).

Table 15 presents the results by baseline weight strata for the approved dose regimens.

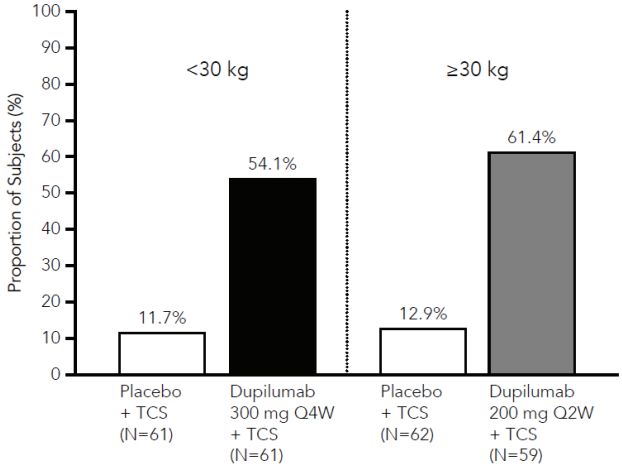
Table 15: Efficacy Results of DUPIXENT with Concomitant TCS in AD-1652 at Week 16 (FAS)[a] in Pediatric Subjects 6 to 11 Years of Age with AD

	DUPIXENT 300 mg Q4W[d] + TCS (N=61)	Placebo + TCS (N=61)	DUPIXENT 200 mg Q2W[e] + TCS (N=59)	Placebo + TCS (N=62)
	<30 kg	<30 kg	≥30 kg	≥30 kg
IGA 0 or 1[b,c]	30%	13%	39%	10%
EASI-75[c]	75%	28%	75%	26%
EASI-90[c]	46%	7%	36%	8%
Peak Pruritus NRS (≥4-point improvement)[c]	54%	12%	61%	13%

[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").
[c] Subjects who received rescue treatment or with missing data were considered as non-responders.
[d] At Day 1, subjects received 600 mg of DUPIXENT.
[e] At Day 1, subjects received 200 mg (baseline weight <30 kg) or 400 mg (baseline weight ≥30 kg of DUPIXENT.

A greater proportion of subjects randomized to DUPIXENT + TCS achieved an improvement in the Peak Pruritus NRS compared to placebo + TCS (defined as ≥4-point improvement at Week 16). See Figure 3.

Figure 3: Proportion of Pediatric Subjects 6 to 11 Years of Age with AD with ≥4-point Improvement on the Peak Pruritus NRS at Week 16 in AD-1652[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.

Pediatric Subjects 6 Months to 5 Years of Age with Atopic Dermatitis

The efficacy and safety of DUPIXENT use concomitantly with TCS in pediatric subjects was evaluated in a multicenter, randomized, double-blind, placebo-controlled trial (AD-1539; NCT03346434) in 162 subjects 6 months to 5 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 ≥10%. Eligible subjects enrolled into this trial had previous inadequate response to topical medication. Enrollment was stratified by baseline weight (≥5 to <15 kg and ≥15 to <30 kg).

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

In AD-1539, the mean age was 3.8 years, the median weight was 16.5 kg, 39% of subjects were female, 69% were White, 19% were Black, and 6% were Asian. At baseline, the mean BSA involvement was 58%, and 29% of subjects had received prior systemic immunosuppressants. Also, at baseline the mean EASI score was 34.1, and the weekly average of daily worst scratch/itch score was 7.6 on a scale of 0-10. Overall, 81.4% of subjects had at least one co-morbid allergic condition; 68.3% had food allergies, 52.8% had other allergies, 44.1% had allergic rhinitis, and 25.5% had asthma.

The primary endpoint was the proportion of subjects with an IGA 0 (clear) or 1 (almost clear) at 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 Worst Scratch/Itch NRS (≥4-point improvement).

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

Table 16: Efficacy Results of DUPIXENT with Concomitant TCS in AD-1539 at Week 16 (FAS)[a] in Pediatric Subjects 6 Months to 5 Years of Age with Moderate-to-Severe AD

	DUPIXENT + TCS 200 mg (5 to <15 kg) or 300 mg (15 to <30 kg) Q4W[d] (N=83)[a]	Placebo + TCS (N=79)[a]	Difference vs. Placebo (95 % CI
IGA 0 or 1[b,c]	28%	4%	24% (13%, 34%
EASI-75[c]	53%	11%	42% (29%, 55%
EASI-90[c]	25%	3%	23% (12%, 33%
Worst Scratch/Itch NRS (≥4-point improvement)[c]	48%	9%	39% (26%, 52%

CI = confidence interval

[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").

[c] Subjects who received rescue treatment 63% and 19% in the placebo and DUPIXENT arms, respectively) or with missing data were considered as non-responders.

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

Atopic Dermatitis with Hand and/or Foot Involvement

The efficacy and safety of DUPIXENT was evaluated in a 16-week, multicenter, randomized, double-blind, parallel-group, placebo-controlled trial (Liberty-AD-HAFT; NCT04417894) in

133 adult and pediatric subjects 12 to 17 years of age with atopic dermatitis with moderate-to-severe hand and/or foot involvement, defined by an established diagnosis of atopic dermatitis and screening to rule out irritant and allergic contact dermatitis through history and appropriate patch testing, and by an IGA (hand and foot) score ≥3 (scale of 0 to 4) and a hand and foot Peak Pruritus Numeric Rating Scale (NRS) score for maximum itch intensity ≥4 (scale of 0 to 10). Fifty-three (53) percent (N=70/133) of the subjects also had moderate-to-severe AD outside of the hands or feet (IGA global ≥3). Eligible subjects had previous inadequate response or intolerance to treatment of hand and/or foot dermatitis with topical AD medications. In this trial 67 subjects received DUPIXENT, and 66 subjects received placebo. DUPIXENT-treated subjects received the recommended dosage based on their age and body weight *[see Dosage and Administration (2.3)]*. Subjects were not allowed concomitant use of topical treatments for AD on the hands and feet during the trial, but were allowed the use of topical treatments for AD on other parts of the body with certain restrictions.

In Liberty-AD-HAFT, 38% of subjects were male, 80% were White, 13% were Asian, and 5% were Black or African American. For ethnicity, 4% were identified as Hispanic or Latino and 96% were identified as not Hispanic or Latino. Seventy-two (72) percent (N=96/133) of subjects had a baseline IGA (hand and foot) score of 3 (atopic dermatitis with moderate hand and/or foot involvement , and 28% (N=37/133) of subjects had a baseline IGA (hand and foot) score of 4 (atopic dermatitis with severe hand and/or foot involvement). The baseline weekly averaged hand and foot Peak Pruritus NRS score was 7.1.

The primary endpoint was the proportion of subjects with an IGA hand and foot score of 0 (clear) or 1 (almost clear) at Week 16. The key secondary endpoint was reduction of itch as measured by the hand and foot Peak Pruritus NRS (≥4-point improvement).

The efficacy results at Week 16 for Liberty-AD-HAFT are presented in Table 17.

Table 17: Efficacy Results of DUPIXENT in Liberty-AD-HAFT at Week 16 (FAS)[a] in Adult and Pediatric Subjects 12 to 17 Years of Age with AD with Moderate-to-Severe Hand and/or Foot Involvement

	DUPIXENT 200/300 mg Q2W[d] (N=67)[a]	Placebo (N=66)[a]	Difference vs. Placebo (95 % CI
IGA (hand and foot) 0 or 1[b,c]	40%	17%	24% (9%, 38%
Improvement (reduction) of weekly averaged hand and foot Peak Pruritus NRS ≥4[c]	52%	14%	39% (24%, 53%

CI = confidence interval

[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”).

[c] Subjects who received rescue treatment (21% and 3% in the placebo and DUPIXENT arms, respectively) or with missing data were considered as non-responders.

[d] Adults received a loading dose of DUPIXENT 600 mg SC followed by 300 mg SC Q2W. Pediatric subjects 12 to 17 years of age received a loading dose of DUPIXENT 600 mg SC followed by 300 mg SC Q2W (for body weight ≥60 kg) or a loading dose of DUPIXENT 400 mg SC followed by 200 mg SC Q2W (for body weight <60 kg).

14.2 Asthma

The asthma development program for patients aged 12 years and older included three randomized, double-blind, placebo-controlled, parallel-group, multicenter trials (DRI12544

(NCT01854047), QUEST (NCT02414854), and VENTURE (NCT02528214)) of 24 to 52 weeks in treatment duration which enrolled a total of 2888 subjects. Subjects enrolled in DRI12544 and QUEST 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 VENTURE 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 QUEST and VENTURE, 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 VENTURE in which OCS dose was tapered as described below.

DRI12544

DRI12544 was a 24-week dose-ranging study which included 776 adult 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 FEV_1 (L) in subjects with baseline blood eosinophils ≥300 cells/mcL. Other endpoints included percent change from baseline in FEV_1 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.

QUEST

QUEST was a 52-week study which included 1902 adult and pediatric subjects (12 years of age and older). DUPIXENT compared with placebo was evaluated in 107 pediatric subjects 12 to 17 years of age 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 FEV_1 at Week 12 in the overall population (unrestricted by minimum baseline blood eosinophils count). Additional secondary endpoints included annualized severe exacerbation rates and FEV_1 in subjects with different baseline levels of blood eosinophils as well as responder rates in the ACQ-5 and AQLQ(S) scores.

VENTURE

VENTURE was a 24-week oral corticosteroid-reduction study in 210 adult and pediatric subjects 15 years of age and older 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 18 below.

Table 18: Demographics and Baseline Characteristics of Asthma Trials

Parameter	DRI12544 (N=776)	QUEST (N=1902)	VENTURE (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 (± SD)	22 (15)	21 (15)	20 (14)
Never smoked %)	77	81	81
Mean exacerbations in previous year (± 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 (± SD)	1.84 (0.54)	1.78 (0.60)	1.58 (0.57)
Mean percent predicted FEV_1 at baseline %) (± SD)	61 (11)	58 (14)	52 (15)
% Reversibility (± SD)	27 (15)	26 (22)	19 (23)
Atopic Medical History % Overall AD %, NP %, AR %)	73 (8, 11, 62)	78 (10, 13, 69)	72 (8, 21, 56)
Mean FeNO ppb (± SD)	39 (35)	35 (33)	38 (31)
Mean total IgE IU/mL (± SD)	435 (754)	432 (747)	431 (776)
Mean baseline blood Eosinophil count (± SD) cells/mcL	350 (430)	360 (370)	350 (310)

ICS = inhaled corticosteroid; FEV_1 = Forced expiratory volume in 1 second; AD = atopic dermatitis; NP = nasal polyps; AR = allergic rhinitis; FeNO = fraction of exhaled nitric oxide

Exacerbations in Subjects with Asthma

DRI12544 and QUEST 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 DRI12544 and the overall population in QUEST), 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 QUEST, 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 DRI12544 and QUEST are shown in Table 19.

Response rates by baseline blood eosinophils and baseline FeNO for QUEST are shown for the overall population in Figure 4 and Figure 5, respectively. Elevation of FeNO can be a marker of the eosinophilic asthma phenotype when supported by clinical data. Pre-specified subgroup analyses of DRI12544 and QUEST demonstrated that there were greater reductions in severe exacerbations in subjects with higher baseline blood eosinophil levels (≥150 cells/mcL) or FeNO ≥25 ppb). In QUEST, 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 and FeNO <25 ppb, similar severe exacerbation rates were observed between DUPIXENT and placebo.

In QUEST, 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 19: Rate of Severe Exacerbations in Asthma Trials (DRI12544 and QUEST)

Trial	Treatment	Baseline Blood EOS ≥300 cells/mcL (primary analysis population, DRI12544)		
		N	Rate (95% CI	Rate Ratio (95% CI
DRI12544	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)	
QUEST	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 4: Relative Risk in Annualized Event Rate of Severe Exacerbations across Baseline Blood Eosinophil Count (cells/mcL) in Subjects with Moderate-to-Severe Asthma (QUEST)

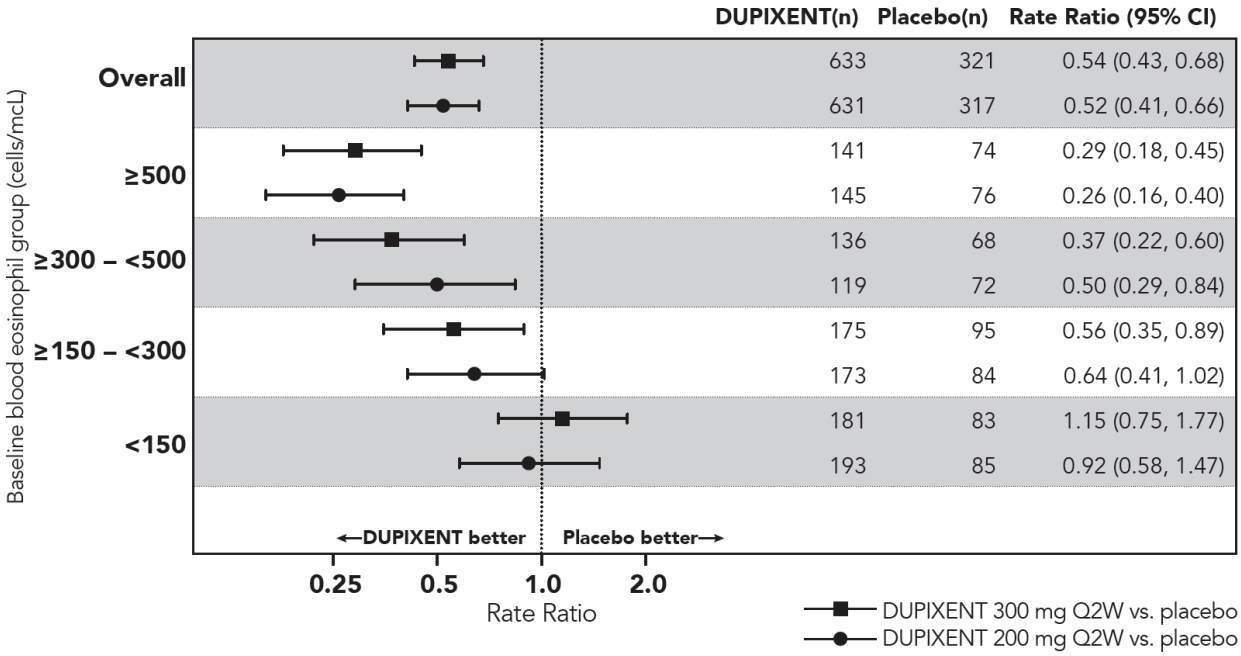
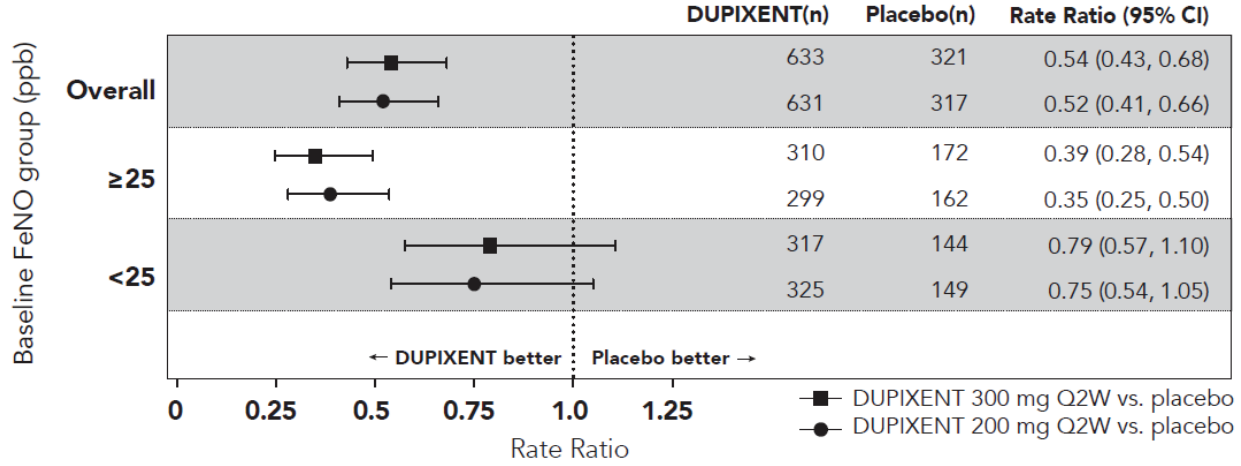
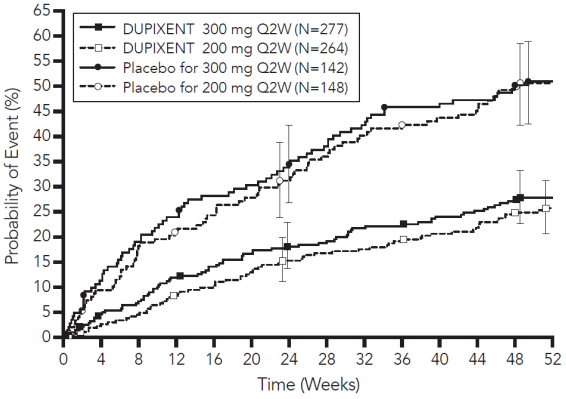


Figure 5: Relative Risk in Annualized Event Rate of Severe Exacerbations across Baseline FeNO Group (ppb) in Subjects with Moderate-to-Severe Asthma (QUEST)



The time to first exacerbation was longer for the subjects receiving DUPIXENT compared to placebo in QUEST (Figure 6).

Figure 6: Kaplan Meier Incidence Curve for Time to First Severe Exacerbation in Subjects with Moderate-to-Severe Asthma with Baseline Blood Eosinophils ≥300 cells/mcL (QUEST)[a]



Number at Risk

DUPIXENT 300 mg Q2W	277	244	221	208	189	145
DUPIXENT 200 mg Q2W	264	240	220	210	195	154
Placebo for 300 mg Q2W	142	108	94	75	69	54
Placebo for 200 mg Q2W	148	116	100	84	72	52

[a] At the time of the database lock, not all subjects had completed Week 52

Lung Function in Subjects with Asthma

Significant increases in pre-bronchodilator FEV_1 were observed at Week 12 for DRI12544 and QUEST in the primary analysis populations (subjects with baseline blood eosinophil count of ≥300 cells/mcL in DRI12544 and the overall population in QUEST). In the overall population in QUEST, the FEV_1 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 DRI12544 and QUEST are shown in Table 20.

Improvements in FEV_1 by baseline blood eosinophils and baseline FeNO for QUEST are shown in Figure 7 and 8, respectively. Subgroup analysis of DRI12544 and QUEST demonstrated greater improvement in subjects with higher baseline blood eosinophils (≥150 cells/mcL) or FeNO (≥25 ppb). In subjects with baseline blood eosinophil count <150 cells/mcL and FeNO <25 ppb, similar differences in FEV_1 were observed between DUPIXENT and placebo.

Mean changes in FEV_1 over time in QUEST are shown in Figure 9.

Table 20: Mean Change from Baseline and Difference vs Placebo in Pre-Bronchodilator FEV_1 at Week 12 in Subjects with Moderate-to-Severe Asthma (DRI12544 and QUEST)

Trial	Treatment	Baseline Blood EOS ≥300 cells/mcL (primary analysis population, DRI12544)		
		N	LS Mean Change from baseline L (%)	LS Mean Difference vs. placebo (95% CI
DRI12544	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)	
QUEST	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 7: LS Mean Difference in Change from Baseline vs Placebo to Week 12 in Pre-Bronchodilator FEV_1 across Baseline Blood Eosinophil Counts (cells/mcL) in Subjects with Moderate-to-Severe Asthma (QUEST)

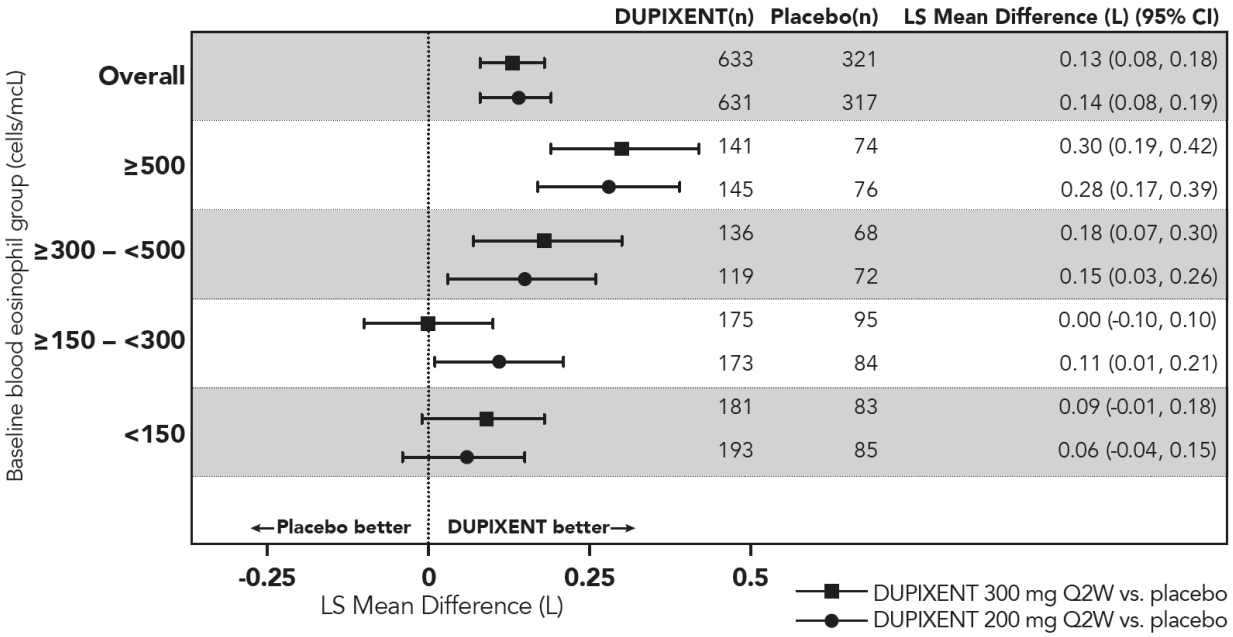


Figure 8: LS Mean Difference in Change from Baseline vs Placebo to Week 12 in Pre-bronchodilator FEV_1 across Baseline FeNO (ppb) in Subjects with Moderate-to-Severe Asthma (QUEST)

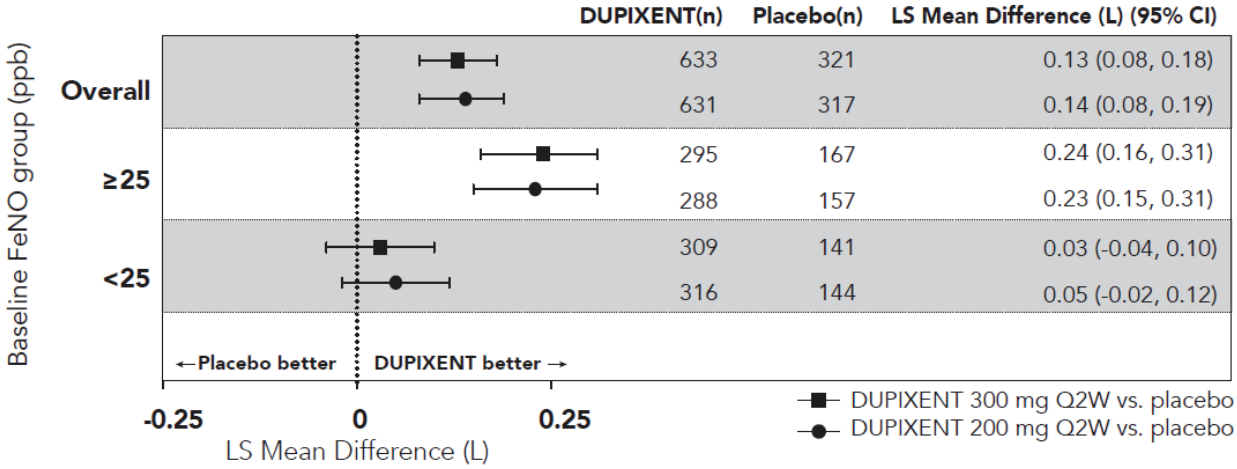
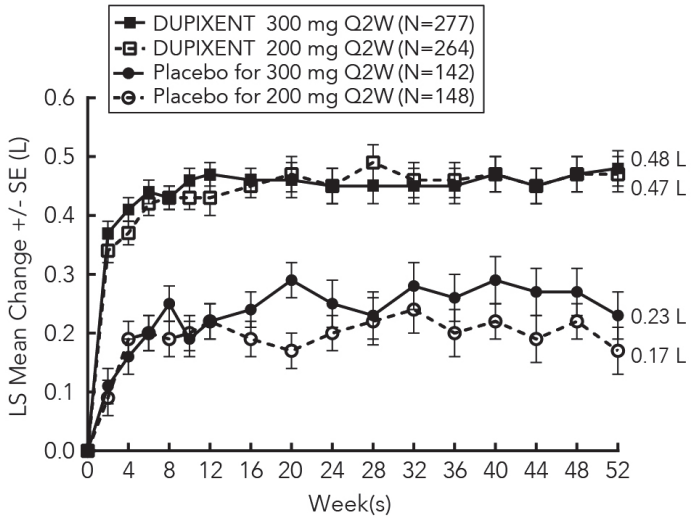


Figure 9: Mean Change from Baseline in Pre-Bronchodilator FEV_1 (L) Over Time in Subjects with Moderate-to-Severe Asthma with Baseline Blood Eosinophils ≥300 cells/mcL (QUEST)



Additional Secondary Endpoints in Asthma Trial (QUEST)

ACQ-5 and AQLQ(S) were assessed in QUEST 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 in Asthma Trial (VENTURE)

VENTURE 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 Week 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 FEV_1 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 VENTURE and showed improvements similar to those in QUEST.

Pediatric Subjects 6 to 11 Years of Age with Asthma

The efficacy and safety of DUPIXENT in pediatric subjects was evaluated in a 52-week multicenter, randomized, double-blind, placebo-controlled study (VOYAGE; NCT02948959) in 408 subjects 6 to 11 years of age, with moderate-to-severe asthma on a medium or high-dose ICS and a second controller medication or high-dose ICS alone. Subjects were required to have a history of 1 or more asthma exacerbation(s) 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 were randomized to DUPIXENT (N=273) or matching placebo (N=135) every other week based on body weight <30 kg (100 mg Q2W) or ≥30 kg (200 mg Q2W). The effectiveness of DUPIXENT 300 mg Q4W was extrapolated from efficacy of 100 mg Q2W in VOYAGE with support from population pharmacokinetic analyses showing higher drug exposure levels with 300 mg Q4W *[see Pediatric Use (8.4) and Pharmacokinetics (12.3)]*.

The primary endpoint was the annualized rate of severe asthma exacerbation events during the 52-week placebo-controlled period. Severe asthma exacerbations were 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. The key secondary endpoint was the change from baseline in pre-bronchodilator FEV_1 percent predicted at Week 12. Additional secondary endpoints included mean change from baseline and responder rates in the ACQ-7-IA (Asthma Control Questionnaire-7-Interviewer Administered) and PAQLQ(S)-IA (Pediatric Asthma Quality of Life Questionnaire with Standardized Activities Interviewer Administered) scores.

The demographics and baseline characteristics for VOYAGE are provided in Table 21 below.

Table 21: Demographics and Baseline Characteristics of Pediatric Subjects 6 to 11 Years of Age with Asthma (VOYAGE)

Parameter	VOYAGE (N=408)
Mean age (years) (SD)	9 (2)
% Female	36
% White	88
Mean body weight (kg)	36
Mean exacerbations in previous year (± SD)	2.4 (2.2)
High dose ICS use %)	44
Pre-dose FEV_1 (L) at baseline (± SD)	1.48 (0.41)
Mean percent predicted FEV_1 (%) ±SD	78 (15)
Mean % Reversibility (± SD	20 (21)
Atopic Medical History % Overall AD %, AR %)	92 (36, 82)
Mean FeNO ppb (± SD)	28 (24)
% subjects with FeNO ppb ≥20	50
Median total IgE IU/mL (±SD)	792 (1093)
Mean baseline Eosinophil count (± SD) cells/mcL	502 (395)

ICS = inhaled corticosteroid; FEV_1 = Forced expiratory volume in 1 second; AD = atopic dermatitis; AR = allergic rhinitis; FeNO = fraction of exhaled nitric oxide

DUPIXENT significantly reduced the annualized rate of severe asthma exacerbation events during the 52-week treatment period compared to placebo in populations with an eosinophilic phenotype as indicated by elevated blood eosinophils and/or the population with elevated FeNO. Subgroup analyses for results of DUPIXENT treatment based upon either baseline eosinophil level or baseline FeNO level were similar to the pediatric (12 to 17 years of age) and adult trials and are described for the adult and pediatric (12 to 17 years of age) asthma population above. In subjects with baseline blood eosinophil count <150 cells/mcL and FeNO <20 ppb, similar severe asthma exacerbation rates were observed between DUPIXENT and placebo.

Significant improvements in percent predicted pre-bronchodilator FEV_1 were observed at Week 12. Significant improvements in percent predicted FEV_1 were observed as early as Week 2 and were maintained through Week 52 in VOYAGE (Figure 10).

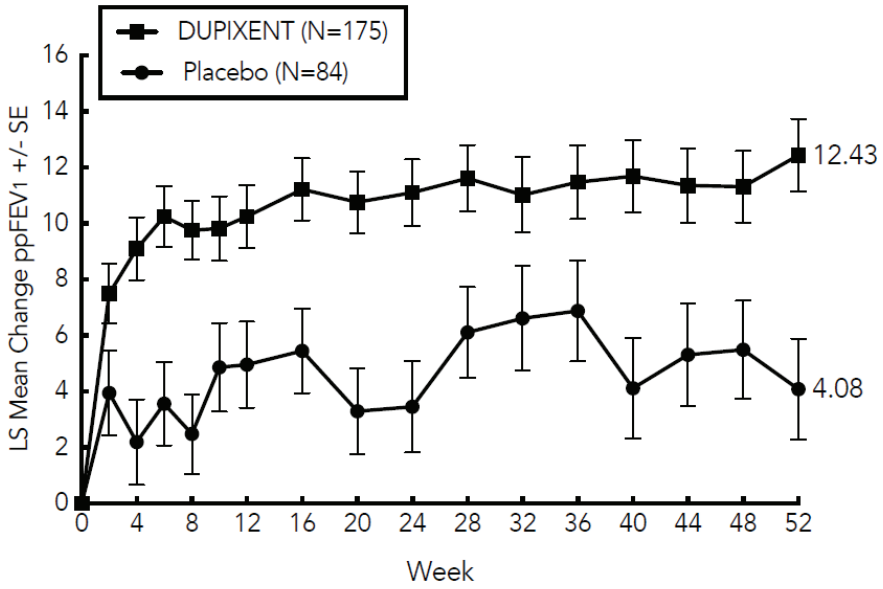
The efficacy results for VOYAGE are presented in Table 22.

Table 22: Efficacy Results of DUPIXENT in Pediatric Subjects 6 to 11 Years of Age with Asthma (VOYAGE)

Treatment	EOS ≥300 cells/mcL[a]		
Annualized Severe Exacerbations Rate over 52 Weeks			
	N	**Rate (95% CI**	**Rate Ratio (95% CI**
DUPIXENT 100 mg Q2W[b] (<30 kg)/ 200 mg Q2W ≥30 kg	175	0.24 (0.16, 0.35)	0.35 (0.22, 0.56)
Placebo	84	0.67 (0.47, 0.95)	
Mean Change from Baseline in Percent Predicted FEV_1 at Week 12			
	N	**LS mean Δ from Baseline**	**LS mean difference vs. Placebo (95% CI)**
DUPIXENT 100 mg Q2W[b] (<30 kg)/ 200 mg Q2W ≥30 kg	168	10.15	5.32 (1.76, 8.88)
Placebo	80	4.83	

[a] This reflects the prespecified primary analysis population for VOYAGE in the United States.
[b] The effectiveness of DUPIXENT 300 mg Q4W was extrapolated from efficacy of 100 mg Q2W.

Figure 10: Mean Change from Baseline in Percent Predicted Pre-bronchodilator FEV_1 (L) Over Time in Pediatric Subjects 6 to 11 Years of Age in VOYAGE (Baseline Blood Eosinophils ≥300 cells/mcL)



Improvements were also observed for ACQ-7-IA and PAQLQ(S)-IA at Week 24 and were sustained at Week 52. Greater responder rates were observed for ACQ-7-IA and PAQLQ(S)-IA compared to placebo at Week 24. The responder rate was defined as an improvement in score of 0.5 or more (scale range 0-6 for ACQ-7-IA and 1-7 for PAQLQ(S)-IA). In the subgroup of subjects with baseline blood eosinophil count ≥300 cells/mcL, DUPIXENT led to a higher proportion of subjects with a response in ACQ-7-IA (80.6% versus 64.3% for placebo) with an

OR of 2.79 (95% CI: 1.43, 5.44), and in PAQLQ(S)-IA (72.8% versus 63.0% for placebo) with an OR of 1.84 (95% CI: 0.92, 3.65) at Week 24.

14.3 Chronic Rhinosinusitis with Nasal Polyps

The efficacy of DUPIXENT as an add-on maintenance treatment in adults with inadequately controlled chronic rhinosinusitis with nasal polyps (CRSwNP) was evaluated in two randomized, double-blind, parallel-group, multicenter, placebo-controlled studies (SINUS-24 (NCT02912468) and SINUS-52 (NCT02898454)) in 724 adult subjects 18 years of age 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. Subjects with chronic rhinosinusitis without nasal polyps were not included in these trials. Rescue with systemic corticosteroids or surgery was allowed during the studies at the investigator's discretion. In SINUS-24, 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 SINUS-52, 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 subject 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 23 below.

Table 23: Demographics and Baseline Characteristics of Adult Subjects in CRSwNP Trials

Parameter	SINUS-24 (N=276)	SINUS-52 (N=448)
Mean age (years) (SD)	50 (13)	52 (12)
% Male	57	62
Mean CRSwNP duration (years) (SD)	11 (9)	11 (10)
Subjects with ≥1 prior surgery (%)	72	58
Subjects 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 % Overall	75	82
Asthma (%)	58	60
NSAID-ERD (%)	30	27

[a] Higher 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 (SINUS-24 and SINUS-52)

The results for primary endpoints in CRSwNP studies are presented in Table 24.

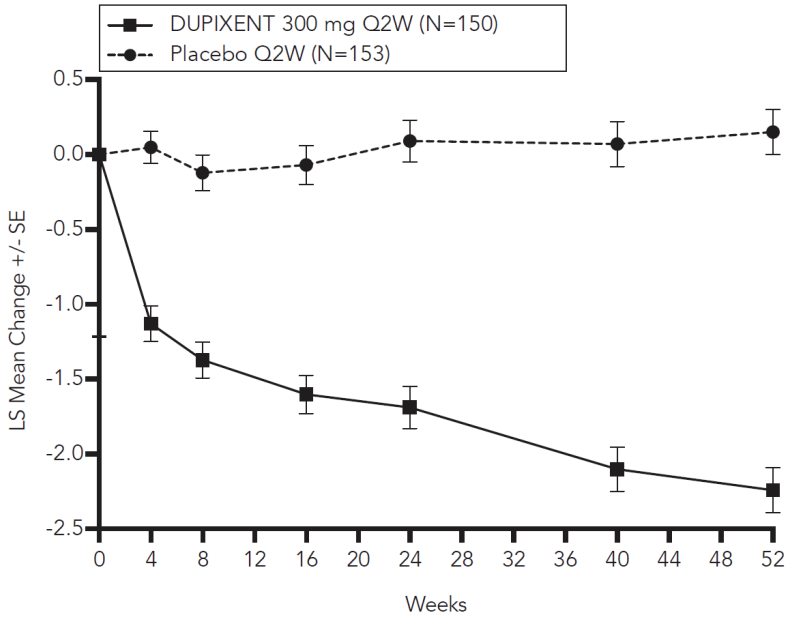
Table 24: Results of the Primary Endpoints in CRSwNP Trials

	SINUS-24					SINUS-52				
	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

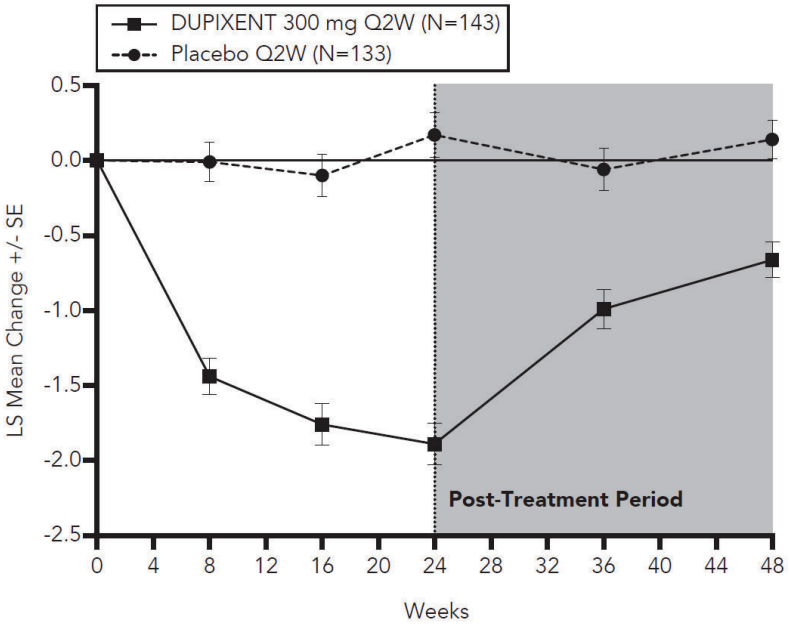
Statistically significant efficacy was observed in SINUS-52 with regard to improvement in bilateral endoscopic NPS score at week 24 and week 52 (see Figure 11).

Figure 11: LS Mean Change from Baseline in Bilateral Nasal Polyps Score (NPS) up to Week 52 in Subjects 18 Years of Age and Older with CRSwNP (SINUS-52 - ITT Population)



Similar results were seen in SINUS-24 at Week 24. In the post-treatment period when subjects were off DUPIXENT, the treatment effect diminished over time (see Figure 12).

Figure 12: LS Mean Change from Baseline in Bilateral Nasal Polyps Score (NPS) up to Week 48 in Subjects 18 Years of Age and Older with CRSwNP (SINUS-24 - 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 SINUS-24 and -0.37 (95% CI: -0.46, -0.27) in SINUS-52.

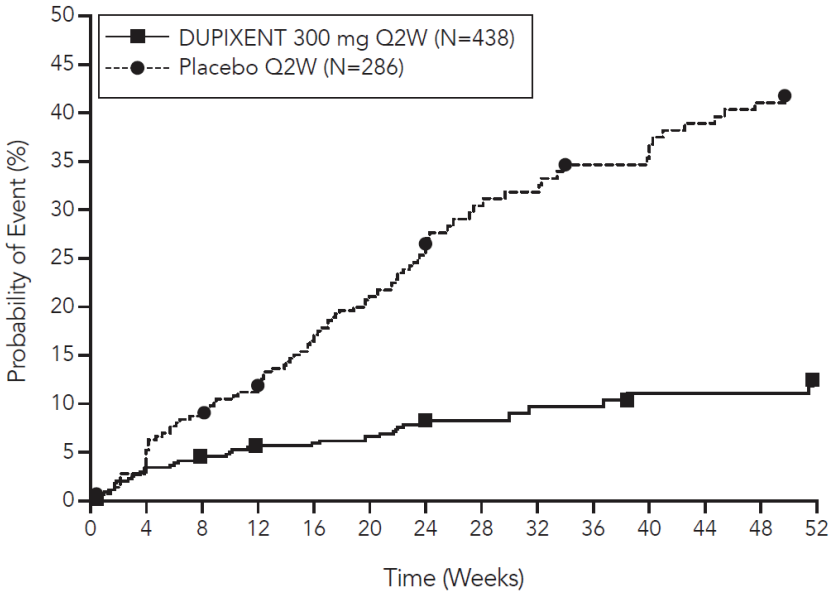
A significant decrease in the LMK sinus CT scan score was observed. The LS mean difference for LMK sinus CT scan score at Week 24 in the DUPIXENT group versus placebo was -7.44 95% CI: -8.35, -6.53) in SINUS-24 and -5.13 (95% CI: -5.80, -4.46) in SINUS-52. At Week 52, in SINUS-52 the LS mean difference 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 SINUS-24 and -0.98 (95% CI: -1.15, -0.81) in SINUS-52. 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 SINUS-24 and -17.36 (95% CI: -20.87, -13.85) in SINUS-52. 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 13). 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 13: Kaplan Meier Curve for Time to First Systemic Corticosteroid Use and/or Sino-Nasal Surgery During Treatment Period in Subjects 18 Years of Age and Older with CRSwNP (SINUS-24 and SINUS-52 Pooled - ITT Population)



Number at Risk

DUPIXENT 300 mg Q2W	438	416	411	376	129	100
Placebo Q2W	286	260	253	187	93	61

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 subjects with prior surgery and without prior surgery.

In subjects with co-morbid asthma, improvements in pre-bronchodilator FEV_1 were similar to subjects in the asthma program.

14.4 Eosinophilic Esophagitis

Adult and Pediatric Subjects 12 Years of Age and Older with EoE

A single randomized, double-blind, parallel-group, multicenter, placebo-controlled trial, including two 24-week treatment periods (Study EoE-1 Parts A and B) was conducted in adult and pediatric subjects 12 years of age and older, weighing at least 40 kg, with EoE (NCT03633617). In both parts, subjects were randomized to receive 300 mg DUPIXENT every week or placebo. Eligible subjects had ≥15 intraepithelial eosinophils per high-power field (eos/hpf) following a treatment course of a proton pump inhibitor (PPI) either prior to or during the screening period and symptoms of dysphagia as measured by the Dysphagia Symptom Questionnaire (DSQ). At baseline, 43% of subjects in Part A and 37% of subjects in Part B had a history of prior esophageal dilations.

Demographics and baseline characteristics were similar in Parts A and B. A total of 81 subjects (61 adults and 20 pediatric subjects) were enrolled in Part A and 159 subjects (107 adults and 52 pediatric subjects) were enrolled in Part B. The mean age in years was 32 years (range 13 to 62

years) in Part A and 28 years (range 12 to 66 years) in Part B. The majority of subjects were male (60% in Part A and 68% in Part B) and White (96% in Part A and 90% in Part B). The mean baseline DSQ score (SD) was 33.6 (12.4) in Part A and 37.2 (10.7) in Part B.

The coprimary efficacy endpoints in Parts A and B were the (1) proportion of subjects achieving histological remission defined as peak esophageal intraepithelial eosinophil count of ≤6 eos/hpf at Week 24; and (2) the absolute change in the subject-reported DSQ score from baseline to Week 24.

Efficacy results for Parts A and B are presented in Table 25.

Table 25: Efficacy Results of DUPIXENT at Week 24 in Adult and Pediatric Subjects 12 Years of Age and Older with EoE (Study EoE-1 Parts A and B)

	Study EoE-1 Part A			Study EoE-1 Part B		
	DUPIXENT 300 mg QW[b] N = 42	Placebo[b] N = 39	Difference vs. Placebo (95% CI [b]	DUPIXENT 300 mg QW[b] N = 80	Placebo[b] N = 79	Difference vs. Placebo (95% CI [b]
Co-primary Endpoints						
Proportion of subjects achieving histological remission (peak esophageal intraepithelial eosinophil count ≤6 eos/hpf), n (%)	25 (59.5)	2 (5.1)	57.0 (40.9, 73.1)	47 (58.8)	5 (6.3)	53.5 (41.2, 65.8)
Absolute change from baseline in DSQ score (0-84[a]), LS mean (SE)	-21.9 (2.5)	-9.6 (2.8)	-12.3 (-19.1, -5.5)	-23.8 (1.9)	-13.9 (1.9)	-9.9 (-14.8, -5.0)

[a] Total biweekly DSQ scores range from 0 to 84; higher scores indicate greater frequency and severity of dysphagia

[b] For histological remission, the difference in percentages is estimated using the Cochran Mantel Haenszel method, adjusting for randomization stratification factors. For absolute change in DSQ score, the LS mean changes, standard errors, and differences are estimated using an ANCOVA model with treatment group, randomization stratification factors, and baseline measurement as covariates.

In Parts A and B, a greater proportion of subjects randomized to DUPIXENT achieved histological remission (peak esophageal intraepithelial eosinophil count ≤6 eos/hpf) compared to placebo. Treatment with DUPIXENT also resulted in a significant improvement in LS mean change in DSQ score compared to placebo at Week 24. The results of the anchor-based analyses that incorporated the subjects' perspectives indicated that the observed improvement in dysphagia from Parts A and B is representative of a clinically meaningful within-subject improvement.

Pediatric Subjects 1 to 11 Years of Age, Weighing at Least 15 kg, with EoE

The efficacy and safety of DUPIXENT was evaluated in pediatric subjects 1 to 11 years of age, weighing at least 15 kg, with EoE in a randomized, blinded, parallel-group, multicenter trial (Study EoE-2 Parts A and B; NCT04394351). Eligible subjects had ≥15 intraepithelial eosinophils per high-power field (eos/hpf) despite a treatment course of a proton pump inhibitor (PPI) either prior to or during the screening period and a history of EoE signs and symptoms. Part A evaluated weight-based dosing regimens of DUPIXENT, 200 mg Q2W (≥15 to <30 kg) and 300 mg Q2W (≥30 to <60 kg), or placebo in 61 subjects during the 16-week treatment period.

The recommended dosage of 300 mg QW for pediatric subjects 1 to 11 years of age weighing ≥40 kg is based on modeled pharmacokinetic data to provide comparable exposures to the 300 mg QW dosage in adult and pediatric subjects 12 years of age and older weighing ≥40 kg with EoE *[see Dosage and Administration (2.6) and Pharmacokinetics (12.3)]*.

Forty-seven subjects who completed Part A were evaluated in the 36-week extended active treatment period (Study EoE-2 Part B). All subjects in Part B were treated with the weight-based dosing regimens of DUPIXENT described for Part A.

Of the total subjects evaluated in Part A, the mean age was 8 years, the median weight was 28 kg, and 75% were male. Seven percent identified as Hispanic or Latino; 85% identified as White, 12% as Black, 2% as Asian, and 2% identified as another racial subgroup.

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

Efficacy results for Part A are presented in Table 26.

Table 26: Efficacy Results of DUPIXENT at Week 16 in Subjects 1 to 11 Years of Age with EoE, Weighing at Least 15 kg (Study EoE-2 Part A)

	DUPIXENT[a] N=32	Placebo N=29	Difference vs Placebo (95% CI
Proportion of subjects achieving histological remission (peak esophageal intraepithelial eosinophil count ≤6 eos/hpf), n %)[b]	21 (65.6)	1 (3.4)	62.0 (44.00, 79.95)

[a] DUPIXENT was evaluated at tiered dosing regimens based on body weight: ≥15 to <30 kg 200 mg Q2W and ≥30 to <60 kg (300 mg Q2W). The 300 mg Q2W dosing regimen is lower than the recommended dosage of DUPIXENT in subjects ≥40 kg *[see Dosage and Administration (2.6)]*.

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

In Part B, histological remission was achieved at Week 52 in 17/32 subjects treated with DUPIXENT in Parts A and B and 8/15 subjects treated with placebo in Part A and DUPIXENT in Part B.

In Study EoE-2 Part A, an observer-reported outcome, the Pediatric EoE Sign/Symptom Questionnaire-Caregiver (PESQ-C), was used to measure signs of EoE. A greater decrease in the proportion of days with 1 or more signs of EoE (based on the PESQ-C) was observed for subjects treated with DUPIXENT compared to placebo after 16 weeks of treatment.

14.5 Prurigo Nodularis

The prurigo nodularis (PN) development program included two 24-week randomized, double-blind, placebo-controlled, multicenter, parallel-group trials (PRIME (NCT04183335) and PRIME 2 (NCT04202679)) in 311 adult subjects 18 years of age and older with pruritus (WI-NRS ≥ 7 on a scale of 0 to 10) and greater than or equal to 20 nodular lesions. PRIME and PRIME 2 assessed the effect of DUPIXENT on pruritus improvement as well as its effect on PN lesions.

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

In these trials, the mean age was 49.5 years, the median weight was 71 kg, 65% of subjects were female, 57% were White, 6% were Black, and 34% were Asian. At baseline, the mean Worst Itch-Numeric Rating Scale (WI-NRS) was 8.5, 66% had 20 to 100 nodules (moderate), and 34% had greater than 100 nodules (severe). Eleven percent (11%) of subjects were taking stable doses of antidepressants at baseline and were instructed to continue taking these medications during the trial. Forty-three percent (43%) had a history of atopy (defined as having a medical history of AD, allergic rhinitis/rhinoconjunctivitis, asthma, or food allergy).

The WI-NRS is comprised of a single item, rated on a scale from 0 ("no itch") to 10 ("worst imaginable itch"). Subjects were asked to rate the intensity of their worst pruritus (itch) over the past 24 hours using this scale. The Investigator's Global Assessment for Prurigo Nodularis-Stage (IGA PN-S) is a scale that measures the approximate number of nodules using a 5-point scale from 0 (clear) to 4 (severe).

Efficacy was assessed with the proportion of subjects with improvement (reduction) in WI-NRS by ≥4 points, the proportion of subjects with IGA PN-S 0 or 1 (the equivalent of 0-5 nodules), and the proportion of subjects who achieved a response in both WI-NRS and IGA PN-S per the criteria described above.

The efficacy results for PRIME and PRIME2 are presented in Table 27 and Figures 14, 15, and 16.

Table 27: Efficacy Results of DUPIXENT in Adult Subjects with PN in PRIME and PRIME2

	PRIME			PRIME2		
	Placebo (N=76)	**DUPIXENT 300 mg Q2W (N=75)**	**Difference (95% CI for DUPIXENT vs. Placebo**	**Placebo (N=82)**	**DUPIXENT 300 mg Q2W (N=78)**	**Difference (95% CI for DUPIXENT vs. Placebo**
Proportion of subjects with both an improvement (reduction) in WI-NRS by ≥4 points from baseline to Week 24 and an IGA PN-S 0 or 1 at Week 24[b]	9.2%	38.7%	29.6% (16.4, 42.8)	8.5%	32.1%	25.5% (13.1, 37.9)
Proportion of subjects with improvement (reduction) in WI-NRS by ≥4 points from baseline at Week 24[b]	18.4%	60.0%	42.7% (27.8, 57.7)	19.5%	57.7%	42.6% (29.1, 56.1)
Proportion of subjects with IGA PN-S 0 or 1 at Week 24[b]	18.4%	48.0%	28.3% (13.4, 43.2)	15.9%	44.9%	30.8% (16.4, 45.2)
Proportion of subjects with improvement (reduction) in WI-NRS by ≥4 points from baseline at Week 12[b]	15.8%[a]	44.0%[a]	29.2% (14.5, 43.8)[a]	22.0%	37.2%	16.8% (2.3, 31.2)

[a] Not adjusted for multiplicity in PRIME.

[b] Subjects who received rescue treatment earlier or had missing data were considered as non-responders.

Figure 14: Proportion of Adult Subjects with PN with Both WI-NRS ≥4-point Improvement and IGA PN-S 0 or 1 Over Time in PRIME and PRIME2

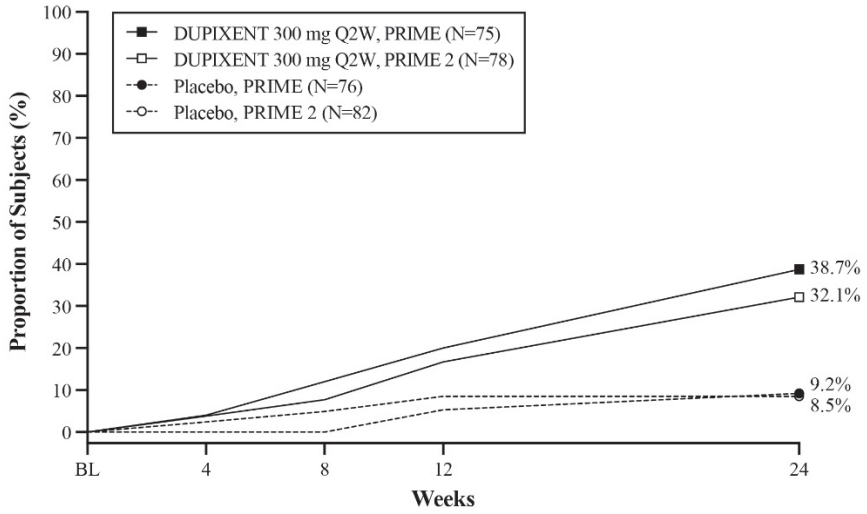


Figure 15: Proportion of Adult Subjects with PN with WI-NRS ≥4-point Improvement Over Time in PRIME and PRIME2

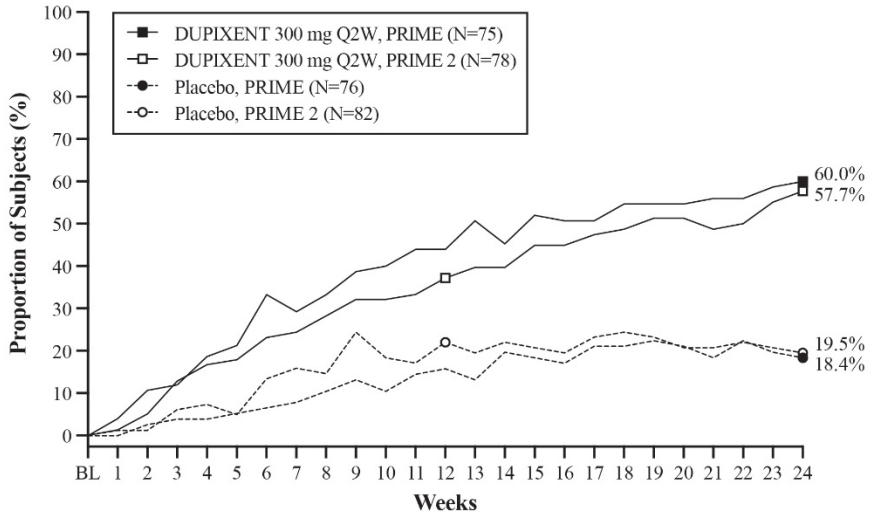
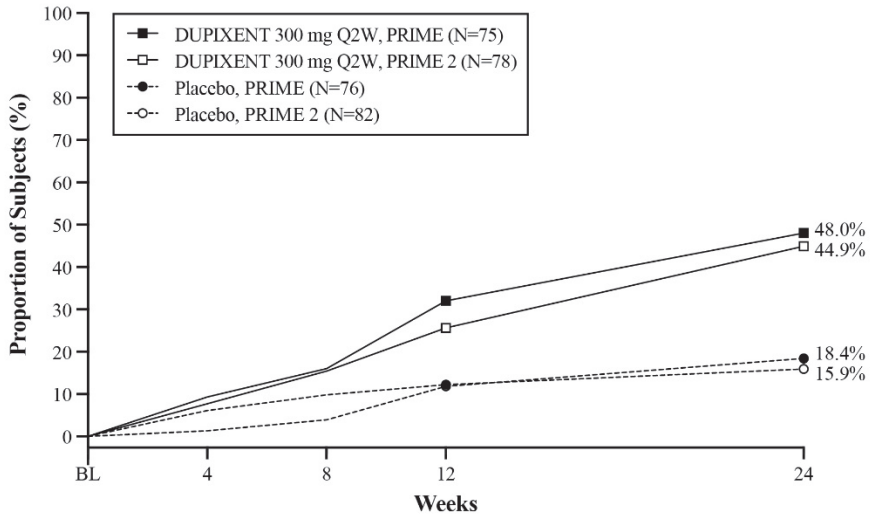


Figure 16: Proportion of Adult Subjects with IGA PN-S 0 or 1 Over Time in PRIME and PRIME 2



The efficacy data did not show differential treatment effect across demographic subgroups.

14.6 Chronic Obstructive Pulmonary Disease

The efficacy of DUPIXENT as add-on maintenance treatment of adult patients with inadequately controlled COPD and an eosinophilic phenotype was evaluated in two randomized, double-blind, multicenter, parallel-group, placebo-controlled trials (BOREAS [NCT03930732] and NOTUS [NCT04456673]) of 52 weeks duration. The two trials enrolled a total of 1874 adult subjects with COPD.

Both trials enrolled subjects with a diagnosis of COPD with moderate to severe airflow limitation (post-bronchodilator FEV_1/FVC ratio <0.7 and post-bronchodilator FEV_1 of 30% to 70% predicted) and a minimum blood eosinophil count of 300 cells/mcL at screening. Trial enrollment required an exacerbation history of at least 2 moderate or 1 severe exacerbation(s) in the previous year despite receiving maintenance triple therapy consisting of a long-acting muscarinic antagonist (LAMA), long-acting beta agonist (LABA), and inhaled corticosteroid (ICS), and symptoms of chronic productive cough for at least 3 months in the past year. Greater than or equal to 95% of subjects in each trial had chronic bronchitis. Subjects also had a Medical Research Council (MRC) dyspnea score ≥2 (range 0-4). Exacerbations of COPD were defined as clinically significant worsening of COPD symptoms including increases in dyspnea, wheezing, cough, sputum volume, and/or increase in sputum purulence. Exacerbation severity was further defined as moderate if treatment with systemic corticosteroids and/or antibiotics was required, or severe if they resulted in hospitalization or observation for over 24 hours in an emergency department or urgent care facility.

In both trials, subjects were randomized to receive DUPIXENT 300 mg subcutaneously every two weeks (Q2W) or placebo in addition to their background maintenance therapy for 52 weeks.

The demographics and baseline characteristics of BOREAS and NOTUS trial populations are provided in Table 28 below.

Table 28: Demographics and Baseline Characteristics of Adult Subjects with COPD for BOREAS and NOTUS Trial Populations

Parameter	BOREAS (N = 939)	NOTUS (N = 935)
Mean age (years) (± SD)	65.1 (8.1)	65.0 (8.3)
Male (%)	66.0	67.6
White, N (%)	790 (84.1)	838 (89.6)
Asian, N (%)	134 (14.3)	10 (1.1)
Black, N (%)	5 (0.5)	12 (1.3)
American Indian or Alaska Native, N %	7 (0.7)	48 (5.1)
Other/Multiple, N (%	3 (0.3)	27 (2.9)
Ethnicity Hispanic/Latino, N %)	261 (27.8)	300 (32.1)
Mean smoking history (pack-years) (± SD)	40.5 (23.4)	40.3 (27.2)
Current smokers (%)	30.0	29.5
Chronic Bronchitis (%)	95.0	99.9
Emphysema (%)	32.6	30.4
Mean number of moderate[a] or severe[b] exacerbations in previous year (± SD)	2.3 (1.0)	2.1 (0.9)
Background COPD medications at randomization: ICS/LAMA/LABA %	97.6	98.8
Mean post-bronchodilator FEV_1/FVC ratio (± SD)	0.49 (0.12)	0.50 (0.12)
Mean post-bronchodilator FEV_1 (L) (± SD)	1.40 (0.47)	1.45 (0.49)
Mean percent predicted post-bronchodilator FEV_1 (%) ± SD)	50.6 (13.1)	50.1 (12.6)
Mean SGRQ total score (± SD)	48.4 (17.4)	51.5 (17.0)
Mean screening blood eosinophil count[c] (cells/mcL) (± SD)	521 (307)	538 (333)
Mean baseline blood eosinophil count[d] (cells/mcL) (± SD)	401 (298)	407 (336)

ICS = inhaled corticosteroid; LAMA = long-acting muscarinic antagonist; LABA = long-acting beta agonist; FEV_1 = forced expiratory volume in 1 second; FVC = forced vital capacity

[a] Exacerbations treated with either systemic corticosteroids and/or antibiotics.

[b] Exacerbations requiring hospitalization or observation for over 24 hours in an emergency department or urgent care facility.

[c] Reported screening eosinophil value is the highest values from up to three retests

[d] Reported baseline eosinophil value was obtained within 4 weeks of screening value

Exacerbations in Adult Subjects with COPD

The primary endpoint for BOREAS and NOTUS trials was the annualized rate of moderate or severe COPD exacerbations during the 52-week treatment period. In both trials, DUPIXENT demonstrated a significant reduction in the annualized rate of moderate or severe COPD

exacerbations compared to placebo when added to background maintenance therapy (see Table 29).

Table 29: Annualized Rate of Moderate[a] or Severe[b] COPD Exacerbations in BOREAS and NOTUS Trials

Trial	Treatment (N)	Rate (exacerbations/year)	Rate Ratio vs. Placebo (95% CI
BOREAS	DUPIXENT 300 mg Q2W (N=468)	0.78	0.71 (0.58, 0.86)
	Placebo (N=471)	1.10	
NOTUS	DUPIXENT 300 mg Q2W (N=470)	0.86	0.66 (0.54, 0.82)
	Placebo (N=465)	1.30	

[a] Exacerbations treated with either systemic corticosteroids and/or antibiotics.
[b] Exacerbations requiring hospitalization or observation for over 24 hours in an emergency department or urgent care facility or resulting in death.

Treatment with DUPIXENT decreased the risk of a moderate to severe COPD exacerbation as measured by time to first exacerbation when compared with placebo in BOREAS (HR: 0.80; 95% CI: 0.66, 0.98) and NOTUS (HR: 0.71; 95% CI: 0.57, 0.89).

Lung Function in Adult Subjects with COPD

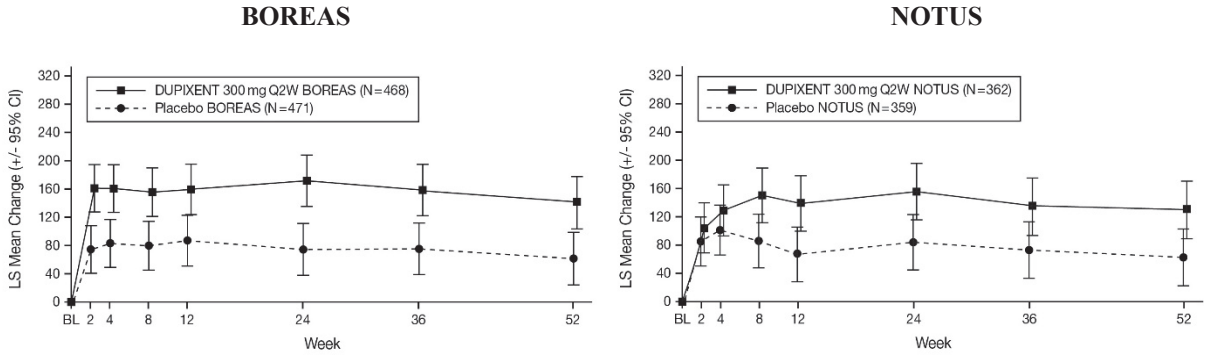
In both trials (BOREAS and NOTUS), DUPIXENT demonstrated numerical improvement in post-bronchodilator FEV_1 at Weeks 12 and 52 compared to placebo when added to background maintenance therapy (see Table 30 and Figure 17). Significant improvements of similar magnitude were observed in change from baseline in pre-bronchodilator FEV_1 at Weeks 12 and 52 in subjects treated with DUPIXENT compared to placebo across both trials.

Table 30: Mean Change from Baseline and Difference in Post-Bronchodilator FEV_1 at Weeks 12 and 52 in BOREAS and NOTUS Trials for COPD

Trial	Treatment (N)	LS Mean Change from baseline mL	LS Mean Difference vs. placebo mL (95% CI
Post-bronchodilator FEV_1 at Week 12			
BOREAS	DUPIXENT 300 mg Q2W (N=468)	158	74 (31, 117)
	Placebo (N=471)	84	
NOTUS	DUPIXENT 300 mg Q2W (N=470)	134	68 (26, 110)
	Placebo (N=465)	67	
Post-bronchodilator FEV_1 at Week 52			
BOREAS	DUPIXENT 300 mg Q2W (N=468)	138	79 (34, 124)
	Placebo (N=471)	58	
NOTUS[a]	DUPIXENT 300 mg Q2W (N=362)	127	67 (16, 119)
	Placebo (N=359)	59	

[a] Efficacy results for mean change from baseline in post-bronchodilator FEV_1 at Week 52 are presented for 721 out of 935 subjects who completed the 52-week treatment period or had discontinued the trial at the time of data analysis.

Figure 17: LS Mean Change from Baseline in Post-Bronchodilator FEV_1 (mL) Over Time in BOREAS and NOTUS[a] Trials for COPD



[a] Efficacy results for mean change from baseline in post-bronchodilator FEV_1 over time are presented for 721 out of 935 subjects who completed the 52-week treatment period or had discontinued the trial at the time of data analysis.

Health-Related Quality of Life

In both trials (BOREAS and NOTUS), the St. George's Respiratory Questionnaire (SGRQ) total score responder rate (defined as the proportion of subjects with SGRQ improvement from baseline of at least 4 points) at Week 52 was evaluated. In BOREAS, the responder rate was 51%

for subjects treated with DUPIXENT versus 43% for placebo (N=939, odds ratio: 1.44; 95% CI: 1.10, 1.89). In NOTUS, the responder rate was 51% for subjects treated with DUPIXENT versus 47% for placebo (N=721, odds ratio: 1.16; 95% CI: 0.86, 1.58).

16 HOW SUPPLIED/STORAGE AND HANDLING

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 or pre-filled pens.

The pre-filled syringe with needle shield is designed to deliver:

- 300 mg of DUPIXENT in 2 mL solution (NDC 0024-5914-00)
- 200 mg of DUPIXENT in 1.14 mL solution (NDC 0024-5918-00)

The pre-filled pen is designed to deliver:

- 300 mg of DUPIXENT in 2 mL solution (NDC 0024-5915-00)
- 200 mg of DUPIXENT in 1.14 mL solution (NDC 0024-5919-00)

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

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

Pack Size	**300 mg/2 mL Pre-filled Pen**	**200 mg/1.14 mL Pre-filled Pen**
Pack of 2 pens	NDC 0024-5915-02	NDC 0024-5919-02

Storage and Handling

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

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

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

Do not expose DUPIXENT 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 and advise patients about how they may enroll 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 Dosage and Administration (2.1) and 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 Symptoms of Asthma or Chronic Obstructive Pulmonary Disease or Acute Deteriorating Disease

Inform patients that DUPIXENT does not treat acute symptoms or acute exacerbations of asthma or COPD. Inform patients to seek medical advice if their asthma or COPD 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 healthcare provider. 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 co-morbid asthma not to adjust or stop their asthma treatment without talking to their healthcare providers *[see Warnings and Precautions (5.6)]*.

Arthralgia

Advise patients to report new onset or worsening joint symptoms to their healthcare provider *[see Warnings and Precautions (5.7)]*.

Parasitic (Helminth) Infections

Advise patients to notify their healthcare provider if they present with clinical features consistent with helminthic infection *[see Warnings and Precautions (5.8)]*.

Vaccinations

Advise patients that vaccination with live vaccines is not recommended immediately prior to and while they are receiving DUPIXENT. Instruct patients to inform their healthcare provider that they are taking DUPIXENT prior to a potential vaccination *[see Warnings and Precautions (5.9)]*.

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)

For patent information: www.dupixent-patents.com

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REGENERON sanofi

ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

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

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Dupilumab 300 mg solution for injection in pre-filled syringe

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

Dupilumab 300 mg solution for injection in pre-filled pen

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

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

Excipients with known effect

This medicine contains 4 mg of polysorbate 80 in each 300 mg dose (2mL). Polysorbates may cause allergic reactions.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection (injection)

Clear to slightly opalescent, colourless to pale yellow sterile solution, which is free from visible particulates, with a pH of approximately 5.9.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Atopic dermatitis

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

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

Asthma

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

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

Chronic rhinosinusitis with nasal polyposis (CRSwNP)

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

Prurigo Nodularis (PN)

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

Eosinophilic esophagitis (EoE)

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

Chronic obstructive pulmonary disease (COPD)

Dupixent is indicated in adults as add-on maintenance treatment for uncontrolled chronic obstructive pulmonary disease (COPD) characterised by raised blood eosinophils on a combination of an inhaled corticosteroid (ICS), a long-acting beta2-agonist (LABA), and a long-acting muscarinic antagonist (LAMA), or on a combination of a LABA and a LAMA if ICS is not appropriate (see Section 5.1).

4.2 Posology and method of administration

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

Posology

Atopic dermatitis

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

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

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

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

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

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

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

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

Children 6 months to 5 years of age

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

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

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

Dupilumab can be used with or without topical corticosteroids. Topical calcineurin inhibitors may be used, but should be reserved for problem areas only, such as the face, neck, intertriginous and genital areas.

Consideration should be given to discontinuing treatment in patients who have shown no response after 16 weeks of treatment for atopic dermatitis. Some patients with initial partial response may subsequently improve with continued treatment beyond 16 weeks. If dupilumab treatment interruption becomes necessary, patients can still be successfully re-treated.

Asthma

Adults and adolescents

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

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

Children 6 to 11 years of age

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

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

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

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

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

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

Chronic rhinosinusitis with nasal polyposis (CRSwNP)

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

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

Prurigo Nodularis (PN)

The recommended dose of dupilumab for adult patients is an initial dose of 600 mg (two 300 mg injections), followed by 300 mg given every other week.
Dupilumab can be used with or without topical corticosteroids.

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

Eosinophilic esophagitis (EoE)

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

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

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

Dupilumab is intended for long-term treatment.

Chronic obstructive pulmonary disease (COPD)

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

Dupilumab is intended for long-term treatment. Dosing beyond 52 weeks has not been studied. Consideration should be given to discontinuing treatment in patients who have shown no response after 52 weeks of treatment for COPD.

Missed dose

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

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

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

Special populations

Elderly
No dose adjustment is recommended for elderly (≥ 65 years) patients (see section 5.2).

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

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

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

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

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

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

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

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

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

Method of administration

Subcutaneous use

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

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

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

For indications that require an initial dose of 600 mg (see Posology in section 4.2), two 300 mg injections should be administered consecutively in different injection sites.

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

A patient may self-inject dupilumab or the patient's caregiver may administer dupilumab if their healthcare professional determines that this is appropriate. Proper training should be provided to patients and/or caregivers on the preparation and administration of dupilumab prior to use according to the Instructions for Use (IFU) section at the end of the package leaflet. In children 12 years of age and older, it is recommended that dupilumab is administered by or under supervision of an adult. In children 6 months to less than 12 years of age, dupilumab should be given by a caregiver.

4.3 Contraindications

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

4.4 Special warnings and precautions for use

Traceability

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

Acute exacerbations of Asthma or COPD

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

Corticosteroids

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

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

Hypersensitivity

If a systemic hypersensitivity reaction (immediate or delayed) occurs, administration of dupilumab should be discontinued immediately and appropriate therapy initiated. Cases of anaphylactic reaction, angioedema, and serum sickness/serum sickness-like reaction have been reported. Anaphylactic reactions and angioedema have occurred from minutes to up to seven days after the dupilumab injection (see section 4.8).

Eosinophilic conditions

Cases of eosinophilic pneumonia and cases of vasculitis consistent with eosinophilic granulomatosis with polyangiitis (EGPA) have been reported with dupilumab in adult patients who participated in the asthma development program. Cases of vasculitis consistent with EGPA have been reported with dupilumab and placebo in adult patients with co-morbid asthma in the CRSwNP development program. Physicians should be alert to vasculitic rash, worsening pulmonary symptoms, cardiac

complications, and/or neuropathy presenting in their patients with eosinophilia. Patients being treated for asthma may present with serious systemic eosinophilia sometimes presenting with clinical features of eosinophilic pneumonia or vasculitis consistent with eosinophilic granulomatosis with polyangiitis, conditions which are often treated with systemic corticosteroid therapy. These events usually, but not always, may be associated with the reduction of oral corticosteroid therapy.

Helminth infection

Patients with known helminth infections were excluded from participation in clinical studies. Dupilumab may influence the immune response against helminth infections by inhibiting IL-4/IL-13 signalling. Patients with pre-existing helminth infections should be treated before initiating dupilumab. If patients become infected while receiving treatment with dupilumab and do not respond to anti-helminth treatment, treatment with dupilumab should be discontinued until infection resolves. Cases of enterobiasis were reported in children 6 to 11 years old who participated in the paediatric asthma development program (see section 4.8).

Conjunctivitis and keratitis related events

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

Patients should be advised to report new onset or worsening eye symptoms to their healthcare provider. Patients treated with dupilumab who develop conjunctivitis that does not resolve following standard treatment or signs and symptoms suggestive of keratitis should undergo ophthalmological examination, as appropriate (see section 4.8).

Patients with comorbid asthma

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

Vaccinations

Concurrent use of live and live attenuated vaccines with dupilumab should be avoided as clinical safety and efficacy have not been established. It is recommended that patients should be brought up to date with live and live attenuated immunisations in agreement with current immunisation guidelines prior to treatment with dupilumab. Clinical data are not available to support more specific guidance for live or live attenuated vaccines administration in patients treated with dupilumab. Immune responses to TdaP vaccine and meningococcal polysaccharide vaccine were assessed (see section 4.5).

Sodium content

This medicinal product contains less than 1 mmol sodium (23 mg) per 300 mg dose, that is to say essentially ‘sodium-free’.

Polysorbate 80 (E433)

This medicine contains 4 mg of polysorbate 80 in each 300 mg dose (2mL). Polysorbates may cause allergic reactions.

4.5 Interaction with other medicinal products and other forms of interaction

Immune responses to vaccination were assessed in a study in which patients with atopic dermatitis were treated once weekly for 16 weeks with 300 mg of dupilumab. After 12 weeks of dupilumab

administration, patients were vaccinated with a Tdap vaccine (T cell-dependent), and a meningococcal polysaccharide vaccine (T cell-independent) and immune responses were assessed 4 weeks later. Antibody responses to both tetanus vaccine and meningococcal polysaccharide vaccine were similar in dupilumab-treated and placebo-treated patients. No adverse interactions between either of the non-live vaccines and dupilumab were noted in the study.

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

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

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

4.6 Fertility, pregnancy and lactation

Pregnancy

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

Breast-feeding

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

Fertility

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

4.7 Effects on ability to drive and use machines

Dupilumab has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

Summary of the safety profile

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

Tabulated list of adverse reactions

The dupilumab safety data presented in Table 6 were predominantly derived from 12 randomised, placebo-controlled trials, including atopic dermatitis, asthma, and CRSwNP patients. These studies

involved 4,206 patients receiving dupilumab and 2,326 patients receiving placebo during the controlled period are representative of the overall safety profile for dupilumab.

Listed in Table 6 are adverse reactions observed in clinical trials and/or postmarketing setting presented by system organ class and frequency, using the following categories: very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1 000 to < 1/100); rare (≥ 1/10 000 to < 1/1 000); very rare (< 1/10 000); not known (cannot be estimated from the available data). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Table 6: List of adverse reactions

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

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

Description of selected adverse reactions

Hypersensitivity
Cases of anaphylactic reaction, angioedema, and serum sickness/serum sickness-like reaction have been reported following administration of dupilumab (see section 4.4).

Conjunctivitis and keratitis related events
Conjunctivitis and keratitis occurred more frequently in atopic dermatitis patients who received dupilumab compared to placebo in atopic dermatitis studies. Most patients with conjunctivitis or keratitis recovered or were recovering during the treatment period. In the long-term OLE atopic dermatitis study (AD-1225) at 5 years, the respective rates of conjunctivitis and keratitis remained similar to those in the dupilumab arm in the placebo controlled atopic dermatitis studies. Among asthma and COPD patients, the frequency of conjunctivitis and keratitis was low and similar between dupilumab and placebo. Among CRSwNP and Prurigo Nodularis (PN) patients the frequency of conjunctivitis was higher in dupilumab than placebo, though lower than that observed in atopic dermatitis patients. There were no cases of keratitis reported in the CRSwNP or PN development

program. Among patients with EoE, the frequency of conjunctivitis was low and similar between dupilumab and placebo groups. There were no cases of keratitis in the EoE development program (see section 4.4).

Eczema herpeticum
Eczema herpeticum was reported in < 1% of the dupilumab groups and in < 1 % of the placebo group in the 16-week atopic dermatitis monotherapy adult studies. In the 52-week atopic dermatitis dupilumab + TCS adult study, eczema herpeticum was reported in 0.2 % of the dupilumab + TCS group and 1.9 % of the placebo + TCS group. These rates remained stable at 5 years in the long-term OLE study (AD-1225).

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

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

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

Infections
In the 16-week atopic dermatitis monotherapy clinical adult studies, serious infections were reported in 1.0 % of patients treated with placebo and 0.5 % of patients treated with dupilumab. In the 52-week atopic dermatitis CHRONOS adult study, serious infections were reported in 0.6 % of patients treated with placebo and 0.2 % of patients treated with dupilumab. The rates of serious infections remained stable at 5 years in the long-term OLE study (AD-1225).

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

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

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

The overall incidence of infections was numerically higher with dupilumab (32.0%) compared to placebo (24.8%) in the 24-week safety pool for the EoE TREET (Parts A and B) studies. The overall incidence of infections was numerically higher in placebo (41.2%) compared to dupilumab (35.8%) in the EoE KIDS (Part A) study. In the 24-week safety pool for the EoE TREET (Parts A and B) studies,

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

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

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

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

Approximately 5 % of patients with atopic dermatitis, asthma, or CRSwNP who received dupilumab 300 mg Q2W for 52 weeks developed ADA to dupilumab; approximately 2 % exhibited persistent ADA responses and approximately 2 % had neutralizing antibodies. Similar results were observed in adult patients with PN who received dupilumab 300 mg Q2W for 24 weeks, paediatric patients (6 months to 11 years of age) with atopic dermatitis who received either dupilumab 200 mg Q2W, 200 mg Q4W, or 300 mg Q4W for 16 weeks and patients (6 to 11 years of age) with asthma who received dupilumab 100 mg Q2W or 200 mg Q2W for 52 weeks. Similar ADA responses were observed in adult patients with atopic dermatitis treated with dupilumab for up to 5 years in the long-term OLE study (AD-1225).

Approximately 16 % of adolescent patients with atopic dermatitis who received dupilumab 300 mg or 200 mg Q2W for 16 weeks developed antibodies to dupilumab; approximately 3 % exhibited persistent ADA responses, and approximately 5 % had neutralizing antibodies.

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

Approximately 1% of patients 1 year of age and older with EoE who received dupilumab 300 mg QW (≥40 kg), 300 mg Q2W (≥30 to <60 kg), 200 mg Q2W (≥15 to <30 kg), or 100 mg Q2W (≥5 to <15 kg) for 52 weeks developed antibodies to dupilumab; the ADA responses were neither persistent nor neutralizing..

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

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

Less than 1 % of patients who received dupilumab at approved dosing regimens exhibited high titer ADA responses associated with reduced exposure and efficacy. In addition, there was one patient with serum sickness and one with serum sickness-like reaction (< 0.1 %) associated with high ADA titers (see section 4.4).

Paediatric population

Atopic dermatitis

Adolescents (12 to 17 years of age)
The safety of dupilumab was assessed in a study of 250 patients 12 to 17 years of age with moderate-to-severe atopic dermatitis (AD-1526). The safety profile of dupilumab in these patients followed through week 16 was similar to the safety profile from studies in adults with atopic dermatitis.

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

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

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

Asthma

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

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

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

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

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

The long-term safety profile of dupilumab in EXCURSION was consistent with the safety profile observed in the pivotal asthma study (VOYAGE) for 52 weeks of treatment.

EoE

Adolescents (12 to 17 years of age)

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

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

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

Long-term safety

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

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

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

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

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

Eosinophilic esophagitis

The safety profile of dupilumab through week 52 in adult and adolescent patients 12 years of age and older (TREET Part C) and in children 1 to 11 years of age (EoE KIDS Part B) was generally consistent with the safety profile observed at week 24 in TREET Parts A and B and at Week 16 in EoE KIDS Part A.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

Mechanism of action

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

Pharmacodynamic effects

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

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

In COPD patients, dupilumab treatment decreased type 2 biomarkers including FeNO and total IgE compared to placebo. Decreases in FeNO were observed by Week 4. These effects on type 2 biomarkers were sustained throughout treatment with dupilumab.

Clinical efficacy and safety in atopic dermatitis

Adults with atopic dermatitis

The efficacy and safety of dupilumab as monotherapy and with concomitant topical corticosteroids

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

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

Endpoints
In all three pivotal studies, the co-primary endpoints were the proportion of patients with IGA 0 or 1 ("clear" or "almost clear") with a reduction of ≥ 2 points on a 0-4 IGA scale and the proportion of patients with improvement of at least 75 % in EASI (EASI-75). Key secondary and other clinically relevant secondary endpoints are presented in Table 7.

Baseline Characteristics
In the monotherapy studies (SOLO 1 and SOLO 2), across all treatment groups, the mean age was 38.3, the mean weight was 76.9 kg, 42.1 % were female, 68.1 % were white, 21.8 % were Asian, and 6.8 % were black. In these studies, 51.6 % of patients had a baseline IGA score of 3 (moderate AD), 48.3 % of patients had a baseline IGA of 4 (severe AD) and 32.4 % of patients had received prior systemic immunosuppressants. The baseline mean EASI score was 33.0, the baseline weekly averaged pruritus Numerical Rating Scale (NRS) was 7.4, the baseline mean POEM score was 20.5, the baseline mean DLQI was 15.0, and the baseline mean HADS total score was 13.3.

In the concomitant TCS study (CHRONOS), across all treatment groups, the mean age was 37.1, the mean weight was 74.5 kg, 39.7 % were female, 66.2 % were white, 27.2 % were Asian, and 4.6 % were black. In this study, 53.1 % of patients had a baseline IGA score of 3 and 46.9 % of patients had a baseline IGA of 4 and 33.6 % of patients received prior systemic immunosuppressants. The baseline mean EASI score was 32.5, the baseline weekly pruritus NRS was 7.3, the baseline mean POEM score was 20.1, the baseline mean DLQI was 14.5, and the baseline mean HADS total score was 12.7.

Clinical Response

16-week monotherapy studies (SOLO 1 and SOLO 2) and 52-week concomitant TCS study (CHRONOS)

In SOLO 1, SOLO 2, and CHRONOS from baseline to week 16, a significantly greater proportion of patients randomised to dupilumab achieved an IGA 0 or 1 response, EASI-75, and/or an improvement of ≥ 4 points on the pruritus NRS (key secondary endpoint) compared to placebo (see Table 7).

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

A persistent treatment effect of dupilumab was observed in the CHRONOS study up to week 52 (see Table 7).

The efficacy results for co-primary, key secondary and other clinically relevant secondary endpoints for all three studies are presented in Table 7.

Table 7: Efficacy results of dupilumab monotherapy at week 16 (FAS) and with concomitant TCS[a] at week 16 and week 52

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

LS = least squares; SE= standard error

[a]all patients were on background topical corticosteroids therapy and patients were permitted to use topical calcineurin inhibitors.

[b]full analysis set (FAS) includes all patients randomised.

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

[d]patients who received rescue treatment or with missing data were considered as non-responders.

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

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

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

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

[i]nominal p-value = 0.0005

[j]nominal p-value < 0.0001

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

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

Figure 2a and Figure 2b show the mean percent change from baseline in EASI and the mean percent change from baseline in NRS, respectively up to week 52 in CHRONOS.

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

Figure 1a. SOLO 1 and SOLO 2 EASI

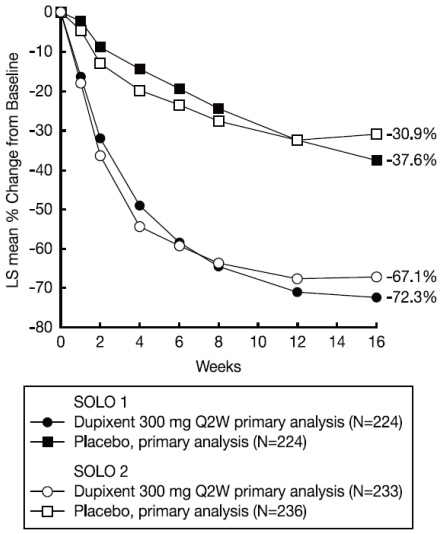
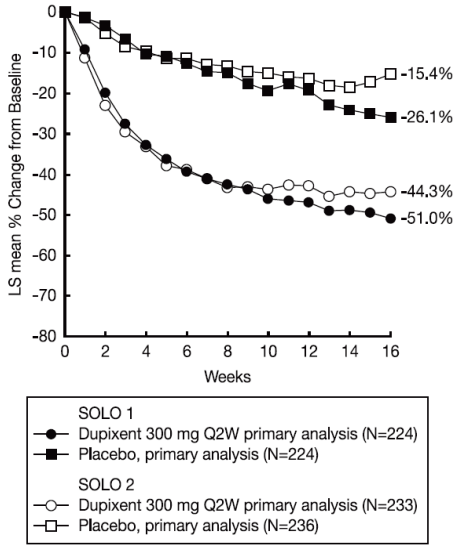


Figure 1b. SOLO 1 and SOLO 2 NRS



LS = least squares

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

[b] Full analysis set (FAS) includes all patients randomised.

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

Figure 2a. CHRONOS EASI

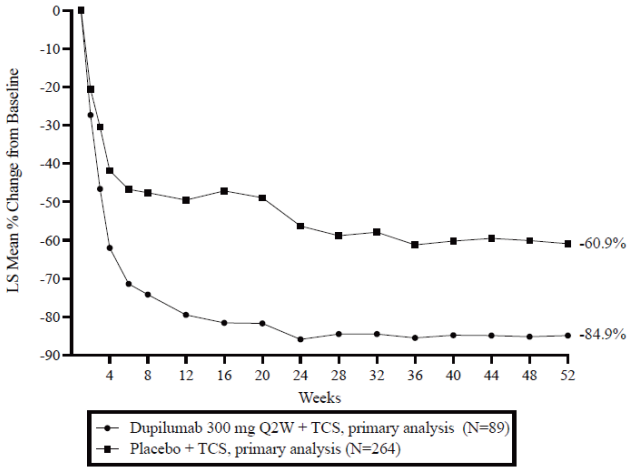
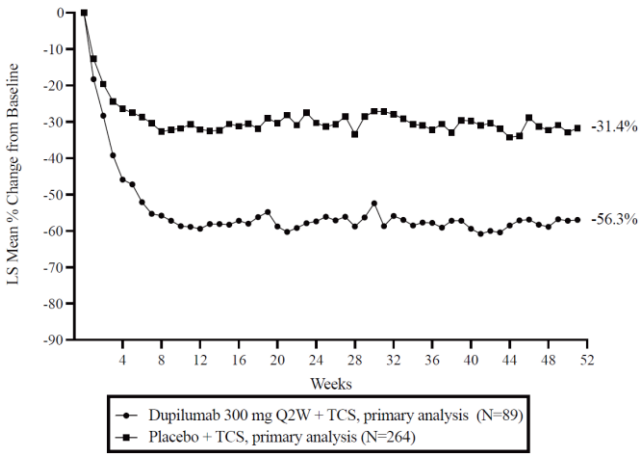


Figure 2b. CHRONOS NRS



LS = least squares

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

[b] FAS week 52 includes all patients randomised at least one year before the cutoff date of the primary analysis.

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

Clinical response in patients not adequately controlled with, intolerant to, or for whom ciclosporin treatment was inadvisable (CAFE study)

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

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

Primary endpoint (proportion of patients with EASI-75) and secondary endpoints for the 16 week CAFE study are summarized in Table 8.

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

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

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

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

Maintenance and durability of response (SOLO CONTINUE study)

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

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

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

Primary and secondary endpoints for the 52 week SOLO CONTINUE study are summarized in Table 9.

Table 9: Results of the primary and secondary endpoints in SOLO CONTINUE study

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

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

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

Quality of life/patient-reported outcomes in atopic dermatitis

In both monotherapy studies (SOLO 1 and SOLO 2), both dupilumab 300 mg Q2W and 300 mg QW groups significantly improved patient-reported symptoms and the impact of AD on sleep, anxiety and depression symptoms as measured by HADS, and health-related quality of life as measured by POEM and DLQI total scores, respectively, at 16 weeks compared to placebo (see Table 10).

Similarly, in the concomitant TCS study (CHRONOS), dupilumab 300 mg Q2W + TCS and dupilumab 300 mg QW + TCS improved patient-reported symptoms and the impact of AD on sleep and health-related quality of life as measured by POEM and DLQI total scores, respectively, at 52 weeks compared to placebo + TCS (see Table 10).

Table 10: Additional secondary endpoint results of dupilumab monotherapy at week 16 and concomitant use of TCS at week 16 and week 52

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

LS = least squares; SE = standard error

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

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

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

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

Adolescents with atopic dermatitis (12 to 17 years of age)

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

Patients received dupilumab was administered by subcutaneous (SC) injections either as:1) an initial dose of 400 mg dupilumab (two 200 mg injections) on day 1, followed by 200 mg once

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

In this study, the mean age was 14.5 years, the median weight was 59.4 kg, 41.0 % were female, 62.5 % were White, 15.1 % were Asian, and 12.0 % were Black. At baseline 46.2 % of patients had a baseline IGA score of 3 (moderate AD), 53.8 % of patients had a baseline IGA of 4 (severe AD), the mean BSA involvement was 56.5 %, and 42.4 % of patients had received prior systemic immunosuppressants. Also at baseline the mean Eczema Area and Severity Index (EASI) score was 35.5, the baseline weekly averaged pruritus Numerical Rating Scale (NRS) was 7.6, the baseline mean Patient Oriented Eczema Measure (POEM) score was 21.0, and the baseline mean Children Dermatology Life Quality Index (CDLQI) was 13.6. Overall, 92.0 % of patients had at least one co-morbid allergic condition; 65.6 % had allergic rhinitis, 53.6 % had asthma, and 60.8 % had food allergies.

The co-primary endpoint was the proportion of patients with IGA 0 or 1 ("clear" or "almost clear") least a 2-point improvement and the proportion of patients with EASI-75 (improvement of at least 75 % in EASI), from baseline to week 16.

Clinical Response

The efficacy results at week 16 for adolescent atopic dermatitis study are presented in Table 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**
Patients randomised	**85[a]**	**82[a]**
IGA 0 or 1[b], % responders[c]	2.4 %	24.4 %[d]
EASI-50, % responders[c]	12.9 %	61.0 %[d]
EASI-75, % responders[c]	8.2 %	41.5 %[d]
EASI-90, % responders[c]	2.4 %	23.2 %[d]
EASI, LS mean % change from baseline (+/-SE)	-23.6 % (5.49)	-65.9 %[d] (3.99)
Pruritus NRS, LS mean % change from baseline (+/- SE)	-19.0 % (4.09)	-47.9 %[d] (3.43)
Pruritus NRS (≥ 4-point improvement), % responders[c]	4.8 %	36.6 %[d]
CDLQI, LS mean change from baseline (+/-SE)	-5.1 (0.62)	-8.5[d] (0.50)
CDLQI, (≥ 6-point improvement), % responders	19.7 %	60.6 %[e]
POEM, LS mean change from baseline (+/- SE)	-3.8 (0.96)	-10.1[d] (0.76)
POEM, (≥ 6-point improvement), % responders	9.5 %	63.4 %[e]

[a]full Analysis Set (FAS) includes all patients randomised.
[b]responder was defined as a subject with IGA 0 or 1 ("clear" or "almost clear") with a reduction of ≥ 2 points on a 0-4 IGA scale.
[c]patients who received rescue treatment or with missing data were considered as non-responders (58.8 % and 20.7 % in the placebo and dupilumab arms, respectively).
[d]p–value < 0.0001 (statistically significant vs placebo with adjustment for multiplicity)
[e]nominal p-value < 0.0001

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

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

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

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

Paediatrics (6 to 11 years of age)

The efficacy and safety of dupilumab in paediatric patients concomitantly with TCS was evaluated in a multicentre, randomised, double-blind, placebo-controlled study (AD-1652) in 367 subjects 6 to 11 years of age, with severe AD defined by an IGA score of 4 (scale of 0 to 4), an EASI score ≥ 21 (scale of 0 to 72), and a minimum BSA involvement of ≥ 15 %. Eligible patients enrolled into this trial had previous inadequate response to topical medication. Enrolment was stratified by baseline weight (< 30 kg; ≥ 30 kg).

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

In this study, the mean age was 8.5 years, the median weight was 29.8 kg, 50.1 % of patients were female, 69.2 % were White, 16.9 % were Black, and 7.6 % were Asian. At baseline, the mean BSA involvement was 57.6 %, and 16.9 % had received prior systemic non-steroidal immunosuppressants. Also, at baseline the mean EASI score was 37.9, and the weekly average of daily worst itch score was 7.8 on a scale of 0-10, the baseline mean SCORAD score was 73.6, the baseline POEM score was 20.9, and the baseline mean CDLQI was 15.1. Overall, 91.7 % of subjects had at least one co-morbid allergic condition; 64.4 % had food allergies, 62.7 % had other allergies, 60.2 % had allergic rhinitis, and 46.7 % had asthma.

The co-primary endpoint was the proportion of patients with IGA 0 or 1 (“clear” or “almost clear”) at least a 2-point improvement and the proportion of patients with EASI-75 (improvement of at least 75 % in EASI), from baseline to week 16.

Clinical Response

Table 12 presents the results by baseline weight strata for the approved dose regimens.

Table 12: Efficacy results of dupilumab with concomitant TCS in AD-1652 at week 16 (FAS)[a]

	Dupilumab 300 mg Q4W[d] + TCS	Placebo +TCS	Dupilumab 200 mg Q2W[e] + TCS	Placebo + TCS
	(N=122)	(N=123)	(N=59)	(N=62)
	≥ 15 kg	≥ 15 kg	≥ 30 kg	≥ 30 kg
IGA 0 or 1[b], % responders[c]	32.8 %[f]	11.4 %	39.0 %[h]	9.7 %
EASI-50, % responders[c]	91.0 %[f]	43.1 %	86.4 %[g]	43.5 %
EASI-75, % responders[c]	69.7 %[f]	26.8 %	74.6 %[g]	25.8 %
EASI-90, % responders[c]	41.8 %[f]	7.3 %	35.6 %[h]	8.1 %
EASI, LS mean % change from baseline (+/-SE)	-82.1 %[f] (2.37)	-48.6 % (2.46)	-80.4 %[g] (3.61)	-48.3 % (3.63)
Pruritus NRS, LS mean % change from baseline (+/- SE)	-54.6 %[f] (2.89)	-25.9 % (2.90)	-58.2 %[g] (4.01)	-25.0 % (3.95)
Pruritus NRS (≥4-point improvement), % responders[c]	50.8 %[f]	12.3 %	61.4 %[g]	12.9 %
CDLQI, LS mean change from baseline (+/-SE)	-10.6[f] (0.47)	-6.4 (0.51)	-9.8[g] (0.63)	-5.6 (0.66)
CDLQI, (≥ 6-point improvement), % responders	77.3 %[g]	38.8 %	80.8 %[g]	35.8 %
POEM, LS mean change from baseline (+/- SE)	-13.6[f] (0.65)	-5.3 (0.69)	-13.6[g] (0.90)	-4.7 (0.91)
POEM, (≥ 6-point improvement), % responders	81.7 %[g]	32.0 %	79.3 %[g]	31.1 %

[a]full Analysis Set (FAS) includes all patients randomised.
[b]responder was defined as a patient with an IGA 0 or 1 ("clear" or "almost clear").
[c]patients who received rescue treatment or with missing data were considered as non-responders.
[d]at Day 1, patients received 600 mg of dupilumab (see section 5.2).
[e]at Day 1, patients received 400 mg (baseline weight ≥ 30 kg) of dupilumab.
[f]p-value < 0.0001 (statistically significant vs placebo with adjustment for multiplicity)
[g]nominal p-values < 0.0001
[h]nominal p-value = 0.0002

A greater proportion of patients randomised to dupilumab + TCS achieved an improvement in the peak pruritus NRS compared to placebo + TCS (defined as ≥4-point improvement at week 4).

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

The long-term efficacy and safety of dupilumab + TCS in paediatric patients with moderate to severe atopic dermatitis who had participated in the previous clinical trials of dupilumab + TCS was assessed in an open-label extension study (AD-1434). Efficacy data from this trial suggests that clinical benefit provided at week 16 was sustained through week 52. Some patients receiving dupilumab 300 mg Q4W + TCS showed further clinical benefit when escalated to dupilumab 200 mg Q2W + TCS. The safety profile of dupilumab in patients followed through week 52 was similar to the safety profile observed at week 16 in the AD-1526 and AD-1652 studies.

Paediatrics (6 Months to 5 years of age)

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

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

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

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

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

The co-primary endpoint was the proportion of patients with IGA 0 or 1 ("clear" or "almost clear", at least a 2-point improvement) and the proportion of patients with EASI-75 (improvement of at least 75 % in EASI), from baseline to week 16. The primary endpoint was the proportion of patients with an IGA 0 (clear) or 1 (almost clear) at week 16.

Clinical Response

The efficacy results at week 16 for AD-1539 are presented in Table 13.

Table 13: Efficacy results of dupilumab with concomitant TCS in AD-1539 at Week 16 (FAS)[a]

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

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

[a]Full Analysis Set (FAS) includes all patients randomised.
[b]Responder was defined as a patient with an IGA 0 or 1 ("clear" or "almost clear").
[c]Patients who received rescue treatment (62% and 19% in the placebo and dupilumab arms, respectively) or with missing data were considered as non-responders.
[d]At Day 1, patients received 200 mg (5 to <15kg) or 300 mg (15 to <30 kg) of dupilumab.
[e]p–values < 0.0001,[f]nominal p-value < 0.05, [g]nominal p-value < 0.0001, [h]nominal p-value < 0.005, [i]nominal p-value < 0.001
*Caregiver reported outcome

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

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

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

Atopic Hand and Foot Dermatitis (adults and adolescents)

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

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

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

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

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

Clinical efficacy and safety in asthma

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

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

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

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

The demographics and baseline characteristics of these 3 studies are provided in Table 14 below.

Table 14: Demographics and baseline characteristics of asthma trials

Parameter	**DRI12544 (n = 776)**	**QUEST (n = 1902)**	**VENTURE (n=210)**
Mean age (years) (SD)	48.6 (13.0)	47.9 (15.3)	51.3 (12.6)
% Female	63.1	62.9	60.5
% White	78.2	82.9	93.8
Duration of Asthma (years), mean ± SD	22.03 (15.42)	20.94 (15.36)	19.95 (13.90)
Never smoked, (%)	77.4	80.7	80.5

Mean exacerbations in previous year ± SD	2.17 (2.14)	2.09 (2.15)	2.09 (2.16)
High dose ICS use (%)[a]	49.5	51.5	88.6
Pre-dose FEV_1 (L) at baseline ± SD	1.84 (0.54)	1.78 (0.60)	1.58 (0.57)
Mean percent predicted FEV_1 at baseline (%)(± SD)	60.77 (10.72)	58.43 (13.52)	52.18 (15.18)
% Reversibility (± SD)	26.85 (15.43)	26.29 (21.73)	19.47 (23.25)
Mean ACQ-5 score (± SD)	2.74 (0.81)	2.76 (0.77)	2.50 (1.16)
Mean AQLQ score (± SD)	4.02 (1.09)	4.29 (1.05)	4.35 (1.17)
Atopic Medical History % Overall (AD %, NP %, AR %)	72.9 (8.0, 10.6, 61.7)	77.7 (10.3, 12.7, 68.6)	72.4 (7.6, 21.0, 55.7)
Mean FeNO ppb (± SD)	39.10 (35.09)	34.97 (32.85)	37.61 (31.38)
% patients with FeNO ppb ≥ 25 ≥ 50	 49.9 21.6	 49.6 20.5	 54.3 25.2
Mean total IgE IU/mL (± SD)	435.05 (753.88)	432.40 (746.66)	430.58 (775.96)
Mean baseline Eosinophil count (± SD) cells/mcL	350 (430)	360 (370)	350 (310)
% patients with EOS ≥ 150 cells/mcL ≥ 300 cells/mcL	 77.8 41.9	 71.4 43.7	 71.4 42.4

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

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

Exacerbations

In the overall population in DRI12544 and QUEST subjects receiving either dupilumab 200 mg or 300 mg every other week had significant reductions in the rate of severe asthma exacerbations compared to placebo. There were greater reductions in exacerbations in subjects with higher baseline levels of type 2 inflammatory biomarkers such as blood eosinophils or FeNO (Table 15 and Table 16).

Table 15: Rate of severe exacerbations in DRI12544 and QUEST (baseline blood eosinophil levels ≥ 150 and ≥ 300 cells/mcL)

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

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

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

Table 16. Rate of severe exacerbations in QUEST defined by baseline FeNO subgroups

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

[a]nominal p-value < 0.0001

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

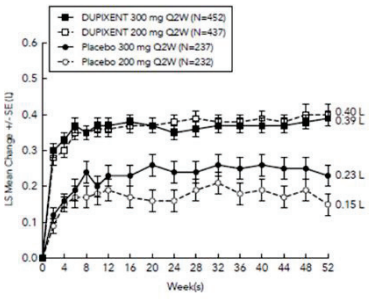
Lung function

Clinically significant increases in pre-bronchodilator FEV_1 were observed at week 12 for DRI12544 and QUEST. There were greater improvements in FEV_1 in the subjects with higher baseline levels of type 2 inflammatory biomarkers such as blood eosinophils or FeNO (Table 17 and Table 18).

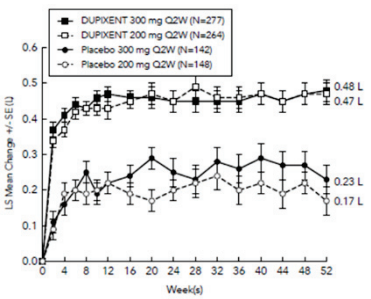
Significant improvements in FEV_1 were observed as early as week 2 following the first dose of dupilumab for both the 200 mg and 300 mg dose strengths and were maintained through week 24 (DRI12544) and week 52 in QUEST (see Figure 3).

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

QUEST: blood eosinophils ≥ 150 cells/mcL



QUEST: blood eosinophils ≥ 300 cells/mcL



QUEST: FeNO ≥ 25 ppb

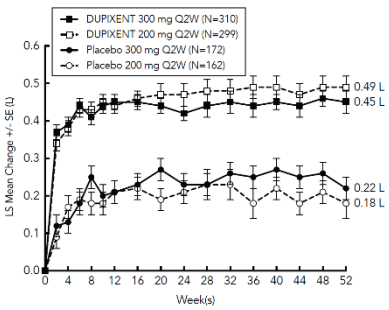


Table 17: Mean change from baseline in pre-bronchodilator FEV_1 at week 12 in DRI12544 and QUEST (baseline blood eosinophil Levels ≥ 150 and ≥ 300 cells/mcL)

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

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

Table 18: Mean change from baseline in pre-bronchodilator FEV_1 at week 12 and week 52 in 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 %)	

[a]nominal p-value < 0.0001

Quality of life/patient-reported outcomes in asthma

Pre-specified secondary endpoint of ACQ-5 and AQLQ(S) responder rates were analysed at 24 weeks (DRI12544 and VENTURE) and at 52 weeks (QUEST, Table 19). The responder rate was defined as an improvement in score of 0.5 or more (scale range 0-6 for ACQ-5 and 1-7 for AQLQ(S)). Improvements in ACQ-5 and AQLQ(S) were observed as early as week 2 and maintained for 24 weeks in DRI12544 study and 52 weeks in QUEST study. Similar results were observed in VENTURE.

Table 19: 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 14. All patients were on oral corticosteroids for at least 6 months prior to the study initiation. The baseline mean oral corticosteroid use was 11.75 mg in the placebo group and 10.75 mg in the group receiving dupilumab.

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

The results for VENTURE by baseline biomarkers are presented in the Table 20.

Table 20: Effect of dupilumab on OCS dose reduction, VENTURE (baseline blood eosinophil levels ≥ 150 and ≥ 300 cells/mcL and FeNO ≥ 25 ppb)

	Baseline blood EOS ≥ 150 cells/mcL		**Baseline blood EOS ≥ 300 cells/mcL**		**FeNO ≥ 25 ppb**	
	Dupilumab 300 mg Q2W N=81	**Placebo N=69**	**Dupilumab 300 mg Q2W N=48**	**Placebo N=41**	**Dupilumab 300 mg Q2W N=57**	**Placebo N=57**
Primary endpoint (week 24)						
Percent reduction in OCS from baseline						
Mean overall percent reduction from baseline (%)	75.91	46.51	79.54	42.71	77.46	42.93
Difference (% [95% CI]) (Dupilumab vs. placebo)	29.39[b] (15.67, 43.12)		36.83[b] (18.94, 54.71)		34.53[b] (19.08, 49.97)	
Median % reduction in daily OCS dose from baseline	100	50	100	50	100	50
Percent reduction from baseline						
100% %	54.3	33.3	60.4	31.7	52.6	28.1
≥ 90 %	58.0	34.8	66.7	34.1	54.4	29.8
≥ 75 %	72.8	44.9	77.1	41.5	73.7	36.8
≥ 50 %	82.7	55.1	85.4	53.7	86.0	50.9
> 0 %	87.7	66.7	85.4	63.4	89.5	66.7
No reduction or any increase in OCS dose, or dropped out of study	12.3	33.3	14.6	36.6	10.5	33.3
Secondary endpoint (week 24)[a]						
Proportion of patients achieving a reduction of OCS dose to < 5 mg/day	77	44	84	40	79	34
Odds ratio (95% CI)	4.29[c] (2.04, 9.04)		8.04[d] (2.71, 23.82)		7.21[b] (2.69, 19.28)	

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

Long-term extension study (TRAVERSE)

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

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

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

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

The demographics and baseline characteristics for VOYAGE are provided in Table 21 below.

Table 21. Demographics and baseline characteristics for VOYAGE

Parameter	**EOS ≥ 150 cells/mcL or FeNO ≥ 20 ppb (N = 350)**	**EOS ≥ 300 cells/mcL (N = 259)**
Mean age (years) (SD)	8.9 (1.6)	9.0 (1.6)
% Female	34.3	32.8
% White	88.6	87.3
Mean body weight (kg)	36.09	35.94
Mean exacerbations in previous year (± SD)	2.47 (2.30)	2.64 (2.58)
ICS dose (%) Medium High	 55.7 43.4	 54.4 44.4
Pre-dose FEV_1 (L) at baseline (± SD)	1.49 (0.41)	1.47 (0.42)
Mean percent predicted FEV_1 (%) (±SD)	77.89 (14.40)	76.85 (14.78)
Mean % Reversibility (± SD)	27.79 (19.34)	22.59 (20.78)
Mean ACQ-7-IA score (± SD)	2.14 (0.72)	2.16 (0.75)
Mean PAQLQ(S)-IA score (± SD)	4.94 (1.10)	4.93 (1.12)
Atopic Medical History % Overall (AD %, AR %)	94 (38.9, 82.6)	96.5 (44.4, 85.7)

Median total IgE IU/mL (± SD)	905.52 (1140.41)	1077.00 (1230.83)
Mean FeNO ppb (± SD)	30.71 (24.42)	33.50 (25.11)
% patients with FeNO ≥ 20 ppb	58	64.1
Mean baseline Eosinophil count (± SD) cells/mcL	570 (380)	710 (360)
% patients with EOS ≥ 150 cells/mcL ≥ 300 cells/mcL	 94.6 74	 0 100

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

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

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

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

In both primary efficacy populations, there was a rapid improvement in FEF25-75% and FEV_1/FVC (onset of a difference was observed as early as week 2) and sustained over the 52-week treatment period, see Table 22.

Table 22: Rate of severe exacerbations, mean change from baseline in FEV_1, ACQ-7-IA and PAQLQ(S)-IA responder rates in VOYAGE

Treatment	**EOS ≥ 150 cells/mcL or FeNO ≥ 20 ppb**			**EOS ≥ 300 cells/mcL**			**FeNO ≥20 ppb**		
Annualised severe exacerbations rate over 52 weeks									
	N	**Rate (95% CI)**	**Rate ratio (95% CI)**	**N**	**Rate (95% CI)**	**Rate ratio (95% CI)**	**N**	**Rate (95% CI)**	**Rate ratio (95% CI)**
Dupilumab 100 mg Q2W (<30 kg)/ 200 mg Q2W (≥30 kg)	236	0.305 (0.223, 0.416)	0.407[b] (0.274, 0.605)	175	0.235 (0.160, 0.345)	0.353[b] (0.222, 0.562)	141	0.271 (0.170, 0.432)	0.384[c] (0.227, 0.649)
Placebo	114	0.748 (0.542, 1.034)		84	0.665 (0.467, 0.949)		62	0.705 (0.421, 1.180)	
Mean change from baseline in percent predicted FEV1 at week 12									

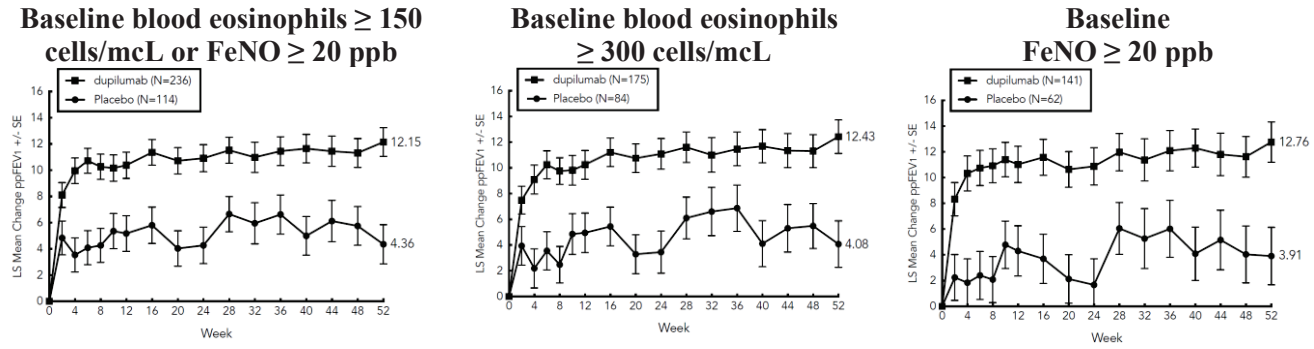
	N	LS mean Δ from baseline	LS mean difference vs. placebo (95% CI)	N	LS mean Δ from baseline	LS mean difference vs. placebo (95% CI)	N	LS mean Δ from baseline i	LS mean difference vs. placebo (95% CI)
Dupilumab 100 mg Q2W (<30 kg)/ 200 mg Q2W (≥30 kg)	229	10.53	5.21[c] (2.14, 8.27)	168	10.15	5.32[d] (1.76, 8.88)	141	11.36	6.74[d] (2.54, 10.93)
Placebo	110	5.32		80	4.83		62	4.62	
Mean change from baseline in percent predicted FEF 25-75% at week 12									
	N	**LS mean Δ from baseline**	**LS mean difference vs. placebo (95% CI)**	**N**	**LS mean Δ from baseline**	**LS mean difference vs. placebo (95% CI)**	**N**	**LS mean Δ from baseline**	**LS mean difference vs. placebo (95% CI)**
Dupilumab 100 mg Q2W (<30 kg)/ 200 mg Q2W (≥30 kg)	229	16.70	11.93[e] (7.44, 16.43)	168	16.91	13.92[e] (8.89, 18.95)	141	17.96	13.97[e] (8.30, 19.65)
Placebo	110	4.76		80	2.99		62	3.98	
Mean change from baseline in FEV_1/FVC % at week 12									
	N	**LS mean Δ from baseline**	**LS mean difference vs. placebo (95% CI)**	**N**	**LS mean Δ from baseline**	**LS mean difference vs. placebo (95% CI)**	**N**	**LS mean Δ from baseline**	**LS mean difference vs. placebo (95% CI)**
Dupilumab 100 mg Q2W (<30 kg)/ 200 mg Q2W (≥30 kg)	229	5.67	3.73[e] (2.25, 5.21)	168	6.10	4.63[e] (2.97, 6.29)	141	6.84	4.95[e] (3.08, 6.81)
Placebo	110	1.94		80	1.47		62	1.89	
ACQ-7-IA at week 24[a]									
	N	**Responder rate %**	**OR vs. placebo (95% CI)**	**N**	**Responder rate %**	**OR vs. placebo (95% CI)**	**N**	**Responder rate %**	**OR vs. placebo (95% CI)**
Dupilumab 100 mg Q2W (<30 kg)/ 200 mg Q2W (≥30 kg)	236	79.2	1.82[g] (1.02, 3.24)	175	80.6	2.79[f] (1.43, 5.44)	141	80.9	2.60[g] (1.21, 5.59)
Placebo	114	69.3		84	64.3		62	66.1	
PAQLQ(S)-IA at week 24[a]									
	N	**Responder rate %**	**OR vs. placebo (95% CI)**	**N**	**Responder rate %**	**OR vs. placebo (95% CI)**	**N**	**Responder rate %**	**OR vs. placebo (95% CI)**
Dupilumab 100 mg Q2W (<30 kg)/ 200 mg Q2W (≥30 kg)	211	73.0	1.57 (0.87, 2.84)	158	72.8	1.84 (0.92, 3.65)	131	75.6	2.09 (0.95, 4.61)
Placebo	107	65.4		81	63.0		61	67.2	

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

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

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

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



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

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

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

Long-term extension study (EXCURSION)

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

Clinical efficacy in chronic rhinosinusitis with nasal polyposis (CRSwNP)

The chronic rhinosinusitis with nasal polyposis (CRSwNP) development program included two randomised, double-blind, parallel-group, multicentre, placebo-controlled studies (SINUS-24 and SINUS-52) in 724 patients aged 18 years and older on background intranasal corticosteroids (INCS). These studies included patients with severe CRSwNP despite prior sino-nasal surgery or treatment

with, or who were ineligible to receive, systemic corticosteroids in the past 2 years. Rescue with systemic corticosteroids or surgery was allowed during the studies at the investigator's discretion All patients had evidence of sinus opacification on the Lund MacKay (LMK) sinus CT scan and 73 % to 90 % of patients had opacification of all sinuses. Patients were stratified based on their histories of prior surgery and co-morbid asthma/nonsteroidal anti-inflammatory drug exacerbated respiratory disease (NSAID-ERD).

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

The demographics and baseline characteristics of these 2 studies are provided in Table 23 below.

Table 23: Demographics and baseline characteristics of CRSwNP studies

Parameter	**SINUS-24 (N=276)**	**SINUS-52 (N=448)**
Mean age (years) (SD)	50.49 (13.39)	51.95 (12.45)
% Male	57.2	62.3
Mean CRSwNP duration (years)(SD)	11.11 (9.16)	10.94 (9.63)
Patients with ≥ 1 prior surgery (%)	71.7	58.3
Patients with systemic corticosteroid use in the previous 2 years (%)	64.9	80.1
Mean Bilateral endoscopic NPS[a] (SD), range 0–8	5.75 (1.28)	6.10 (1.21)
Mean Nasal congestion (NC) score[a] (SD) range 0–3	2.35 (0.57)	2.43 (0.59)
Mean LMK sinus CT total score[a](SD), range 0–24	19.03 (4.44)	17.96 (3.76)
Mean Smell test (UPSIT) score[a] (SD), range 0–40	14.56 (8.48)	13.61 (8.02)
Mean loss of smell score[a] (AM), (SD) range 0–3	2.71 (0.54)	2.75 (0.52)
Mean SNOT-22 total score[a] (SD), range 0–110	49.40 (20.20)	51.86 (20.90)
Mean Rhinosinusitis severity scale[a] (VAS), (SD) 0–10 cm	7.68 (2.05)	8.00 (2.08)
Mean blood eosinophils (cells/mcL)(SD)	437 (333)	431 (353)
Mean total IgE IU/mL (SD)	211.97 (275.73)	239.84 (341.53)
Atopic (type 2 inflammatory disease) Medical History % Overall	75.4 %	82.4 %
Asthma (%)	58.3	59.6
Mean FEV_1 (L)(SD)	2.69 (0.96)	2.57 (0.83)
Mean FEV_1 percent predicted (%)(SD)	85.30 (20.23)	83.39 (17.72)
Mean ACQ-6 score[a] (SD)	1.62 (1.14)	1.58 (1.09)
NSAID-ERD (%)	30.4	26.8

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

Clinical Response (SINUS-24 and SINUS-52)

The results for primary and secondary endpoints in CRSwNP studies are presented in the Table 24.

Table 24: Results of the primary and secondary endpoints in CRSwNP trials

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

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

The results of SINUS-52 study at week 52 are presented in Table 25.

Table 25: Results of the efficacy at week 52 in SINUS-52 study

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

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

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

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

Figure 5a. SINUS-24

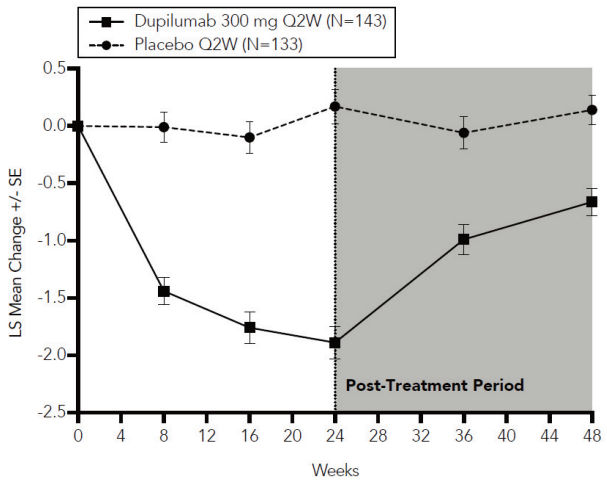
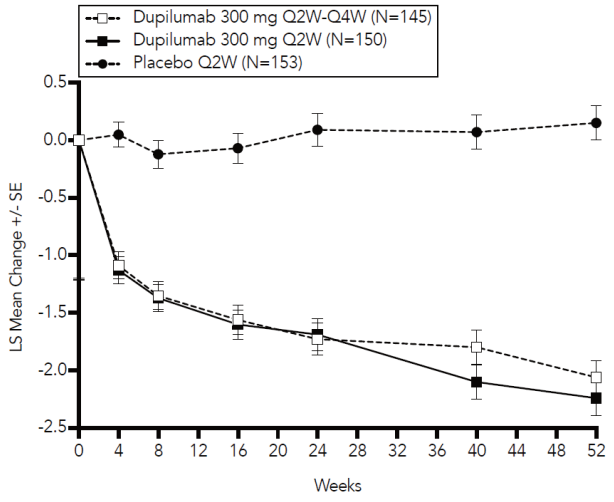


Figure 5b. SINUS-52

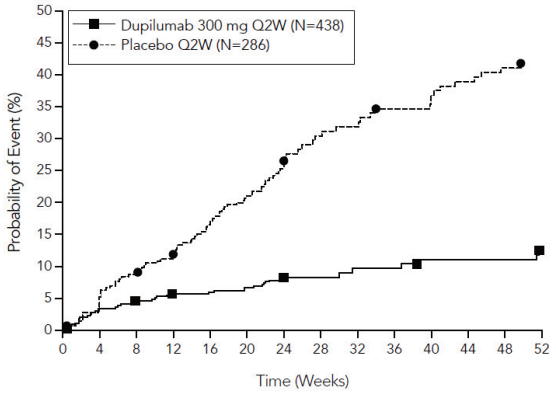


In both studies, significant improvements in NC and daily loss of smell severity were observed as early as the first assessment at week 4. The LS mean difference for NC at week 4 in the dupilumab group versus placebo was -0.41 (95% CI: -0.52, -0.30) in SINUS-24 and -0.37 (95% CI: -0.46, -0.27) in SINUS-52.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

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

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

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



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

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

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

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

Clinical efficacy in prurigo nodularis (PN)

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

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

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

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

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

The efficacy results for PRIME and PRIME2 are presented in Table 26 and Figures 7 and 8.

Table 26: Results of the Primary and Secondary Endpoints in PRIME and PRIME2

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

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

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

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

Fig 7a. PRIME

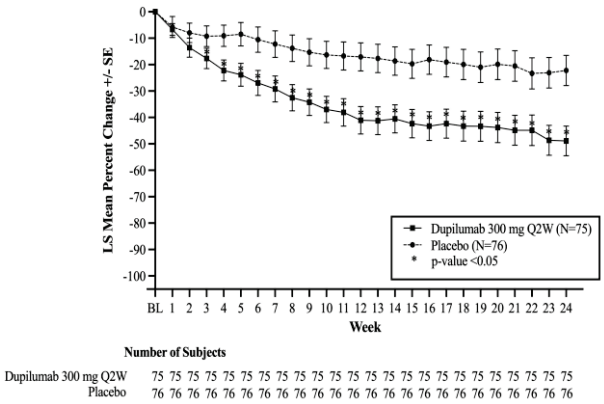
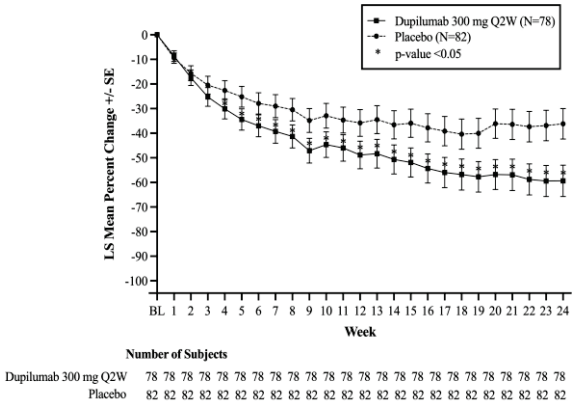


Fig 7b. PRIME2



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

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

Fig 8a. PRIME

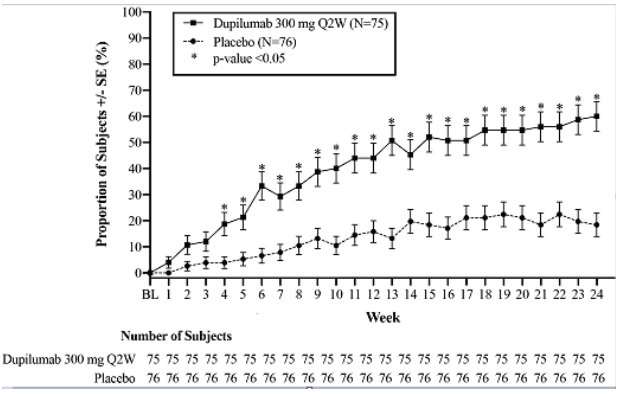
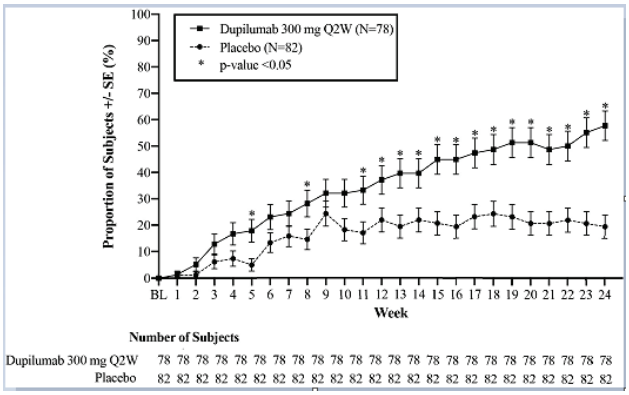


Fig 8b. PRIME2



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

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

Clinical efficacy in eosinophilic esophagitis (EoE)

Adult and Paediatric Patients 12 to 17 Years of Age with EoE

The eosinophilic esophagitis (EoE) development program included a three-part protocol up to 52-weeks (TREET) consisting of two separately randomised, double-blind, parallel-group, multicentre, placebo-controlled, 24-week treatment studies (TREET Part A and TREET Part B) followed by a 28 week active treatment extension study (TREET C) in adult and paediatric patients 12 to 17 years of age, excluding patients <40 kg. In TREET Parts A and B, all enrolled patients had to have failed

conventional medicinal therapy (proton pump inhibitors), 74% were treated with another conventional medicinal therapy (swallowed topical corticosteroids) prior to inclusion. In TREET Part B, 49% of patients were inadequately controlled, intolerant or contraindicated to swallowed topical corticosteroid treatment. In both parts, patients were required to have ≥15 intraepithelial eosinophils per high-power field (eos/hpf) following an at least 8-week course of a high-dose proton pump inhibitor (PPI) either prior to or during the screening period and a Dysphagia Symptom Questionnaire (DSQ) score ≥10 on a scale of 0 to 84. Patients were stratified based on age at the time of the screening visit (12 to 17 years of age vs. 18 years and older) and use of PPI at randomisation. TREET Part A was conducted first. TREET Part B opened after enrolment into TREET Part A was complete. Patients completing the 24 weeks of the double-blind treatment period in Parts A or B were provided an option to enrol in a 28-week active treatment extension study (TREET Part C).

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

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

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

The demographics and baseline characteristics of TREET Parts A and B are provided in Table 27.

Table 27: Demographics and baseline characteristics (TREET Parts A and B)

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

Mean esophageal intraepithelial EOS count of 3 regions, mean (SD)	64.3 (37.6)	60.5 (32.9)
EoEHSS grade Score [0-3[a]], mean (SD)	1.3 (0.4)	1.3 (0.4)
EoEHSS stage Score [0-3[a]], mean (SD)	1.3 (0.4)	1.3 (0.3)
EREFS total Score [0-18[a]], mean (SD)	6.3 (2.8)	7.2 (3.2)

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

The results for TREET Parts A and B are presented in Table 28.

Table 28: Efficacy results of dupilumab at week 24 in patients 12 years of age and older with EoE (TREET Parts A and B)

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

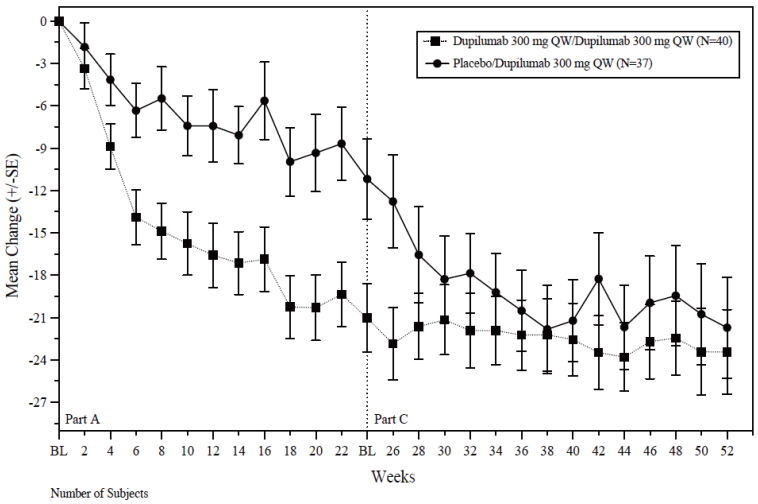
[a]Total biweekly DSQ scores range from 0 to 84; higher scores indicate greater frequency and severity of dysphagia
[b]EoEHSS scores range from 0 to 3; higher scores indicate greater severity and extent of histological abnormalities
[c]EoE-EREFS overall scores range from 0 to 18; higher scores indicate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

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

In Parts A and B, a greater proportion of patients randomised to dupilumab achieved histological remission (peak esophageal intraepithelial eosinophil count ≤6 eos/hpf) compared to placebo. The proportion of patients with histological remission observed after 24 weeks of treatment in Part A and B was maintained for 52 weeks in Part C. Similarly, other histological and endoscopic improvement were maintained through 52 weeks.

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

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

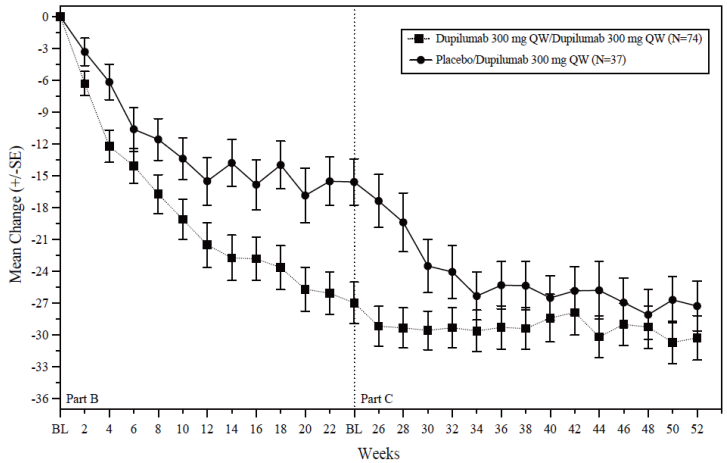


Number of Subjects

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

All observed values were used regardless of rescue treatment use

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



Number of Subjects

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

All observed values were used regardless of rescue treatment use

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

Paediatric Patients 1 to 11 Years of Age with EoE

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

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

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

The primary efficacy endpoint in Part A was the proportion of patients achieving histological remission defined as peak esophageal intraepithelial eosinophil count of ≤6 eos/hpf at Week 16. Secondary endpoints included the proportion of patients achieving peak esophageal intraepithelial eosinophil count of <15 eos/hpf and the change from baseline in the following: peak esophageal intraepithelial eosinophil count (eos/hpf), absolute change in Mean Grade Score from the Histology Scoring System (EoEHSS), absolute change in Mean Stage Score from the EoEHSS, and absolute change in EoE-Endoscopic Reference Score (EoE-EREFS). The impact on signs of EoE was measured using observer reported outcomes; Paediatric EoE Sign/Symptom Questionnaire-Caregiver (PESQ-C) assessed the proportion of days with one or more EoE signs and Paediatric Eosinophilic Esophagitis Symptom Score (PEESS) assessed the frequency and severity of EoE signs.

Efficacy results for Part A are presented in Table 29 and below.

Table 29: Efficacy Results of dupilumab at Week 16 in Subjects 1 to 11 Years of Age with EoE (EoE KIDS Part A)

	Dupilumab [a] N=37	**Placebo N=34**	**Difference vs Placebo (95% CI)**
Primary Endpoint			
Proportion of subjects achieving histological remission (peak esophageal intraepithelial eosinophil count ≤6 eos/hpf), n (%)[b]	25 (67.6)	1 (2.9)	64.5 (48.19, 80.85)

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

[a] DUPIXENT was evaluated at tiered dosing regimens based on body weight: ≥5 to <15 kg (100 mg Q2W), ≥15 to <30 kg (200 mg Q2W), and ≥30 to <60 kg (300 mg Q2W).
[b] For histological remission, the difference in percentages is estimated using the Mantel-Haenszel method, adjusting for baseline weight group (≥5 to <15 kg, ≥15 to <30 kg, and ≥30 to <60 kg).
[c] The difference in absolute change or percent change is estimated using ANCOVA model with baseline measurement as covariate and the treatment, baseline weight group (≥5 to <15 kg, ≥15 to <30 kg, and ≥30 to <60 kg) strata as fixed factors.
[d] EoEHSS scores range from 0 to 3; higher scores indicate greater severity and extent of histological abnormalities.
[e] EoE-EREFS overall scores range from 0 to 18; higher scores indicate worse endoscopic inflammatory and remodelling findings.

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

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

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

Clinical efficacy in chronic obstructive pulmonary disease (COPD)

The chronic obstructive pulmonary disease (COPD) program included two randomized, double-blind, multicenter, parallel-group, placebo-controlled trials (BOREAS and NOTUS) of 52 weeks in treatment duration which enrolled a total of 1874 adult patients with COPD to evaluate dupilumab as add-on maintenance therapy.

Both trials enrolled patients with a diagnosis of COPD with moderate to severe airflow limitation (post-bronchodilator FEV_1/FVC ratio <0.7 and post-bronchodilator FEV_1 of 30% to 70% predicted), chronic productive cough for at least 3 months in the past year, and a minimum blood eosinophil count

of 300 cells/mcL at screening. Patients were uncontrolled with a Medical Research Council (MRC) dyspnoea score ≥ 2 (range 0-4) and an exacerbation history of at least 2 moderate or 1 severe exacerbation in the previous year despite receiving maintenance triple therapy consisting of a long-acting muscarinic antagonist (LAMA), long-acting beta agonist (LABA), and inhaled corticosteroid (ICS). Patients were allowed to receive maintenance therapy consisting of a LAMA and LABA if an ICS was not appropriate. Exacerbations were defined as moderate severity if treatment with systemic corticosteroids and/or antibiotics was required or severe if they resulted in hospitalization or observation for over 24 hours in an emergency department or urgent care facility.

In both trials, patients were randomized to receive dupilumab 300 mg every two weeks (Q2W) or placebo in addition to their background maintenance therapy for 52 weeks.

In both trials, the primary endpoint was the annualized rate of moderate or severe COPD exacerbations during the 52-week treatment period. Secondary endpoints included change from baseline in pre-bronchodilator FEV_1 in the overall population and in the subgroup of patients with baseline FeNO ≥ 20 ppb at Weeks 12 and 52, change from baseline in St. George's Respiratory Questionnaire (SGRQ) total score at Week 52, and annualized rate of moderate or severe COPD exacerbations in the subgroup of patients with baseline FeNO ≥ 20 ppb during the 52-week treatment period.

The demographics and baseline characteristics of BOREAS and NOTUS are provided in Table 30.

Table 30: Demographics and baseline characteristics (BOREAS and NOTUS)

Parameter	BOREAS (N = 939)	NOTUS (N = 935)
Mean age (years) (± SD)	65.1 (8.1)	65.0 (8.3)
Male (%)	66.0	67.6
White (%)[c]	84.1	89.6
Mean smoking history (pack-years) (± SD)	40.48 (23.35)	40.3 (27.2)
Current Smokers (%)	30	29.5
Emphysema (%)	32.6	30.4
Mean Duration of COPD (years) (± SD)	8.8 (6.0)	9.3 (6.4)
Mean number of moderate[a] or severe[b] exacerbations in previous year (± SD)	2.3 (1.0)	2.1 (0.9)
Mean number of severe exacerbations[b] in previous year (± SD)	0.3 (0.7)	0.3 (0.6)
Background COPD medications at randomization: ICS/LAMA/LABA (%)	97.6	98.8
Mean post-bronchodilator FEV_1/FVC ratio (± SD)	0.49 (0.12)	0.50 (0.12)
Mean pre-bronchodilator FEV_1 (L) (± SD)	1.30 (0.46)	1.36 (0.50)
Mean post-bronchodilator FEV_1 (L) (± SD)	1.40 (0.47)	1.45 (0.49)
Mean percent predicted post-bronchodilator FEV_1 (%) (± SD)	50.6 (13.1)	50.1 (12.6)
Mean percent predicted post-bronchodilator FEV_1 <50% (%) (± SD)	467 (49.7)	478 (51.3)
Mean SGRQ Total score (± SD)	48.42 (17.42)	51.5 (17.0)
Mean E-RS:COPD [total score] (± SD)	12.9 (7.1)	13.3 (7.0)
Mean BODE index score (± SD)	4.06 (1.66)	4.0 (1.6)
Mean FeNO ppb (± SD)	24.3 (22.4)	24.6 (26.0)
Mean baseline blood eosinophil count (cells/mcL) (± SD)	401 (298)	407 (336)
Median baseline blood eosinophil count (cells/mcL) (Q1-Q3)	340 (240-460)	330 (220-460)

ICS = inhaled corticosteroid; LAMA = long acting muscarinic antagonist; LABA = long acting beta agonist, FEV_1= forced expiratory volume in 1 second; FVC = forced vital capacity; FeNO = fraction of exhaled nitric oxide; BODE = body-mass index, airflow obstruction, dyspnea, exercise capacity
[a] Exacerbations treated with either systemic corticosteroids and/or antibiotics
[b] Exacerbations requiring hospitalization or observation for over 24 hours in an emergency department or urgent care facility
[c] In BOREAS, 0.5% of participants were Black and 14.3% were Asian. In NOTUS, 1.3% of participants were Black and 1.1% were Asian

Exacerbations

In both trials, dupilumab demonstrated a statistically significant reduction in the annualized rate of moderate or severe COPD exacerbations compared to placebo when added to background maintenance therapy (see Table 31).

Table 31: Annualized Rate of moderate[a] or severe[b] COPD exacerbations in BOREAS and NOTUS

Trial	Treatment (N)	Rate (exacerbations/year)	Rate Ratio vs. Placebo (95% CI)	% Reduction in Exacerbation Rate vs. Placebo
Primary Endpoint: Moderate[a] or Severe[b] COPD exacerbations				
BOREAS	**Dupilumab** 300 mg Q2W (N=468)	0.78	0.705 (0.581, 0.857)[c]	30%
	Placebo (N=471)	1.10		
NOTUS	**Dupilumab** 300 mg Q2W (N=470)	0.86	0.664 (0.535, 0.823)[d]	34%
	Placebo (N=465)	1.30		
Pooled Component of Primary Endpoint[e]: Severe[b] COPD exacerbations				
BOREAS and NOTUS	**Dupilumab** 300 mg Q2W (N=938)	0.08	0.674 (0.438 to 1.037)	33%
	Placebo (N=936)	0.12		

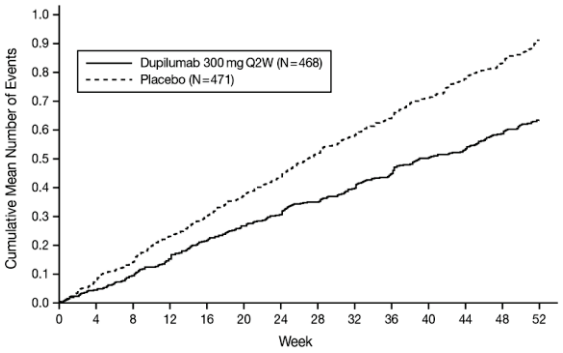
[a] Exacerbations treated with either systemic corticosteroids and/or antibiotics
[b] Exacerbations requiring hospitalization, or observation for >24 hours in an emergency department/urgent care facility or resulting in death
[c] p value = 0.0005
[d] p value = 0.0002
[e] Analysis of the component of the primary endpoint was not adjusted for multiplicity

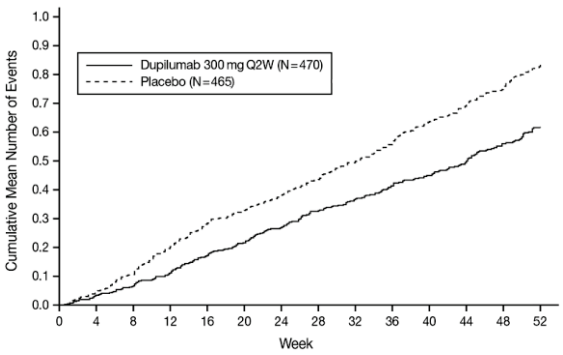
In both trials, the cumulative mean number of moderate or severe exacerbations observed over 52 weeks was lower in patients receiving dupilumab compared to placebo (see Figure 11a and 11b).

Figure 11: Cumulative mean number of moderate or severe COPD exacerbations over 52 weeks in BOREAS and NOTUS

Fig 11a. BOREAS

Fig 11b. NOTUS





The time to first moderate or severe COPD exacerbation was longer for patients receiving dupilumab compared to placebo in BOREAS (HR: 0.803; 95% CI: 0.658, 0.980) and NOTUS (HR: 0.71.; 95% CI: 0.57, 0.889).

In the subgroup analysis of patients with a higher baseline FeNO (≥ 20 ppb) in BOREAS (N=383), treatment with dupilumab statistically significantly reduced the annualized rate of moderate or severe COPD exacerbations compared to placebo (Rate Ratio: 0.625; 95% CI: 0.45, 0.869; p=0.005). In NOTUS, treatment with dupilumab showed a nominally significant reduction in the annualized rate of moderate or severe COPD exacerbations in the subgroup of patients with a higher baseline FeNO (≥20 ppb) (N=355) compared to placebo (Rate Ratio: 0.471; 95% CI: 0.328, 0.675; p<0.0001).

Reductions in the annualized rate of moderate or severe exacerbations were observed across all predefined subgroups including age, gender, race, smoking status, blood eosinophil counts, number of exacerbations in previous year (≤2, 3, and ≥4), high-dose ICS at baseline, and baseline percent predicted post-bronchodilator FEV_1 (<50%, ≥50%). In patients with emphysema, reduction in the rate of moderate or severe exacerbations was consistent with the overall population.

Lung Function

In both trials, dupilumab demonstrated a statistically significant improvement in pre-bronchodilator FEV_1 at Weeks 12 and 52 compared to placebo when added to background maintenance therapy (see Table 30). Greater improvements in lung function (LS mean change from baseline in pre-bronchodilator FEV_1) were observed in patients treated with dupilumab compared to placebo as early as Week 2 (BOREAS) (first assessment) and Week 4 (NOTUS) and were sustained at Week 52 (see Figures 12a and 12b).

In BOREAS, rapid improvements in post-bronchodilator FEV_1, post-bronchodilator FEV_1/FVC ratio, and pre-bronchodilator FVC were observed with dupilumab treatment compared to placebo as early as Week 2 (first assessment) and were maintained through Week 52. In NOTUS, rapid improvements in post-bronchodilator FEV_1 and post-bronchodilator FEV_1/FVC ratio were observed with dupilumab treatment compared to placebo as early as week 8 and week 2, respectively, and were maintained through Week 52.

Table 32: Mean change from baseline for lung function endpoints in BOREAS and NOTUS

	BOREAS			**NOTUS**		
	Dupilumab (N=468)	**Placebo (N=471)**	**Difference (95% CI) for Dupilumab vs. Placebo**	**Dupilumab (N=470)**	**Placebo (N=465)**	**Difference (95% CI) for Dupilumab vs. Placebo**
Change from baseline in pre-bronchodilator FEV_1 at Week 12, LS Mean (SE)	0.160 (0.018)	0.077 (0.018)	0.083 (0.042 to 0.125)[a]	0.139 (0.017)	0.057 (0.017)	0.082 (0.040 to 0.124)[f]

Change from baseline in pre-bronchodilator FEV_1 at Week 52, LS Mean (SE)[k]	0.153 (0.019)	0.070 (0.019)	0.083 (0.038 to 0.128)[b]	0.115 (0.021)	0.054 (0.020)	0.062 (0.011 to 0.113)[g]
Change from baseline in post-bronchodilator FEV_1 at Week 12, LS Mean (SE)	0.156 (0.018)	0.084 (0.018)	0.072 (0.030 to 0.115)[c]	0.136 (0.020)	0.064 (0.020)	0.072 (0.023 to 0.121)[h]
Change from baseline in post-bronchodilator FEV_1/FVC ratio at Week 12, LS Mean (SE)	0.037 (0.004)	0.023 (0.004)	0.014 (0.005 to0.023)[d]	0.030 (0.004)	0.013 (0.004)	0.017 (0.006 to 0.028)[i]
Change from baseline in pre-bronchodilator FVC at Week 12, LS Mean (SE)	0.098 (0.022)	0.029 (0.022)	0.069 (0.016 to 0.121)[e]	0.083 (0.024)	0.018 (0.024)	0.066 (0.005 to 0.126)[j]

LS = least squares, SE = standard error, FEV_1 = forced expiratory volume in 1 second, FVC = forced vital capacity

[a]p-value < 0.0001, [b]p-value = 0.0003 (all statistically significant vs placebo with adjustment for multiplicity)
[c]nominal p-value = 0.0010, [d]nominal p-value = 0.0016 [e]nominal p-value = 0.0103
[f]p-value=0.0001, [g]p-value=0.0182 (all statistically significant vs placebo with adjustment for multiplicity)
[h]nominal p-value=0.0042 ,[i]nominal p-value=0.0020, [j]nominal p-value=0.0327
[k] Efficacy results for mean change from baseline in pre-bronchodilator FEV_1 at Week 52 are presented for 721 out of 935 patients who completed the 52-week treatment period or had discontinued the trial at the time of data analysis.

Figure 12: Mean change from baseline in pre-bronchodilator FEV_1 (L) over time in BOREAS and NOTUS[a]

Fig12a. BOREAS

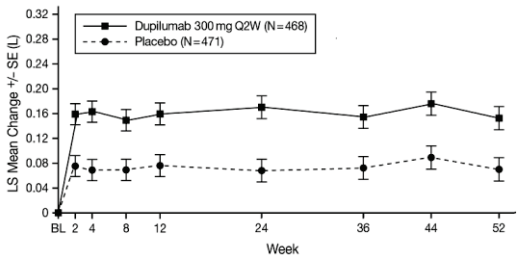
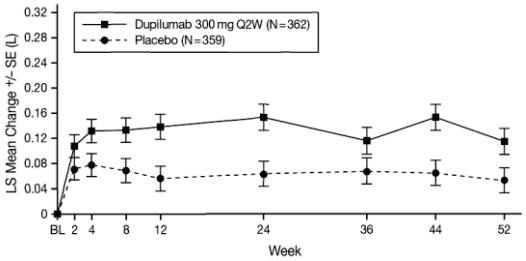


Fig12b. NOTUS



[a] Efficacy results for mean change from baseline in pre-bronchodilator FEV_1 over time are presented for 721 out of 935 patients who completed the 52-week treatment period or had discontinued the trial at the time of data analysis.

In the subgroup analysis of patients with higher baseline FeNO (≥ 20 ppb) in BOREAS (N=383), treatment with dupilumab statistically significantly improved pre-bronchodilator FEV_1 from baseline at Week 12 (LS mean change: 0.232 dupilumab vs 0.108 placebo; LS mean difference: 0.124 [95% CI: 0.045, 0.203]; p=0.002) and Week 52 (LS mean change: 0.247 dupilumab vs 0.120 placebo; LS mean difference: 0.127 [95% CI: 0.042, 0.212]; p=0.003) compared to placebo. In NOTUS, statistically significant improvement from baseline was observed in the subgroup of patients with a higher baseline FeNO (≥20 ppb) at Week 12 (N=355; LS mean change: 0.221 dupilumab vs 0.081 placebo; LS mean difference: 0.141 [95% CI: 0.058, 0.223]; p=0.001). Treatment with dupilumab improved pre-bronchodilator FEV_1 at Week 52 in the subgroup of patients with higher baseline FeNO (≥20 ppb) compared to placebo in NOTUS (N=264; LS mean change: 0.176 dupilumab vs 0.095 placebo; LS mean difference: 0.081[95% CI: -0.019, 0.181]) but did not meet statistical significance.

Improvements in lung function as measured by pre-bronchodilator FEV_1 were observed across all predefined subgroups including age, gender, race, smoking status, blood eosinophil counts, number of exacerbations in previous year (≤2, 3, and ≥4), high-dose ICS at baseline, and baseline percent

predicted post-bronchodilator FEV_1 (<50%, ≥50%). In patients with emphysema, improvement in lung function as measured by pre-bronchodilator FEV_1 was consistent with the overall population.

Health-Related Quality of Life

In BOREAS, a statistically significant improvement in SGRQ total score was observed in patients treated with dupilumab compared to placebo (LS mean change: -9.73 dupilumab vs -6.37 placebo; LS mean difference: -3.36 [95% CI: -5.46, -1.27]; p=0.0017). In NOTUS, dupilumab nominally improved SGRQ total score at Week 52 compared to placebo (LS mean change: -9.82 dupilumab vs -6.44 placebo; LS mean difference: -3.37; 95% CI: -5.81, -0.93]; p=0.007).

Patients with post-bronchodilator FEV_1 <30% or >70%

Patients with post-bronchodilator FEV_1 <30% or >70% at screening were excluded from BOREAS and NOTUS. However, limited data are available in patients with post-bronchodilator FEV_1 <30% or >70% at baseline.

Paediatric population

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

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

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

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

Eosinophilic Esophagitis
The safety and efficacy of dupilumab for the treatment of EoE have been established in paediatric patients 1 to 17 years of age. Use of dupilumab in this population is supported by adequate and well-controlled studies and additional pharmacokinetic data. A total of 72 paediatric patients 12 to 17 years of age received dupilumab 300 mg QW or placebo for 24 weeks (TREET Parts A and B). Of these, there were 37 dupilumab treated patients in Parts A and B; 34 continued treatment with 300 mg QW for an additional 28 weeks (TREET Part C). A total of 71 paediatric patients 1 to 11 years of age received dupilumab 100 mg Q2W, 200 mg Q2W, 300 mg Q2W, or placebo for 16 weeks (EoE KIDS Part A). Of these, there were 37 dupilumab treated patients in Part A all of whom continued treatment with these dupilumab regimens for an additional 36 weeks (EoE KIDS Part B). The use of dupilumab 300 mg QW in patients 1 to 11 years of age with EoE with a body weight ≥ 40 kg is also supported by a population pharmacokinetic analysis [see section 5.1]. The safety and efficacy of dupilumab in adults and paediatric patients were similar [see section 4.8 and section 5.1].

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

5.2 Pharmacokinetic properties

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

Absorption

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

Steady-state concentrations were achieved by week 16 following the administration of 600 mg starting dose and 300 mg dose every other week or 300 mg dose every other week without a loading dose. Across clinical trials, the mean ±SD steady-state trough concentrations ranged from 55.3±34.3 mcg/mL to 81.5±43.9 mcg/mL for 300 mg administered Q2W, from 172±76.6 mcg/ml to 195±71.7 mcg/ml for 300 mg administered weekly, and from 29.2±18.7 to 36.5±22.2 mcg/mL for 200 mg administered Q2W.

Distribution

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

Biotransformation

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

Elimination

Dupilumab elimination is mediated by parallel linear and nonlinear pathways. At higher concentrations, dupilumab elimination is primarily through a non-saturable proteolytic pathway, while at lower concentrations, the non-linear saturable IL-4R α target-mediated elimination predominates. After the last steady state dose of 300 mg QW, 300 mg Q2W, 200 mg Q2W, 300 mg Q4W, or 200 mg Q4W dupilumab, the median times to decrease below the lower limit of detection, estimated by population PK analysis, ranged from 9-13 weeks in adults and adolescents and are approximately 1.5 times and 2.5 times longer in paediatric patients 6 to 11 years of age and paediatric patients less than 6 years of age, respectively .

Linearity/non-linearity

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

Special populations

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

Elderly
Of the 1539 patients with atopic dermatitis, including patients with atopic hand and foot dermatitis exposed to dupilumab in a phase 2 dose-ranging study or phase 3 placebo-controlled studies, a total of 71 were 65 years or older. Although no differences in safety or efficacy were observed between older and younger adult atopic dermatitis patients, the number of patients aged 65 and over is not sufficient to determine whether they respond differently from younger patients.

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

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

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

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

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

Of the 1872 patients with COPD exposed to dupilumab, a total of 1071 were 65 years of age and older including 244 patients 75 years of age and older. Efficacy and safety in this age group were similar to the overall study population.

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

Hepatic impairment

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

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

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

Paediatric population

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

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

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

For children 6 to 11 years of age with atopic dermatitis receiving every four week dosing (Q4W) with 300 mg (≥ 15 kg) in AD-1652, the mean ± SD steady-state trough concentration was 76.3±37.2 mcg/mL. At week 16 in AD-1434 in children 6 to 11 years of age who initiated every four week dosing (Q4W) with 300 mg (≥ 15 kg), and whose dose was increased to every other week dosing (Q2W) with 200 mg (≥ 15 to < 60 kg) or 300 mg (≥ 60 kg), the mean±SD steady-state trough concentration was 108±53.8 mcg/mL. For children 6 to 11 years of age receiving 300 mg Q4W, initial doses of 300 mg on Days 1 and 15 produce similar steady-state exposure as an initial dose of 600 mg on Day 1, based on PK simulations.

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

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

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

In the VOYAGE study, dupilumab pharmacokinetics was investigated in 270 patients with moderate-to-severe asthma following subcutaneous administration of either 100 mg Q2W (for 91 children weighing < 30 kg) or 200 mg Q2W (for 179 children weighing ≥ 30 kg). The volume of distribution for dupilumab of approximately 3.7 L was estimated by population PK analysis. Steady-state concentrations were achieved by week 12. The mean ± SD steady-state trough concentration was

58.4±28.0 mcg/mL and 85.1±44.9 mcg/mL, respectively. Simulation of a 300 mg Q4W subcutaneous dose in children aged 6 to 11 years with body weight of ≥ 15 kg to < 30 kg and ≥ 30 kg to < 60 kg resulted in predicted steady-state trough concentrations similar to the observed trough concentrations of 200 mg Q2W (≥ 30 kg) and 100 mg Q2W (< 30 kg), respectively. In addition, simulation of a 300 mg Q4W subcutaneous dose in children aged 6 to 11 years with body weight of ≥ 15 kg to < 60 kg resulted in predicted steady-state trough concentrations similar to those demonstrated to be efficacious in adults and adolescents. After the last steady state dose, the median time for dupilumab concentrations to decrease below the lower limit of detection, estimated by population PK analysis, was 14 to 18 weeks for 100 mg Q2W, 200 mg Q2W or 300 mg Q4W.

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

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

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

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

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

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

5.3 Preclinical safety data

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

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

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

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

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

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

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

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

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

6.3 Shelf life

3 years.

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

6.4 Special precautions for storage

Store in a refrigerator (2 °C 8 °C).

Do not freeze.

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

6.5 Nature and contents of container

Dupixent 300 mg solution for injection in pre-filled syringe

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

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

Dupixent 300 mg solution for injection in pre-filled pen

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

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

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

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Comprehensive instructions for the administration of Dupixent in a pre-filled syringe or in a pre-filled pen are given at the end of the package leaflet.

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

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

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

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

7. MARKETING AUTHORISATION HOLDER

Sanofi Winthrop Industrie
82 avenue Raspail
94250 Gentilly
France

8. MARKETING AUTHORISATION NUMBERS

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

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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

10. DATE OF REVISION OF THE TEXT

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

1. NAME OF THE MEDICINAL PRODUCT

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

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Dupilumab 200 mg solution for injection in pre-filled syringe

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

Dupilumab 200 mg solution for injection in pre-filled pen

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

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

Excipients with known effect

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

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection (injection)

Clear to slightly opalescent, colourless to pale yellow sterile solution, which is free from visible particulates, with a pH of approximately 5.9.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Atopic dermatitis

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

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

Asthma

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

Children 6 to 11 years of age

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

Eosinophilic esophagitis (EoE)

Dupixent is indicated for the treatment of eosinophilic esophagitis in adults, adolescents and children aged 1 year and older, weighing at least 15 kg, who are inadequately controlled by, are intolerant to, or who are not candidates for conventional medicinal therapy (see section 5.1).**Error! No document variable supplied.**

4.2 Posology and method of administration

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

Posology

Atopic dermatitis

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

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

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

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

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

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

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

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

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

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

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

Dupilumab can be used with or without topical corticosteroids. Topical calcineurin inhibitors may be used, but should be reserved for problem areas only, such as the face, neck, intertriginous and genital areas.

Consideration should be given to discontinuing treatment in patients who have shown no response after 16 weeks of treatment for atopic dermatitis. Some patients with initial partial response may subsequently improve with continued treatment beyond 16 weeks. If dupilumab treatment interruption becomes necessary, patients can still be successfully re-treated.

Asthma

Adults and adolescents
The recommended dose of dupilumab for adults and adolescents (12 years of age and older) is:
- An initial dose of 400 mg (two 200 mg injections), followed by 200 mg given every other week administered as subcutaneous injection.
- For patients with severe asthma and who are on oral corticosteroids or for patients with severe asthma and co-morbid moderate-to-severe atopic dermatitis or adults with co-morbid severe chronic rhinosinusitis with nasal polyposis, an initial dose of 600 mg (two 300 mg injections), followed by 300 mg every other week administered as subcutaneous injection.

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

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

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

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

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

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

Eosinophilic esophagitis (EoE)

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

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

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

Dupilumab is intended for long-term treatment.

Missed dose

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

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

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

Special populations

Elderly
No dose adjustment is recommended for elderly (≥ 65 years) patients (see section 5.2).

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

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

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

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

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

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

Method of administration

Subcutaneous use

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

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

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

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

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

A patient may self-inject dupilumab or the patient's caregiver may administer dupilumab if their healthcare professional determines that this is appropriate. Proper training should be provided to patients and/or caregivers on the preparation and administration of dupilumab prior to use according to the Instructions for Use (IFU) section at the end of the package leaflet. In children 12 years of age and older, it is recommended that dupilumab is administered by or under supervision of an adult. In children 6 months to less than 12 years of age, dupilumab should be given by a caregiver.

4.3 Contraindications

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

4.4 Special warnings and precautions for use

Traceability

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

Acute exacerbations of Asthma or COPD

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

Corticosteroids

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

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

Hypersensitivity

If a systemic hypersensitivity reaction (immediate or delayed) occurs, administration of dupilumab should be discontinued immediately and appropriate therapy initiated. Cases of anaphylactic reaction, angioedema, and serum sickness/serum sickness-like reaction have been reported. Anaphylactic reactions and angioedema have occurred from minutes to up to seven days after the dupilumab injection (see section 4.8).

Eosinophilic conditions

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

Helminth infection

Patients with known helminth infections were excluded from participation in clinical studies. Dupilumab may influence the immune response against helminth infections by inhibiting IL-4/IL-13 signalling. Patients with pre-existing helminth infections should be treated before initiating dupilumab. If patients become infected while receiving treatment with dupilumab and do not respond to anti-helminth treatment, treatment with dupilumab should be discontinued until infection resolves. Cases of enterobiasis were reported in children 6 to 11 years old who participated in the paediatric asthma development program (see section 4.8).

Conjunctivitis and keratitis related events

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

Patients should be advised to report new onset or worsening eye symptoms to their healthcare provider. Patients treated with dupilumab who develop conjunctivitis that does not resolve following standard treatment or signs and symptoms suggestive of keratitis should undergo ophthalmological examination, as appropriate (see section 4.8).

Patients with comorbid asthma

Patients on dupilumab who also have comorbid asthma should not adjust or stop their asthma treatments without consultation with their physicians. Patients with comorbid asthma should be monitored carefully following discontinuation of dupilumab.

Vaccinations

Concurrent use of live and live attenuated vaccines with dupilumab should be avoided as clinical safety and efficacy have not been established. It is recommended that patients should be brought up to date with live and live attenuated immunisations in agreement with current immunisation guidelines prior to treatment with dupilumab. Clinical data are not available to support more specific guidance for live or live attenuated vaccines administration in patients treated with dupilumab. Immune responses to TdaP vaccine and meningococcal polysaccharide vaccine were assessed (see section 4.5).

Sodium content

This medicinal product contains less than 1 mmol sodium (23 mg) per 200 mg dose, that is to say essentially ‘sodium-free’.

Polysorbate 80 (E433)

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

4.5 Interaction with other medicinal products and other forms of interaction

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

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

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

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

4.6 Fertility, pregnancy and lactation

Pregnancy

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

Breast-feeding

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

Fertility

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

4.7 Effects on ability to drive and use machines

Dupilumab has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

Summary of the safety profile

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

Tabulated list of adverse reactions

The dupilumab safety data presented in Table 6 were predominantly derived from 12 randomised, placebo-controlled trials, including atopic dermatitis, asthma, and CRSwNP patients. These studies involved 4,206 patients receiving dupilumab and 2,326 patients receiving placebo during the controlled period are representative of the overall safety profile for dupilumab.

Listed in Table 6 are adverse reactions observed in clinical trials and/or postmarketing setting presented by system organ class and frequency, using the following categories: very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1 000 to < 1/100); rare (≥ 1/10 000 to < 1/1 000); very rare (< 1/10 000); not known (cannot be estimated from the available data). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Table 6: List of adverse reactions

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

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

Description of selected adverse reactions

Hypersensitivity
Cases of anaphylactic reaction, angioedema, and serum sickness/serum sickness-like reaction have been reported following administration of dupilumab (see section 4.4).

Conjunctivitis and keratitis related events
Conjunctivitis and keratitis occurred more frequently in atopic dermatitis patients who received dupilumab compared to placebo in atopic dermatitis studies. Most patients with conjunctivitis or keratitis recovered or were recovering during the treatment period. In the long-term OLE atopic dermatitis study (AD-1225) at 5 years, the respective rates of conjunctivitis and keratitis remained similar to those in the dupilumab arm in the placebo controlled atopic dermatitis studies. Among asthma and COPD patients, the frequency of conjunctivitis and keratitis was low and similar between dupilumab and placebo. Among CRSwNP and Prurigo Nodularis (PN) patients the frequency of

conjunctivitis was higher in dupilumab than placebo, though lower than that observed in atopic dermatitis patients. There were no cases of keratitis reported in the CRSwNP or PN development program. Among patients with EoE, the frequency of conjunctivitis was low and similar between dupilumab and placebo groups. There were no cases of keratitis in the EoE development program (see section 4.4).

Eczema herpeticum
Eczema herpeticum was reported in < 1 % of the dupilumab groups and in < 1 % of the placebo group in the 16-week atopic dermatitis monotherapy adult studies. In the 52-week atopic dermatitis dupilumab + TCS adult study, eczema herpeticum was reported in 0.2 % of the dupilumab + TCS group and 1.9 % of the placebo + TCS group. These rates remained stable at 5 years in the long-term OLE study (AD-1225).

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

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

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

Infections
In the 16-week atopic dermatitis monotherapy clinical adult studies, serious infections were reported in 1.0 % of patients treated with placebo and 0.5 % of patients treated with dupilumab. In the 52-week atopic dermatitis CHRONOS adult study, serious infections were reported in 0.6 % of patients treated with placebo and 0.2 % of patients treated with dupilumab. The rates of serious infections remained stable at 5 years in the long-term OLE study (AD-1225).

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

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

The overall incidence of infections was numerically higher with dupilumab (32.0%) compared to placebo (24.8%) in the 24-week safety pool for the EoE TREET (Parts A and B) studies. The overall incidence of infections was numerically higher in placebo (41.2%) compared to dupilumab (35.8%) in the EoE KIDS (Part A) study. In the 24-week safety pool for the EoE TREET (Parts A and B) studies

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

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

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

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

Approximately 5 % of patients with atopic dermatitis, asthma, or CRSwNP who received dupilumab 300 mg Q2W for 52 weeks developed ADA to dupilumab; approximately 2 % exhibited persistent ADA responses and approximately 2 % had neutralizing antibodies. Similar results were observed in adult patients with PN who received dupilumab 300 mg Q2W for 24 weeks, paediatric patients (6 months to 11 years of age) with atopic dermatitis who received either dupilumab 200 mg Q2W, 200 mg Q4W or 300 mg Q4W for 16 weeks and patients (6 to 11 years of age) with asthma who received dupilumab 100 mg Q2W or 200 mg Q2W for 52 weeks. Similar ADA responses were observed in adult patients with atopic dermatitis treated with dupilumab for up to 5 years in the long-term OLE study (AD-1225).

Approximately 16 % of adolescent patients with atopic dermatitis who received dupilumab 300 mg or 200 mg Q2W for 16 weeks developed antibodies to dupilumab; approximately 3 % exhibited persistent ADA responses, and approximately 5 % had neutralizing antibodies.

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

Approximately 1% of patients 1 year of age and older with EoE who received dupilumab 300 mg QW (≥40 kg), 300 mg Q2W (≥30 to <60 kg), 200 mg Q2W (≥15 to <30 kg), or 100 mg Q2W (≥5 to <15 kg) for 52 weeks developed antibodies to dupilumab; the ADA responses were neither persistent nor neutralizing.

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

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

Less than 1 % of patients who received dupilumab at approved dosing regimens exhibited high titer ADA responses associated with reduced exposure and efficacy. In addition, there was one patient with serum sickness and one with serum sickness-like reaction (< 0.1 %) associated with high ADA titers (see section 4.4).

Paediatric population

Atopic dermatitis

Adolescents (12 t o17 years of age)
The safety of dupilumab was assessed in a study of 250 patients 12 to 17 years of age with moderate-to-severe atopic dermatitis (AD-1526). The safety profile of dupilumab in these patients followed through week 16 was similar to the safety profile from studies in adults with atopic dermatitis.

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

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

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

Asthma

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

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

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

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

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

EoE

Adolescents (12 to 17 years of age)

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

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

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

Long-term safety

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

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

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

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

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

Eosinophilic esophagitis

The safety profile of dupilumab through week 52 in adult and adolescent patients 12 years of age and older (TREET Part C) and in children 1 to 11 years of age (EoE KIDS Part B) was generally consistent with the safety profile observed at week 24 in TREET Parts A and B and at Week 16 in EoE KIDS Part A.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

Mechanism of action

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

Pharmacodynamic effects

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

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

Clinical efficacy and safety in atopic dermatitis

Adolescents with atopic dermatitis (12 to 17 years of age)

The efficacy and safety of dupilumab monotherapy in adolescent patients was evaluated in a multicentre, randomised, double-blind, placebo-controlled study (AD-1526) in 251 adolescent patients 12 to 17 years of age with moderate-to-severe atopic dermatitis (AD) defined by Investigator's Global Assessment (IGA) score ≥3 in the overall assessment of AD lesions on a severity scale of 0 to 4, an Eczema Area and Severity Index (EASI) score ≥ 16 on a scale of 0 to

72, and a minimum body surface area (BSA) involvement of ≥10 %. Eligible patients enrolled into this study had previous inadequate response to topical medication.

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

In this study, the mean age was 14.5 years, the median weight was 59.4 kg, 41.0 % were female, 62.5 % were White, 15.1 % were Asian, and 12.0 % were Black. At baseline 46.2 % of patients had a baseline IGA score of 3 (moderate AD), 53.8 % of patients had a baseline IGA of 4 (severe AD), the mean BSA involvement was 56.5 %, and 42.4 % of patients had received prior systemic immunosuppressants. Also at baseline the mean Eczema Area and Severity Index (EASI) score was 35.5, the baseline weekly averaged pruritus Numerical Rating Scale (NRS) was 7.6, the baseline mean Patient Oriented Eczema Measure (POEM) score was 21.0, and the baseline mean Children Dermatology Life Quality Index (CDLQI) was 13.6. Overall, 92.0 % of patients had at least one co-morbid allergic condition; 65.6 % had allergic rhinitis, 53.6 % had asthma, and 60.8 % had food allergies.

The co-primary endpoint was the proportion of patients with IGA 0 or 1 ("clear" or "almost clear") least a 2-point improvement and the proportion of patients with EASI-75 (improvement of at least 75 % in EASI), from baseline to week 16.

Clinical Response

The efficacy results at week 16 for adolescent atopic dermatitis study are presented in Table 7.

Table 7: Efficacy results of dupilumab in the adolescent atopic dermatitis study at week 16 (FAS)

	AD-1526(FAS)[a]	
	Placebo	**Dupilumab 200 mg (< 60 kg) and 300 mg (≥ 60 kg) Q2W**
Patients randomised	**85[a]**	**82[a]**
IGA 0 or 1[b], % responders[c]	2.4 %	24.4 %[d]
EASI-50, % responders[c]	12.9 %	61.0 %[d]
EASI-75, % responders[c]	8.2 %	41.5 %[d]
EASI-90, % responders[c]	2.4 %	23.2 %[d]
EASI, LS mean % change from baseline (+/-SE)	-23.6 % (5.49)	-65.9 %[d] (3.99)
Pruritus NRS, LS mean % change from baseline (+/-SE)	-19.0 % (4.09)	-47.9 %[d] (3.43)
Pruritus NRS (≥ 4-point improvement), % responders[c]	4.8 %	36.6 %[d]
CDLQI, LS mean change from baseline (+/-SE)	-5.1 (0.62)	-8.5[d] (0.50)
CDLQI, (≥ 6-point improvement), % responders	19.7 %	60.6 %[e]
POEM, LS mean change from baseline (+/- SE)	-3.8 (0.96)	-10.1[d] (0.76)
POEM, (≥ 6-point improvement), % responders	9.5 %	63.4 %[e]

[a]full Analysis Set (FAS) includes all patients randomised.
[b]responder was defined as a subject with IGA 0 or 1 ("clear" or "almost clear") with a reduction of ≥ 2 points on a 0-4 IGA scale.

[c]patients who received rescue treatment or with missing data were considered as non-responders (58.8 % and 20.7 % in the placebo and dupilumab arms, respectively).
[d]p –value < 0.0001(statistically significant vs placebo with adjustment for multiplicity)
[e]nominal p-value < 0.0001

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

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

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

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

Paediatrics (6 to 11 years of age)

The efficacy and safety of dupilumab in paediatric patients concomitantly with TCS was evaluated in a multicentre, randomised, double-blind, placebo-controlled study (AD-1652) in 367 subjects 6 to 11 years of age, with severe AD defined by an IGA score of 4 (scale of 0 to 4), an EASI score ≥ 21 (scale of 0 to 72), and a minimum BSA involvement of ≥ 15 %. Eligible patients enrolled into this trial had previous inadequate response to topical medication. Enrolment was stratified by baseline weight (< 30 kg; ≥ 30 kg).

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

In this study, the mean age was 8.5 years, the median weight was 29.8 kg, 50.1 % of patients were female, 69.2 % were White, 16.9 % were Black, and 7.6 % were Asian. At baseline, the mean BSA involvement was 57.6 %, and 16.9 % had received prior systemic non-steroidal immunosuppressants. Also, at baseline the mean EASI score was 37.9, and the weekly average of daily worst itch score was 7.8 on a scale of 0-10, the baseline mean SCORAD score was 73.6, the baseline POEM score was 20.9, and the baseline mean CDLQI was 15.1. Overall, 91.7 % of subjects had at least one co-morbid allergic condition; 64.4 % had food allergies, 62.7 % had other allergies, 60.2 % had allergic rhinitis, and 46.7 % had asthma.

The co-primary endpoint was the proportion of patients with IGA 0 or 1 (“clear” or “almost clear”) at least a 2-point improvement and the proportion of patients with EASI-75 (improvement of at least 75 % in EASI), from baseline to week 16.

Clinical Response

Table 8 presents the results by baseline weight strata for the approved dose regimens.

Table 8: Efficacy results of dupilumab with concomitant TCS in AD-1652 at week 16 (FAS)[a]

	Dupilumab 300 mg Q4W[d] + TCS	Placebo +TCS	Dupilumab 200 mg Q2W[e] + TCS	Placebo + TCS
	(N=122)	(N=123)	(N=59)	(N=62)
	≥ 15 kg	≥ 15 kg	≥ 30 kg	≥ 30 kg
IGA 0 or 1[b], % responders[c]	32.8 %[f]	11.4 %	39.0 %[h]	9.7 %
EASI-50, % responders[c]	91.0 %[f]	43.1 %	86.4 %[g]	43.5 %
EASI-75, % responders[c]	69.7 %[f]	26.8 %	74.6 %[g]	25.8 %
EASI-90, % responders[c]	41.8 %[f]	7.3 %	35.6 %[h]	8.1 %
EASI, LS mean % change from baseline (+/-SE)	-82.1 %[f] (2.37)	-48.6 % (2.46)	-80.4 %[g] (3.61)	-48.3 % (3.63)
Pruritus NRS, LS mean % change from baseline (+/- SE)	-54.6 %[f] (2.89)	-25.9 % (2.90)	-58.2 %[g] (4.01)	-25.0 % (3.95)
Pruritus NRS (≥ 4-point improvement), % responders[c]	50.8 %[f]	12.3 %	61.4 %[g]	12.9 %
CDLQI, LS mean change from baseline (+/-SE)	-10.6[f] (0.47)	-6.4 (0.51)	-9.8[g] (0.63)	-5.6 (0.66)
CDLQI, (≥ 6-point improvement), % responders	77.3 %[g]	38.8 %	80.8 %[g]	35.8 %
POEM, LS mean change from baseline (+/- SE)	-13.6[f] (0.65)	-5.3 (0.69)	-13.6[g] (0.90)	-4.7 (0.91)
POEM, (≥ 6-point improvement), % responders	81.7 %[g]	32.0 %	79.3 %[g]	31.1 %

[a]full Analysis Set (FAS) includes all patients randomised.
[b]responder was defined as a patient with an IGA 0 or 1 ("clear" or "almost clear").
[c]patients who received rescue treatment or with missing data were considered as non-responders.
[d]at Day 1, patients received 600 mg of dupilumab (see section 5.2).
[e]at Day 1, patients received 400 mg (baseline weight ≥ 30 kg) of dupilumab.
[f]p-value < 0.0001 (statistically significant vs placebo with adjustment for multiplicity)
[g]nominal p-values < 0.0001
[h]nominal p-value = 0.0002

A greater proportion of patients randomised to dupilumab + TCS achieved an improvement in the peak pruritus NRS compared to placebo + TCS (defined as ≥4-point improvement at week 4).

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

The long-term efficacy and safety of dupilumab + TCS in paediatric patients with moderate to severe atopic dermatitis who had participated in the previous clinical trials of dupilumab + TCS was assessed in an open-label extension study (AD-1434). Efficacy data from this trial suggests that clinical benefit provided at week 16 was sustained through week 52. Some patients receiving dupilumab 300 mg Q4W + TCS showed further clinical benefit when escalated to dupilumab 200 mg Q2W + TCS. The safety profile of dupilumab in patients followed through week 52 was similar to the safety profile observed at week 16 in the AD-1526 and AD-1652 studies.

Paediatrics (6 Months to 5 years of age)

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

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

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

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

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

The co-primary endpoint was the proportion of patients with IGA 0 or 1 ("clear" or "almost clear") at least a 2-point improvement and the proportion of patients with EASI-75 (improvement of at least 75 % in EASI), from baseline to week 16. The primary endpoint was the proportion of patients with an IGA 0 (clear) or 1 (almost clear) at week 16.

Clinical Response

The efficacy results at week 16 for AD-1539 are presented in Table 9.

Table 9: Efficacy results of dupilumab with concomitant TCS in AD-1539 at Week 16 (FAS)[a]

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

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

[a]Full Analysis Set (FAS) includes all patients randomised.
[b]Responder was defined as a patient with an IGA 0 or 1 ("clear" or "almost clear").
[c]Patients who received rescue treatment (62% and 19% in the placebo and dupilumab arms, respectively) or with missing data were considered as non-responders.
[d]At Day 1, patients received 200 mg (5 to <15kg) or 300 mg (15 to <30 kg) of dupilumab.
[e]p–values < 0.0001,[f]nominal p-value < 0.05, [g]nominal p-value < 0.0001, [h]nominal p-value < 0.005, [i]nominal p-value < 0.001
*Caregiver reported outcome

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

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

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

Atopic Hand and Foot Dermatitis (adults and adolescents)

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

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

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

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

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

Adults with atopic dermatitis

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

Clinical efficacy and safety in asthma

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

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

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

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

The demographics and baseline characteristics of these 3 studies are provided in Table 10 below.

Table 10: Demographics and baseline characteristics of asthma trials

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

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

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

Exacerbations

In the overall population in DRI12544 and QUEST subjects receiving either dupilumab 200 mg or 300 mg every other week had significant reductions in the rate of severe asthma exacerbations compared to placebo. There were greater reductions in exacerbations in subjects with higher baseline levels of type 2 inflammatory biomarkers such as blood eosinophils or FeNO (Table 11 and Table 12).

Table 11: Rate of severe exacerbations in DRI12544 and QUEST (baseline blood eosinophil levels ≥ 150 and ≥ 300 cells/mcL)

Treatment	Baseline blood EOS							
	≥150 cells/mcL				≥300 cells/mcL			
	Exacerbations per Year			% reduction	Exacerbations per Year			% reduction
	N	Rate (95% CI)	Rate ratio (95%CI)		N	Rate (95% CI)	Rate ratio (95%CI)	

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

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

Table 12: **Rate of severe exacerbations in QUEST defined by baseline FeNO subgroups**

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

[a]nominal p-value < 0.0001

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

Lung function

Clinically significant increases in pre-bronchodilator FEV_1 were observed at week 12 for DRI12544 and QUEST. There were greater improvements in FEV_1 in the subjects with higher baseline levels of type 2 inflammatory biomarkers such as blood eosinophils or FeNO (Table 13 and Table 14).

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

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

QUEST: blood eosinophils ≥ 150 cells/mcL

QUEST: blood eosinophils ≥ 300 cells/mcL

QUEST: FeNO ≥ 25 ppb

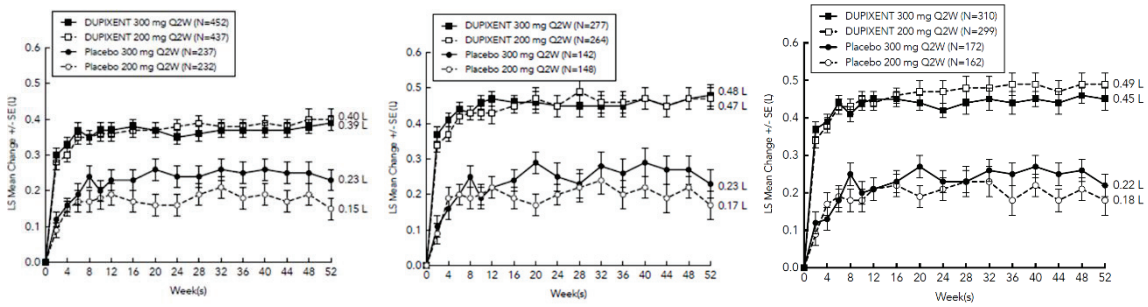


Table 13: Mean change from baseline in pre-bronchodilator FEV_1 at week 12 in DRI12544 and QUEST (baseline blood eosinophil Levels ≥ 150 and ≥ 300 cells/mcL)

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

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

Table 14: Mean change from baseline in pre-bronchodilator FEV_1 at week 12 and week 52 in QUEST by baseline FeNO subgroups

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

[a]nominal p-value < 0.0001

Quality of life/patient-reported outcomes in asthma

Pre-specified secondary endpoint of ACQ-5 and AQLQ(S) responder rates were analysed at 24 weeks (DRI12544 and VENTURE) and at 52 weeks (QUEST, Table 15). The responder rate was defined as an improvement in score of 0.5 or more (scale range 0-6 for ACQ-5 and 1-7 for AQLQ(S)). Improvements in ACQ-5 and AQLQ(S) were observed as early as week 2 and maintained for 24 weeks in DRI12544 study and 52 weeks in QUEST study. Similar results were observed in VENTURE.

Table 15: ACQ-5 and AQLQ(S) responder rates at week 52 in QUEST

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

Oral corticosteroid reduction study (VENTURE)

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

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

The results for VENTURE by baseline biomarkers are presented in the Table 16.

Table 16: Effect of dupilumab on OCS dose reduction, VENTURE (baseline blood eosinophil levels ≥ 150 and ≥ 300 cells/mcL and FeNO ≥ 25 ppb)

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

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

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

Long-term extension study (TRAVERSE)

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

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

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

The primary endpoint was the annualised rate of severe exacerbation events during the 52-week placebo-controlled period and the key secondary endpoint was the change from baseline in pre-bronchodilator FEV_1 percent predicted at week 12. Additional secondary endpoints included mean change from baseline and responder rates in the ACQ-7-IA and PAQLQ(S)-IA scores.
The demographics and baseline characteristics for VOYAGE are provided in Table 17 below.

Table 17. Demographics and baseline characteristics for VOYAGE

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

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

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

Dupilumab significantly reduced the annualised rate of severe asthma exacerbation events during the 52-week treatment period compared to placebo in the population with the type 2 inflammation and in population defined by baseline blood eosinophils ≥ 300 cells/mcL or by baseline FeNO ≥ 20 ppb. Clinically significant improvements in percent predicted pre-bronchodilator FEV_1 were observed at week 12. Improvements were also observed for ACQ-7-IA and PAQLQ(S)-IA at week 24 and were sustained at week 52. Greater responder rates were observed for ACQ-7-IA and PAQLQ(S)-IA compared to placebo at week 24. The efficacy results for VOYAGE are presented in Table 18.

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

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

In both primary efficacy populations, there was a rapid improvement in FEF25-75% and FEV_1/FVC (onset of a difference was observed as early as week 2) and sustained over the 52-week treatment period, see Table 18.

Table 18: Rate of severe exacerbations, mean change from baseline in FEV_1, ACQ-7-IA and PAQLQ(S)-IA responder rates in VOYAGE

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

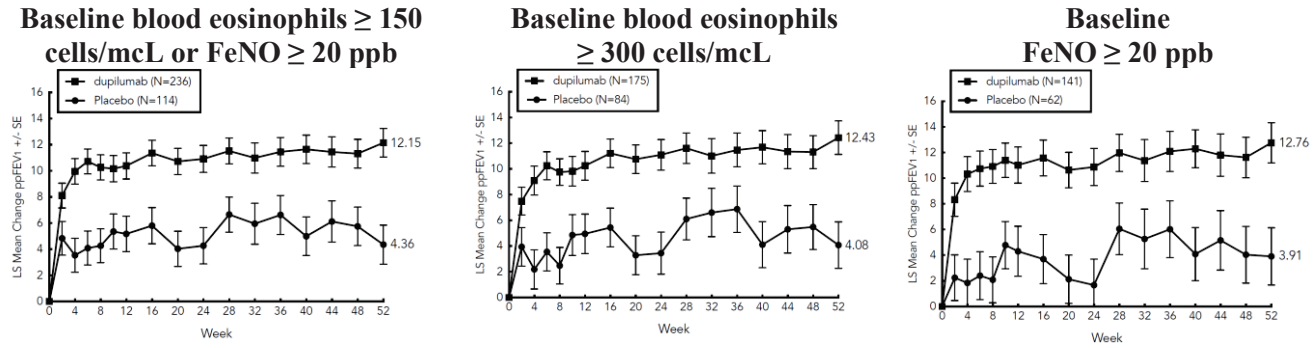
(≥30 kg)									
Placebo	114	69.3		84	64.3		62	66.1	
PAQLQ(S)-IA at week 24[a]									
	N	**Responder rate %**	**OR vs. placebo (95% CI)**	**N**	**Responder rate %**	**OR vs. placebo (95% CI)**	**N**	**Responder rate %**	**OR vs. placebo (95% CI)**
Dupilumab 100 mg Q2W (<30 kg)/ 200 mg Q2W (≥30 kg)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

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

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

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

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



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

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

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

Long-term extension study (EXCURSION)

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

Clinical efficacy and safety in eosinophilic esophagitis

Paediatric Patients 1 to 11 Years of Age with EoE

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

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

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

The primary efficacy endpoint in Part A was the proportion of patients achieving histological remission defined as peak esophageal intraepithelial eosinophil count of ≤6 eos/hpf at Week 16. Secondary endpoints included the proportion of patients achieving peak esophageal intraepithelial eosinophil count of <15 eos/hpf and the change from baseline in the following: peak esophageal intraepithelial eosinophil count (eos/hpf), absolute change in Mean Grade Score from the Histology Scoring System (EoEHSS), absolute change in Mean Stage Score from the EoEHSS, and absolute change in EoE-Endoscopic Reference Score (EoE-EREFS). The impact on signs of EoE was measured using observer reported outcomes; Paediatric EoE Sign/Symptom Questionnaire-Caregiver (PESQ-C) assessed the proportion of days with one or more EoE signs and Paediatric Eosinophilic Esophagitis Symptom Score (PEESS) assessed the frequency and severity of EoE signs.

Efficacy results for Part A are presented in Table 19 and below.

Table 19: Efficacy Results of dupilumab at Week 16 in Subjects 1 to 11 Years of Age with EoE (EoE KIDS Part A)

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

[a] DUPIXENT was evaluated at tiered dosing regimens based on body weight: ≥5 to <15 kg (100 mg Q2W), ≥15 to <30 kg (200 mg Q2W), and ≥30 to <60 kg (300 mg Q2W).
[b] For histological remission, the difference in percentages is estimated using the Mantel-Haenszel method, adjusting for baseline weight group (≥5 to <15 kg, ≥15 to <30 kg, and ≥30 to <60 kg).
[c] The difference in absolute change or percent change is estimated using ANCOVA model with baseline measurement as covariate and the treatment, baseline weight group (≥5 to <15 kg, ≥15 to <30 kg, and ≥30 to <60 kg) strata as fixed factors.
[d] EoEHSS scores range from 0 to 3; higher scores indicate greater severity and extent of histological abnormalities.
[e] EoE-EREFS overall scores range from 0 to 18; higher scores indicate worse endoscopic inflammatory and remodeling findings.

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

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

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

Adults and Adolescents with eosinophilic esophagitis

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

Paediatric population

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

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

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

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

Eosinophilic Esophagitis
The safety and efficacy of dupilumab for the treatment of EoE have been established in paediatric patients 1 to 17 years of age. Use of dupilumab in this population is supported by adequate and well-controlled studies and additional pharmacokinetic data. A total of 72 paediatric patients 12 to 17 years of age received dupilumab 300 mg QW or placebo for 24 weeks (TREET Parts A and B). Of these, there were 37 dupilumab treated patients in Parts A and B; 34 continued treatment with 300 mg QW for an additional 28 weeks (TREET Part C). A total of 71 paediatric patients 1 to 11 years of age received dupilumab 100 mg Q2W, 200 mg Q2W, 300 mg Q2W, or placebo for 16 weeks (EoE KIDS Part A). Of these, there were 37 dupilumab treated patients in Part A all of whom continued treatment with these dupilumab regimens for an additional 36 weeks (EoE KIDS Part B). The use of dupilumab 300 mg QW in patients 1 to 11 years of age with EoE with a body weight 40 ≥ kg is also supported by a population pharmacokinetic analysis [see section 5.1]. The safety and efficacy of dupilumab in adults and paediatric patients were similar [see section 4.8 and section 5.1].

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

5.2 Pharmacokinetic properties

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

Absorption

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

Steady-state concentrations were achieved by week 16 following the administration of 600 mg starting dose and 300 mg dose every other week. Across clinical trials, the mean ±SD steady-state trough concentrations ranged from 69.2±36.9 mcg/mL to 80.2±35.3 mcg/mL for 300 mg dose and from 29.2±18.7 to 36.5±22.2 mcg/mL for 200 mg dose administered every other week to adults.

Distribution

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

Biotransformation

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

Elimination

Dupilumab elimination is mediated by parallel linear and nonlinear pathways. At higher concentrations, dupilumab elimination is primarily through a non-saturable proteolytic pathway, while at lower concentrations, the non-linear saturable IL-4R α target-mediated elimination predominates. After the last steady state dose of 300 mg QW, 300 mg Q2W, 200 mg Q2W, 300 mg Q4W, or 200 mg Q4W dupilumab, the median times to decrease below the lower limit of detection, estimated by population PK analysis, ranged from 9-13 weeks in adults and adolescents and are approximately 1.5 times and 2.5 times longer in paediatric patients 6 to 11 years of age and paediatric subjects less than 6 years of age, respectively.

Linearity/non-linearity

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

Special populations

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

Elderly
Of the 1539 patients with atopic dermatitis, including patients with atopic hand and foot dermatitis exposed to dupilumab in a phase 2 dose-ranging study or phase 3 placebo-controlled studies, a total of

71 were 65 years or older. Although no differences in safety or efficacy were observed between older and younger adult atopic dermatitis patients, the number of patients aged 65 and over is not sufficient to determine whether they respond differently from younger patients.

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

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

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

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

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

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

Paediatric population

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

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

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

For children 6 to 11 years of age with atopic dermatitis receiving every four week dosing (Q4W) with 300 mg (≥ 15 kg) in AD-1652, the mean ± SD steady-state trough concentration was 76.3±37.2 mcg/mL. At week 16 in AD-1434 in children 6 to 11 years of age who initiated every four week dosing (Q4W) with 300 mg (≥ 15 kg), and whose dose was increased to every other week dosing (Q2W) with 200 mg (≥ 15 to < 60 kg) or 300 mg (≥ 60 kg), the mean±SD steady-state trough concentration was 108±53.8 mcg/mL. For children 6 to 11 years of age receiving 300 mg Q4W, initial doses of 300 mg on Days 1 and 15 produce similar steady-state exposure as an initial dose of 600 mg on Day 1, based on PK simulations.

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

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

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

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

Eosinophilic esophagitis

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

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

5.3 Preclinical safety data

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

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

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

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

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

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

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

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

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

6.3 Shelf life

3 years.

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

6.4 Special precautions for storage

Store in a refrigerator (2 °C – 8 °C).

Do not freeze.

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

6.5 Nature and contents of container

<u>Dupixent 200 mg solution for injection in pre-filled syringe</u>

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

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

<u>Dupixent 200 mg solution for injection in pre-filled pen</u>

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

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

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

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Comprehensive instructions for the administration of Dupixent in a pre-filled syringe or in a pre-filled pen are given at the end of the package leaflet.

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

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

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

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

7. MARKETING AUTHORISATION HOLDER

Sanofi Winthrop Industrie
82 avenue Raspail
94250 Gentilly
France

8. MARKETING AUTHORISATION NUMBERS

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

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 26 September 2017

Date of latest renewal: 02 September 2022

10. DATE OF REVISION OF THE TEXT

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（小児気管支喘息）

※　最新の添付文書を参照すること。

Total number of pages:　2

1.7 同種同効品一覧（小児気管支喘息）
SAR231893 - デュピルマブ（遺伝子組換え）

販売名	デュピクセント皮下注 300mg ペン/300mg シリンジ/200mg ペン/200mg シリンジ	[ヌーカラ皮下注 100mg ペン/100mg シリンジ/小児用 40mg シリンジ]	[ファセンラ皮下注 30mg シリンジ/10mg シリンジ]	[ゾレア皮下注用 150mg] [ゾレア皮下注 75mg シリンジ/150mg シリンジ/75mg ペン/150mg ペン/300mg ペン]
一般名	デュピルマブ（遺伝子組換え）	メポリズマブ（遺伝子組換え）	ベンラリズマブ（遺伝子組換え）	オマリズマブ（遺伝子組換え）
会社名	サノフィ株式会社	グラクソ・スミスクライン株式会社	アストラゼネカ株式会社	ノバルティスファーマ株式会社
効能・効果	**300mg ペン、300mg シリンジ** 既存治療で効果不十分な下記皮膚疾患 〇アトピー性皮膚炎 〇結節性痒疹 〇特発性の慢性蕁麻疹 〇気管支喘息（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） 〇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） **200mg ペン、200mg シリンジ** 既存治療で効果不十分な下記皮膚疾患 〇アトピー性皮膚炎 〇特発性の慢性蕁麻疹 〇気管支喘息（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）	**100mg ペン、100mg シリンジ** 〇気管支喘息（既存治療によっても喘息症状をコントロールできない難治の患者に限る） 〇既存治療で効果不十分な好酸球性多発血管炎性肉芽腫症 〇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） **小児用 40mg シリンジ** 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難治の患者に限る）	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難治の患者に限る）	〇気管支喘息（既存治療によっても喘息症状をコントロール できない難治の患者に限る） 〇季節性アレルギー性鼻炎（既存治療で効果不十分な重症又 は最重症患者に限る） 〇特発性の慢性蕁麻疹（既存治療で効果不十分な患者に限る）
添付文書 作成・改訂年月日	ー	2024 年 10 月	2024 年 3 月	2022 年 4 月（150mg） 2024 年 8 月（75mg シリンジ/150mg シリンジ/75mg ペン/150mg ペン/300mg ペン）

＊＊2022年4月改訂（第4版）
＊2021年8月改訂

貯法：2～8℃に保存

有効期間：4年

日本標準商品分類番号
87229、87449

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季節性アレルギー性鼻炎治療剤
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（ヒト化抗ヒトIgEモノクローナル抗体製剤）
オマリズマブ（遺伝子組換え）注射用凍結乾燥製剤

	150mg
承認番号	22300AMX01262000
販売開始	2009年3月

ゾレア®皮下注用150mg
Xolair® for s.c. injection

（一部）最適使用推進ガイドライン対象品目

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）

NOVARTIS

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

販売名	ゾレア皮下注用150mg
有効成分	オマリズマブ（遺伝子組換え）202.5mg ただし、本剤の調製方法に基づき、日局注射用水1.4mLに溶解した溶液1.2mL中に含まれる量は150mgである。※
添加剤	精製白糖 145.5mg L-ヒスチジン塩酸塩水和物 2.8mg L-ヒスチジン 1.8mg ポリソルベート20 0.5mg

本剤の有効成分であるオマリズマブ（遺伝子組換え）は、チャイニーズハムスター卵巣細胞から産生されるヒト化マウスモノクローナル抗体である。オマリズマブ（遺伝子組換え）の製造工程において、ブタペプトン（胃）を使用している。

※本剤溶解後の溶液は粘性があるため、注射液吸引時の損失を考慮し、1バイアルから150mgを注射するに足る量を確保するために過量充填されている。

＊＊3.2 製剤の性状

販売名	ゾレア皮下注用150mg
性状	白色の塊で、溶解後は、無色～微黄色で、澄明又はわずかに混濁した液
pH	5.8～6.5（溶解後）
浸透圧	273～455mmol/kg（溶解後）

4．効能又は効果

○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難治の患者に限る）
○季節性アレルギー性鼻炎（既存治療で効果不十分な重症又は最重症患者に限る）注）
○特発性の慢性蕁麻疹（既存治療で効果不十分な患者に限る）

注）最適使用推進ガイドライン対象

5．効能又は効果に関連する注意

〈気管支喘息〉

5.1 高用量の吸入ステロイド薬及び複数の喘息治療薬を併用しても症状が安定せず、通年性吸入抗原に対して陽性を示し、体重及び初回投与前血清中総IgE濃度が投与量換算表で定義される基準を満たす場合に本剤を追加して投与すること。
症状が安定しないとは、下記の症状のいずれかが改善しないことを示す。

成人の場合
・喘息に起因する明らかな呼吸機能の低下（$FEV_{1.0}$が予測正常値に対し80%未満）
・毎日喘息症状が観察される
・週1回以上夜間症状が観察される

小児の場合
・毎日喘息症状が観察される
・週1回以上夜間症状が観察される
・週1回以上日常生活が障害される

〈季節性アレルギー性鼻炎〉

5.2 最新のガイドライン等を参考に、以下のいずれにも該当する患者に、ヒスタミンH_1受容体拮抗薬に追加して投与すること。[17.1.5参照]
・原因となる花粉抗原に対して血清特異的IgE抗体検査等で陽性を示す
・過去の治療において、花粉抗原の除去と回避を行ったうえで、鼻噴霧用ステロイド薬とケミカルメディエーター受容体拮抗薬を併用しても、重症又は最重症のアレルギー性鼻炎症状が認められた
・体重及び初回投与前血清中総IgE濃度が投与量換算表で定義される基準を満たす

〈特発性の慢性蕁麻疹〉

5.3 食物、物理的刺激等の蕁麻疹の症状を誘発する原因が特定されず、ヒスタミンH_1受容体拮抗薬の増量等の適切な治療を行っても、日常生活に支障をきたすほどの痒みを伴う膨疹が繰り返して継続的に認められる場合に本剤を追加して投与すること。

6．用法及び用量

〈気管支喘息〉

通常、オマリズマブ（遺伝子組換え）として1回75～600mgを2又は4週間毎に皮下に注射する。1回あたりの投与量並びに投与間隔は、初回投与前血清中総IgE濃度及び体重に基づき、下記の投与量換算表により設定する。

〈季節性アレルギー性鼻炎〉

通常、成人及び12歳以上の小児にはオマリズマブ（遺伝子組換え）として1回75～600mgを2又は4週間毎に皮下に注射する。1回あたりの投与量並びに投与間隔は、初回投与前血清中総IgE濃度及び体重に基づき、下記の投与量換算表により設定する。

投与量換算表（1回投与量）
4週間毎投与

投与前の血清中総IgE濃度（IU/mL）	体重（kg）									
	≥20～25	>25～30	>30～40	>40～50	>50～60	>60～70	>70～80	>80～90	>90～125	>125～150
≥30～100	75 mg	75 mg	75 mg	150 mg	150 mg	150 mg	150 mg	150 mg	300 mg	300 mg
>100～200	150 mg	150 mg	150 mg	300 mg	300 mg	300 mg	300 mg	300 mg	450 mg	600 mg
>200～300	150 mg	150 mg	225 mg	300 mg	300 mg	450 mg	450 mg	450 mg	600 mg	
>300～400	225 mg	225 mg	300 mg	450 mg	450 mg	450 mg	600 mg	600 mg		
>400～500	225 mg	300 mg	450 mg	450 mg	600 mg	600 mg				
>500～600	300 mg	300 mg	450 mg	600 mg	600 mg					
>600～700	300 mg		450 mg	600 mg						
>700～800	4週間毎投与の表に該当しない場合には2週間毎投与の表に従い投与すること									
>800～900										
>900～1,000										
>1,000～1,100										
>1,100～1,200										
>1,200～1,300										
>1,300～1,500										

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2週間毎投与

投与前の血清中総IgE濃度（IU/mL）	体重（kg）									
	≥20～25	>25～30	>30～40	>40～50	>50～60	>60～70	>70～80	>80～90	>90～125	>125～150
≥30～100	2週間毎投与の表に該当しない場合には4週間毎投与の表に従い投与すること									
>100～200										
>200～300										375 mg
>300～400									450 mg	525 mg
>400～500							375 mg	375 mg	525 mg	600 mg
>500～600						375 mg	450 mg	450 mg	600 mg	
>600～700		225 mg			375 mg	450 mg	450 mg	525 mg		
>700～800	225 mg	225 mg	300 mg	375 mg	450 mg	450 mg	525 mg	600 mg		
>800～900	225 mg	225 mg	300 mg	375 mg	450 mg	525 mg	600 mg			
>900～1,000	225 mg	300 mg	375 mg	450 mg	525 mg	600 mg				
>1,000～1,100	225 mg	300 mg	375 mg	450 mg	600 mg	投与不可				
>1,100～1,200	300 mg	300 mg	450 mg	525 mg	600 mg					
>1,200～1,300	300 mg	375 mg	450 mg	525 mg						
>1,300～1,500	300 mg	375 mg	525 mg	600 mg						

投与量換算表では、本剤の臨床推奨用量である0.008mg/kg/［IU/mL］以上（2週間間隔皮下投与時）又は0.016mg/kg/［IU/mL］以上（4週間間隔皮下投与時）となるよう投与量が設定されている。

〈特発性の慢性蕁麻疹〉

通常、成人及び12歳以上の小児にはオマリズマブ（遺伝子組換え）として1回300mgを4週間毎に皮下に注射する。

7. 用法及び用量に関連する注意

〈気管支喘息、季節性アレルギー性鼻炎〉

7.1 投与量換算表に該当しない患者への投与は行わないこと。

7.2 本剤投与中に大幅に体重が変化した場合には、本剤の臨床推奨用量が投与されない可能性があるので、投与量換算表に基づいて投与量並びに投与間隔を再設定すること。特に小児では、成長に伴う体重の増加に注意すること。

7.3 本剤投与によりIgEの消失半減期が延長し、血清中総IgE濃度が上昇するので本剤投与中に測定した血清中総IgE濃度による用法・用量の再設定は行わないこと。また、本剤投与中止後1年間は血清中総IgE濃度の上昇が持続する場合があるので、1年未満に投与を再開する場合は、最初の用量設定時に得られた血清中総IgE濃度に基づいて用量を設定すること。ただし、本剤の投与中断期間が1年以上の場合は、血清中総IgE濃度を再測定してもよい。［12.参照］

7.4 本剤投与中に喘息又は季節性アレルギー性鼻炎の症状の改善が認められた場合においても、投与量換算表により設定された投与量を変更しないこと。

〈気管支喘息〉

7.5 用法及び用量どおり、16週間使用しても効果が認められない場合には、漫然と投与を続けないよう注意すること。

〈季節性アレルギー性鼻炎〉

7.6 本剤投与が必要な季節性アレルギー性鼻炎に係る原因花粉抗原の飛散時期にのみ投与すること。なお、日本人を対象とした臨床試験において、本剤の12週以降の使用経験は無いため、12週以降も継続して投与する場合は、患者の状態を考慮し、その必要性を慎重に判断すること。また、症状発現初期に投与を開始することが望ましい。［15.1.5、17.1.5、18.2参照］

〈特発性の慢性蕁麻疹〉

7.7 日本人を対象とした臨床試験において、本剤の12週以降の使用経験は無いため、12週以降も継続して投与する場合は、患者の状態を考慮し、その必要性を慎重に判断すること。特に、用法及び用量どおり、12週間使用しても効果が認められない場合には、漫然と投与を続けないよう注意すること。［15.1.6、17.1.6参照］

8. 重要な基本的注意

〈効能共通〉

8.1 本剤の投与は、各適応疾患の治療に精通している医師のもとで行うこと。

8.2 本剤投与後にショック、アナフィラキシーが発現する可能性があること、及びその徴候や症状について患者に十分説明し、異常が認められた場合には、速やかに担当医師に連絡するよう、患者を指導すること。［11.1.1、15.1.1参照］

8.3 本剤投与中に、好酸球性多発血管炎性肉芽腫症（Churg-Strauss症候群）があらわれることがあり、これらの多くは経口ステロイド剤の減量・中止時に発現している。本剤使用時は、好酸球数の推移及び発疹、肺症状の悪化（肺の浸潤等）、心臓合併症（心筋炎等）、ニューロパシー等の血管炎症状に注意すること。

8.4 本剤の投与中止により、通常、遊離IgE濃度及び症状が治療前の状態に戻る。

8.5 本剤投与中にめまい、疲労、失神、傾眠があらわれることがあるため、自動車の運転等危険を伴う機械の操作に従事する場合には十分に注意させること。

8.6 本剤はIgEと複合体を形成し、遊離IgEを減少させる。IgEは寄生虫感染に対する宿主防御機能に関与する因子の1つと考えられていることから、寄生虫感染のリスクが高い地域に旅行する場合には注意すること。

8.7 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。本剤投与中止・終了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。

〈気管支喘息〉

8.8 本剤は気管支拡張薬、ステロイド薬、ヒスタミンH_1受容体拮抗薬等と異なり、すでに起こっている発作や症状を速やかに軽減する薬剤ではないので、患者に十分説明しておく必要がある。

8.9 本剤を投与中、大発作をみた場合は気管支拡張薬あるいはステロイド薬を投与する必要がある。

8.10 長期ステロイド療法を受けている患者で、本剤投与によりステロイド薬の減量をはかる場合には十分な管理下で徐々に行うこと。

9. 特定の背景を有する患者に関する注意

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。動物実験（サル）で本剤が胎盤を通過することが報告されている。

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。動物実験（サル）で乳汁中への移行が報告されている。

9.7 小児等

〈気管支喘息〉

9.7.1 低出生体重児、新生児、乳児又は6歳未満の幼児を対象とした臨床試験は実施していない。

9.7.2 6歳以上の小児を対象とした臨床試験において、頭痛、発熱、上腹部痛が多く認められている。

〈季節性アレルギー性鼻炎、特発性の慢性蕁麻疹〉

9.7.3 低出生体重児、新生児、乳児、幼児又は12歳未満の小児を対象とした臨床試験は実施していない。

9.8 高齢者

一般に生理機能（腎機能、肝機能、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 ショック、アナフィラキシー（頻度不明）

気管支痙攣、呼吸困難、血圧低下、失神、蕁麻疹、舌浮腫、口唇浮腫、咽・喉頭浮腫等があらわれることがある。本剤投与後2時間以内に発現することが多いが、2時間以上経過してから発現することもある。また、長期間の定期的投与後においても発現することがある。[8.2、15.1.1参照]

11.2 その他の副作用

	5%以上	1%～5%未満	1%未満	頻度不明
感染症及び寄生虫症	—	—	鼻咽頭炎	上気道感染、咽頭炎、副鼻腔炎、寄生虫感染、尿路感染
血液	—	—	血小板数減少	出血
神経系障害	—	頭痛	傾眠、めまい	錯感覚、失神
血管障害	—	—	潮紅	起立性低血圧
呼吸器、胸郭及び縦隔障害	—	—	—	咳嗽、アレルギー性気管支痙攣、喉頭浮腫
胃腸障害	—	—	消化不良、悪心	下痢、上腹部痛
過敏症	—	蕁麻疹	そう痒症、発疹	血管浮腫、血清病[注]
皮膚	—	—	—	光線過敏、脱毛
筋骨格系	—	—	四肢痛、筋骨格痛	関節痛、筋痛、関節腫脹
全身障害	—	—	熱感、疲労、腕の腫脹、発熱、けん怠感	体重増加、インフルエンザ様疾患
注射部位	紅斑、腫脹	そう痒感、疼痛、出血、熱感、硬結	発疹、腫瘤、浮腫、蕁麻疹、しびれ感、不快感	—

注）Ⅲ型過敏反応であり、関節炎及び関節痛、発疹（蕁麻疹又はその他の発疹）、発熱及びリンパ節腫脹を特徴とする。

12. 臨床検査結果に及ぼす影響

本剤は血中IgEと複合体を形成するため、IgEの消失半減期が延長し、血清中総IgE濃度が上昇する。従って、本剤投与中のIgE測定値を、気管支喘息及び季節性アレルギー性鼻炎の用法・用量の再設定には用いないこと。また、高IgE血症を示す疾患（アレルギー性気管支肺アスペルギルス症等）の診断やアレルギー性の喘息の治療効果の診断の根拠として用いないこと。[7.3参照]

14. 適用上の注意

14.1 薬剤調製時の注意

14.1.1 調製前の準備

投与量が150mgを超える場合は投与液量一覧表を参考に、複数のバイアルを使用する。この場合、必要数の注射筒及び注射針（18ゲージ、25ゲージ）を用意すること。

＊＊14.1.2 調製方法

本剤の溶解には日局注射用水以外は使用しないこと。

(1) 溶解時には以下の点に留意すること。

・18ゲージの注射針を装着した注射筒を用いて、1バイアルあたり日局注射用水を1.4mL採取し、バイアル内の粉末にかかるように注入し、バイアルを立てた状態で約1分間渦を描くように回転させる。この間バイアルは振ったりせず静かに回し、泡が立たないようにすること。

・次いで約5分毎に5～10秒間バイアルを回し、完全に粉末を溶解させる。

・溶解には約15～20分程度を要するが、20分以上かかる場合もある。その場合、溶液中にゲル状の粒子が見えなくなるまで約5分毎に5～10秒間バイアルを回す操作を繰り返す。40分以内に溶解しない場合には使用しないこと。また、溶解時に泡立ちが見られることがある。

(2) 溶解後は出来るだけ速やかに使用すること。直ちに使用しない場合は、2～8℃で保存し、8時間以内に使用すること。使用後の残液は使用しないこと。

14.2 薬剤投与時の注意

14.2.1 外観に異常を認めた場合には使用しないこと。

＊＊14.2.2 下記投与液量一覧表を参考に、必要バイアル数を溶解し、投与に必要な総投与液量を18ゲージの注射針を装着した注射筒を用いて採取する。

本剤1バイアルを日局注射用水1.4mLに溶解した溶液1.2mLがオマリズマブ（遺伝子組換え）の投与量150mgに相当する。

14.2.3 採取後25ゲージの注射針に交換し、皮下注射する。溶液は粘性があるため、注射するのに5～10秒を要する場合がある。

14.2.4 1回につき1.2mL（150mg）を超えて投与する場合には、1箇所あたり1.2mLを超えないように部位を分けて投与すること。

＊＊投与液量一覧表

オマリズマブ（遺伝子組換え）投与量	必要バイアル数の例	総投与液量
75mg	1本	0.6mL
150mg	1本	1.2mL
225mg	2本	1.8mL
300mg	2本	2.4mL
375mg	3本	3.0mL
450mg	3本	3.6mL
525mg	4本	4.2mL
600mg	4本	4.8mL

15. その他の注意

15.1 臨床使用に基づく情報

＊15.1.1 国内臨床試験において、アナフィラキシーは報告されていないが、気管支喘息患者を対象とした海外臨床試験において報告されており、発現頻度は成人で0.1%（7例/5,367例）、小児で0.2%（1例/624例）であった。また、海外市販後の自発報告において、アナフィラキシー及びアナフィラキシーの可能性のある過敏症反応の発現頻度は、少なくとも0.2%と推定され、そのうち発現時間別では約30%が本剤投与2時間以降に発現しており、市販後データ及び海外文献報告において、投与回数別では約70%が本剤投与3回目以内に発現していた[1,2]。[8.2、11.1.1参照]

15.1.2 悪性腫瘍の発現頻度は、国内及び海外の無作為化プラセボ対照二重盲検臨床試験において、本剤群4,254例で4.14例/1,000人・年（14例/3,382人・年）、対照群3,178例で4.45例/1,000人・年（11例/2,474人・年）であった（発現頻度比：0.93［95%信頼区間：0.39、2.27］）。また、5年間の追跡調査を行った気管支喘息患者を対象とした海外の市販後観察研究においては、本剤群5,007例で16.01件/1,000人・年（295件/18,426人・年）、対照群2,829例で19.07件/1,000人・年（190件/9,963人・年）であった（発現頻度比：0.84［95%信頼区間：0.62、1.13］）。なお、本剤を悪性腫瘍のリスクが高い患者（例：高齢者、喫煙者）に使用した場合の影響は不明である。本剤のがん原性試験は、一般的にがん原性試験に使用されるマウス及びラットのIgEと結合しないことから、実施されていない。

15.1.3 動脈血栓塞栓イベントの発現頻度は、国内及び海外の投与期間8週間以上無作為化プラセボ対照二重盲検臨床試験において、本剤群3,342例で2.69例/1,000人・年（5例/1,856人・年）、対照群2,895例で2.38例/1,000人・年（4例/1,680人・年）であった（発現頻度比：1.13［95%信頼区間：0.24、5.71］）。内訳は、本剤群で心筋梗塞が2例、脳卒中、不安定狭心症、一過性脳虚血発作がそれぞれ1例、対照群で心血管死が3例、不安定狭心症が1例であった。また、5年間の追跡調査を行った気管支喘息患者を対象とした海外の市販後観察研究においては、本剤群5,007例で7.52件/1,000人・年（115件/15,286人・年）、対照群2,829例で5.12件/1,000人・年（51件/9,963人・年）であり、ベースラインの心血管危険因子で調整した多変量解析では、ハザード比1.32［95%信頼区間：0.91、1.91］であった。

15.1.4 気管支喘息患者を対象とした本剤の臨床試験は、国内成人臨床試験で48週間、国内小児臨床試験で24週間、海外成人臨床試験で5年間、海外小児臨床試験で3年間までの期間で実施されており、これらの期間を超えた本剤の長期投与時の安全性は確立していない。

15.1.5 スギ花粉症患者を対象とした本剤の臨床試験は、日本人の成人及び12歳以上の小児を対象として12週間の期間で実施されており、この期間を超えた本剤の長期投与時の安全性は確立していない。[7.6、17.1.5参照]

15.1.6 特発性の慢性蕁麻疹患者を対象とした本剤の臨床試験は、日本人の成人及び12歳以上の小児を含む臨床試験で12週間、海外の成人及び12歳以上の小児の臨床試験で最長24週間で実施されており、これらの期間を超えた本剤の長期投与時の安全性は確立していない。[7.7、17.1.6参照]

15.1.7 本剤投与により、抗オマリズマブ抗体が発現することがある。

15.2 非臨床試験に基づく情報

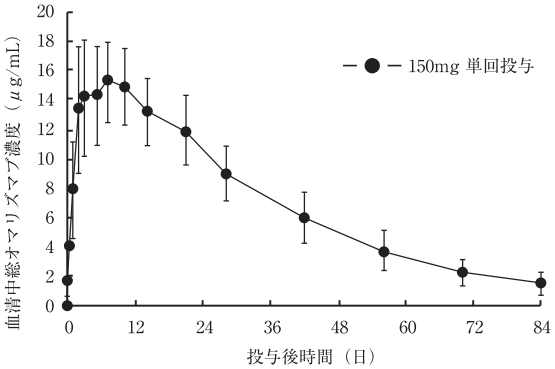
15.2.1 動物を用いた反復皮下投与毒性試験において、カニクイザルでは15mg/kg/週以上（幼若動物）及び30mg/kg/週以上（成熟動物）の群で、チンパンジーでは250mg/kg/週の群で血小板数の減少が報告されている。

16. 薬物動態

16.1 血中濃度

16.1.1 単回投与試験の成績

日本人健康成人男子19名（血清中総IgE濃度：32～96IU/mL、体重：50.5～69.8kg）に、本剤150mgを単回皮下投与した。その時の血清中オマリズマブ（遺伝子組換え）濃度推移及び薬物動態パラメータは次のとおりであった[3]。



血清中オマリズマブ（遺伝子組換え）濃度推移（平均値±標準偏差）

血清中オマリズマブ（遺伝子組換え）の薬物動態パラメータ（n=19）

投与量（mg）	T_{max}（日）	C_{max}（μg/mL）	$T_{1/2}$（日）	$AUC_{0\text{-}inf}$（日・μg/mL）	V_z/F（L）	CL/F（mL/日）
150	7 [2～14]	16.7 ±2.7	21.0 ±3.5	642 ±134	7.25 ±1.33	242 ±45.4

T_{max}は中央値［範囲］、その他は平均値±標準偏差

16.1.2 母集団解析の成績

母集団解析の結果から、日本人及び外国人に投与量換算表に従って本剤（日本人：75～375mg、外国人：75～600mg）を皮下投与した際の薬物動態及び遊離IgE濃度の抑制効果は同様であることが示された[4]。

17. 臨床成績

17.1 有効性及び安全性に関する試験

〈気管支喘息〉

17.1.1 国内第Ⅲ相試験（成人）

中等症から重症のアレルギー性喘息患者（高用量吸入ステロイド薬に加え、喘息治療薬1剤以上を併用してもコントロール不十分な患者）を対象としたプラセボ対照二重盲検比較試験において、本剤を既存治療に上乗せ投与した。朝のピークフローのベースライン値は本剤群（151例）323L/min、プラセボ群（164例）328L/minであり、最終評価時の平均改善量は本剤群で15.45L/min、プラセボ群で2.25L/min、群間差［95%信頼区間］は13.19L/min［5.93、20.46］と、プラセボ群に比して本剤群で有意に多かった（p<0.001、投与群、投与間隔及びベースライン値を共変量としたANCOVA）。

高用量の吸入ステロイド薬及び喘息治療薬を2剤以上併用もしくは経口ステロイド薬を併用しているにもかかわらず、喘息症状がある（毎日の喘息症状がある、週1回以上の夜間症状がある、% $FEV_{1.0}$が予測値の80%未満のいずれかを満たす）という条件に合致する部分集団（効能・効果に合致する部分集団）においては、朝のピークフローのベースライン値は本剤群（70例）308L/min、プラセボ群（91例）301L/minであり、最終評価時の平均改善量は本剤群で13.92L/min、プラセボ群で3.15L/min、群間差［95%信頼区間］は10.77L/min［1.49、20.04］と、プラセボ群に比して本剤群で有意に多く（p=0.023、投与群、投与間隔及びベースライン値を共変量としたANCOVA）、試験全体での結果とほぼ同様であった[5]。

副作用発現頻度は本剤群で48.3%（73/151例）であった。主な副作用は、注射部位紅斑22.5%（34/151例）、注射部位そう痒感11.3%（17/151例）であった。

17.1.2 外国第Ⅲ相試験（成人）

重症持続型アレルギー性喘息患者（高用量吸入ステロイド薬に加え、長時間作用型β_2刺激薬を併用してもコントロール不十分な患者）を対象としたプラセボ対照二重盲検比較試験において、本剤を上乗せ投与した結果、治験薬投与期間（28週間）あたりの喘息増悪（全身性ステロイド薬による治療を必要とする喘息症状の悪化）の頻度は、本剤群（209例）0.68回、プラセボ群（210例）0.91回、群間比［95%信頼区間］は0.738［0.552、0.998］と、プラセボ群に比して本剤群で有意に低かった（p=0.042、投与群、投与間隔、実施国、喘息治療薬及びベースライン値を共変量としたポアソン回帰分析）[6]。

副作用発現頻度は本剤群で11.8%（29/245例）であった。主な副作用は、悪心、注射部位紅斑、頭痛及びそう痒症各1.2%（3/245例）であった。

17.1.3 国内第Ⅲ相試験（小児）

最重症持続型の小児（6～15歳）アレルギー性喘息患者（吸入ステロイド薬（>200μg/day フルチカゾンプロピオン酸エステル又は相当量）に加え、喘息治療薬2剤以上を併用してもコントロール不十分な患者）を対象とした非対照非盲検試験において、本剤を38例に24週間上乗せ投与した。治験薬投与期間（24週間）終了時の血清中遊離IgE濃度（ng/mL）の幾何平均［95%信頼区間］は15.551［13.844、17.469］と、目標濃度の25ng/mL以下に抑制された。また、喘息増悪（吸入ステロイド薬の維持用量からの倍増を3日間以上必要とする、又は全身性ステロイド薬による治療を必要とする喘息症状の悪化）の頻度は、ベースライン（試験開始前1年間と試験中の観察期間を合わせた期間）の2.99回／患者・年に対して治験薬投与期間（24週間）では0.92回／患者・年であった。

副作用発現頻度は26.3%（10/38例）であった。主な副作用は、頭痛10.5%（4/38例）、注射部位疼痛7.9%（3/38例）、注射部位紅斑、注射部位腫脹及び蕁麻疹が各5.3%（2/38例）であった[7]（小児承認時までの集計）。

17.1.4 外国第Ⅲ相試験（小児）

中等症～重症持続型の小児（6～11歳）アレルギー性喘息患者（吸入ステロイド薬（≥200μg/day フルチカゾンプロピオン酸エステル又は相当量）単剤又は他の喘息治療薬を併用してもコントロール不十分な患者）を対象としたプラセボ対照二重盲検比較試験において、本剤を52週間上乗せ投与した。吸入ステロイド薬固定期間（24週間）あたりの喘息増悪（吸入ステロイド薬の維持用量からの倍増を3日間以上、又は全身性ステロイド薬による治療を3日間以上必要とする喘息症状の悪化）の頻度

は、本剤群（384例）0.45回、プラセボ群（192例）0.64回、群間比［95%信頼区間］は0.693［0.553、0.903］（p=0.007）、治験薬投与期間（52週間）あたりの喘息増悪の頻度は、本剤群（384例）0.78回、プラセボ群（192例）1.36回、群間比［95%信頼区間］は0.573［0.453、0.725］（p<0.001）と、いずれもプラセボ群に比して本剤群で有意に低かった（投与群、投与間隔、実施国、喘息増悪歴を共変量としたポアソン回帰分析）。

吸入ステロイド薬（>200μg/day フルチカゾンプロピオン酸エステル又は相当量）及び喘息治療薬を2剤以上併用しているにもかかわらず、喘息症状がある（毎日の喘息症状がある、週1回以上の夜間症状がある、週1回以上の日常生活障害がある、のいずれかを満たす）という条件に合致する部分集団（効能・効果に合致する部分集団）においては、吸入ステロイド薬固定期間（24週間）あたりの喘息増悪の頻度は、本剤群（111例）0.73回、プラセボ群（48例）1.15回、群間比［95%信頼区間］は0.638［0.421、0.966］（p=0.034）、治験薬投与期間（52週間）あたりの喘息増悪の頻度は、本剤群（111例）1.29回、プラセボ群（48例）2.38回、群間比［95%信頼区間］は0.541［0.366、0.799］（p=0.002）と、いずれもプラセボ群に比して本剤群で有意に低く（投与群、投与間隔、喘息増悪歴を共変量としたポアソン回帰分析）、試験全体での結果とほぼ同様であった[8,9]。

副作用発現頻度は、本剤群で6.9%（29/421例）であった。主な副作用は、頭痛1.7%（7/421例）、紅斑1.4%（6/421例）であった。

〈季節性アレルギー性鼻炎〉

17.1.5 国内第Ⅲ相試験

既存治療で鼻症状が効果不十分な12歳以上のスギ花粉症患者（前スギ花粉シーズンに鼻噴霧用ステロイドに加え、経口アレルギー性鼻炎治療薬※1剤以上を投与してもくしゃみ、鼻汁及び鼻閉のすべての症状が発現し、そのうち1つ以上の鼻症状スコア※※が3点以上の重症又は最重症の患者）を対象としたプラセボ対照二重盲検比較試験において、161例に本剤をフェキソフェナジン塩酸塩に上乗せ投与した。本剤投与期間は12週間であり、フェキソフェナジン塩酸塩は12週間を通して投与し、このうち4週間では鼻噴霧用フルチカゾンプロピオン酸エステルも投与した。

症状ピーク期※※※のNasal Symptom Score※※※※（平均値±標準偏差）は、本剤群が3.65±1.56、プラセボ群が4.70±2.18であり、プラセボ群に比べて本剤群で低かった。投与群間差（本剤群－プラセボ群、最小二乗平均値［95%CI］）は－1.03［－1.44、－0.62］であり、投与群間に有意な差が認められた（p<0.001）。［5.2、7.6、15.1.5参照］

※第2世代ヒスタミンH_1受容体拮抗薬、ロイコトリエン受容体拮抗薬及びプロスタグランジンD_2・トロンボキサンA_2受容体拮抗薬

※※くしゃみ（0～4点）、鼻汁（0～4点）、及び鼻閉（0～4点）

※※※鼻噴霧用ステロイド併用期間の70%以上を含む、又は症状ピーク期の70%以上が鼻噴霧用ステロイド併用期間を含む、のいずれかを満たす1日のNasal symptom scoreの平均値の累積値が最大となる3週間以上の最短期間（2018年2月23日～3月24日）。

※※※※鼻症状スコアの合計（0～12点）

副作用発現頻度は本剤群で1.2%（2/161例）であった。主な副作用は、AST増加2例（1.2%）であった[10]。

〈特発性の慢性蕁麻疹〉

17.1.6 国際共同第Ⅲ相試験

既存治療で効果不十分な12歳以上の特発性の慢性蕁麻疹患者（ヒスタミンH_1受容体拮抗薬で効果不十分な患者）を対象としたプラセボ対照二重盲検比較試験において、218例（日本人105例）に本剤をヒスタミンH_1受容体拮抗薬に上乗せ投与した。

プラセボ又は本剤150mg[注]又は300mgを4週間隔で3回皮下投与した。12週後の週間そう痒スコア※のベースラインからの変化量、週間膨疹スコア※※のベースラインからの変化量及びUAS7※※※が0（以下、UAS7=0）となった患者の割合を次表に示す。［7.7、15.1.6参照］

（注）本剤の承認された用法及び用量は1回300mgである。）

※1週間のそう痒スコア（1日0~3）を累計したスコア。

※※1週間の膨疹スコア（1日0~3）を累計したスコア。

※※※7-day Urticaria Activity Score：1週間のそう痒スコア及び膨疹スコアを累計したスコア。

	300mg群	150mg群	プラセボ群	群間差［95%信頼区間］、p値	
				300mg群	150mg群
全体集団					
週間そう痒スコア	−10.22（73例）	−8.80（70例）	−6.51（74例）	−3.70［−5.31、−2.10］p<0.001[a)]	−2.29［−3.92、−0.65］p=0.006[a)]
週間膨疹スコア	−12.17（73例）	−10.04（70例）	−7.41（74例）	−4.76［−6.84、−2.67][b)]	−2.63［−4.75、−0.50][b)]
UAS7=0達成割合	35.6%（26/73例）	18.6%（13/70例）	4.1%（3/74例）		
日本人部分集団					
週間そう痒スコア	−9.54（35例）	−7.29（34例）	−5.17（36例）	−4.37［−6.77、−1.97][c)]	−2.12［−4.54、0.30][c)]
週間膨疹スコア	−12.06（35例）	−8.36（34例）	−5.77（36例）	−6.29［−9.41、−3.17][c)]	−2.59［−5.74、0.55][c)]
UAS7=0達成割合	31.4%（11/35例）	11.8%（4/34例）	2.8%（1/36例）		

a）国、投与群、週、投与群と週の交互作用を固定効果、被験者を変量効果、ベースライン値を共変量とする反復測定混合モデルを用いて検定。

b）国、投与群、週、投与群と週の交互作用を固定効果、被験者を変量効果、ベースライン値を共変量とする反復測定混合モデル。

c）投与群、週、投与群と週の交互作用を固定効果、被験者を変量効果、ベースライン値を共変量とする反復測定混合モデル。

副作用発現頻度は、300mg群で9.6%（7/73例）、150mg群で8.5%（6/71例）であった。主な副作用は、頭痛300mg群2.7%（2/73例）、150mg群1.4%（1/71例）、鼻咽頭炎300mg群1.4%（1/73例）、150mg群1.4%（1/71例）であった[11]。

18. 薬効薬理

18.1 作用機序

本剤は、ヒト化抗ヒトIgEモノクローナル抗体であり、IgEと高親和性受容体（Fcε RI）の結合を阻害することで、好塩基球、肥満細胞等の炎症細胞の活性化を抑制する。

18.2 IgEに対する阻害作用

本剤はヒトIgEとFcε RIの結合を競合的に阻害し、血清中遊離IgE濃度を減少させた。なお、本剤はすでにFcε RIと結合したIgEには結合しない[5,12,13]。［7.6参照］

18.3 ヒスタミン遊離に対する効果

ブタクサ特異的IgEでの感作時に本剤を添加することにより、ブタクサ抗原刺激によるヒト好塩基球からのヒスタミン遊離が抑制された[13]。

18.4 気道収縮に対する効果

気管支喘息患者において、抗原吸入による即時型喘息反応及び遅発型喘息反応が抑制された[14,15]。

18.5 気道過敏性に対する効果

気管支喘息患者において、メサコリンに対する気道過敏性が改善した[16]。

19. 有効成分に関する理化学的知見

一般的名称

オマリズマブ（遺伝子組換え）

Omalizumab（Genetical Recombination）

分子量

約149,000

本質

ヒト化マウス抗ヒトIgEモノクローナル抗体に由来する軽鎖（$C_{1048}H_{1609}N_{278}O_{350}S_6$；分子量：23,895.03）と重鎖（$C_{2204}H_{3389}N_{588}O_{673}S_{15}$；分子量：49,372.00）をコードするDNAの導入によりチャイニーズハムスター卵巣細胞で産生される糖蛋白質

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

1バイアル

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5）Ohta，K．et al.: Respirology 2009;14（8）:1156-1165 ［20100362］

6）Humbert，M．et al.: Allergy 2005;60（3）:309-316［20083599］

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8）Lanier，B．et al.: J Allergy Clin．Immunol．2009;124（6）:1210-1216 ［20132382］

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12）社内資料：薬理試験（阻害様式）（2009年1月21日承認、CTD2.6.2-2.4.3） ［20090915］

13）社内資料：薬理試験（ヒスタミン遊離に対する効果及びFcεRI結合IgEへの影響） ［20090916］

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15）Zielen，S．et al.: Int Arch Allergy Immunol 2013;160（1）:102-110 ［20132833］

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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

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（18）

＊＊2024年8月改訂（第5版）
＊2024年3月改訂（第4版）

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気管支喘息治療剤
季節性アレルギー性鼻炎治療剤
慢性蕁麻疹治療剤
（ヒト化抗ヒトIgEモノクローナル抗体製剤）
オマリズマブ（遺伝子組換え）注射剤

ゾレア®皮下注75mgシリンジ
ゾレア®皮下注150mgシリンジ
＊ゾレア®皮下注75mgペン
＊ゾレア®皮下注150mgペン
＊ゾレア®皮下注300mgペン

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＊Xolair® for s.c. injection pen

（一部）最適使用推進ガイドライン対象品目

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）

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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

販売名	ゾレア皮下注				
	75mg		150mg		300mgペン
	シリンジ	ペン	シリンジ	ペン	
有効成分（1本中）	オマリズマブ（遺伝子組換え）75.0mg		オマリズマブ（遺伝子組換え）150.0mg		オマリズマブ（遺伝子組換え）300.0mg
添加剤（1本中）	0.5mL中 L-アルギニン塩酸塩 21.05mg L-ヒスチジン塩酸塩水和物 1.17mg L-ヒスチジン 0.68mg ポリソルベート20 0.20mg		1.0mL中 L-アルギニン塩酸塩 42.10mg L-ヒスチジン塩酸塩水和物 2.34mg L-ヒスチジン 1.37mg ポリソルベート20 0.40mg		2.0mL中 L-アルギニン塩酸塩 84.20mg L-ヒスチジン塩酸塩水和物 4.68mg L-ヒスチジン 2.74mg ポリソルベート20 0.80mg

本剤の有効成分であるオマリズマブ（遺伝子組換え）は、チャイニーズハムスター卵巣細胞から産生されるヒト化マウスモノクローナル抗体である。オマリズマブ（遺伝子組換え）の製造工程において、ブタペプトン（胃）を使用している。

＊3.2 製剤の性状

販売名	ゾレア皮下注〈全製品共通〉
性状	無色～微褐黄色で、澄明又はわずかに混濁した液
pH	5.8～6.2
浸透圧	390～470mmol/kg

4．効能又は効果

○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難治の患者に限る）
○季節性アレルギー性鼻炎（既存治療で効果不十分な重症又は最重症患者に限る）注)
○特発性の慢性蕁麻疹（既存治療で効果不十分な患者に限る）

注）最適使用推進ガイドライン対象

5．効能又は効果に関連する注意

〈気管支喘息〉

5.1 高用量の吸入ステロイド薬及び複数の喘息治療薬を併用しても症状が安定せず、通年性吸入抗原に対して陽性を示し、体重及び初回投与前血清中総IgE濃度が投与量換算表で定義される基準を満たす場合に本剤を追加して投与すること。
症状が安定しないとは、下記の症状のいずれかが改善しないことを示す。

成人の場合
・喘息に起因する明らかな呼吸機能の低下（$FEV_{1.0}$が予測正常値に対し80%未満）
・毎日喘息症状が観察される
・週1回以上夜間症状が観察される

小児の場合
・毎日喘息症状が観察される
・週1回以上夜間症状が観察される
・週1回以上日常生活が障害される

〈季節性アレルギー性鼻炎〉

5.2 最新のガイドライン等を参考に、以下のいずれにも該当する患者に、ヒスタミンH_1受容体拮抗薬に追加して投与すること。［17.1.5参照］
・原因となる花粉抗原に対して血清特異的IgE抗体検査等で陽性を示す
・過去の治療において、花粉抗原の除去と回避を行ったうえで、鼻噴霧用ステロイド薬とケミカルメディエーター受容体拮抗薬を併用しても、重症又は最重症のアレルギー性鼻炎症状が認められた
・体重及び初回投与前血清中総IgE濃度が投与量換算表で定義される基準を満たす

〈特発性の慢性蕁麻疹〉

5.3 食物、物理的刺激等の蕁麻疹の症状を誘発する原因が特定されず、ヒスタミンH_1受容体拮抗薬の増量等の適切な治療を行っても、日常生活に支障をきたすほどの痒みを伴う膨疹が繰り返して継続的に認められる場合に本剤を追加して投与すること。

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6．用法及び用量

〈気管支喘息〉

通常、オマリズマブ（遺伝子組換え）として1回75～600mgを2又は4週間毎に皮下に注射する。1回あたりの投与量並びに投与間隔は、初回投与前血清中総IgE濃度及び体重に基づき、下記の投与量換算表により設定する。

〈季節性アレルギー性鼻炎〉

通常、成人及び12歳以上の小児にはオマリズマブ（遺伝子組換え）として1回75～600mgを2又は4週間毎に皮下に注射する。1回あたりの投与量並びに投与間隔は、初回投与前血清中総IgE濃度及び体重に基づき、下記の投与量換算表により設定する。

投与量換算表（1回投与量）
4週間毎投与

投与前の血清中総IgE濃度（IU/mL）	体重（kg）									
	≥20～25	>25～30	>30～40	>40～50	>50～60	>60～70	>70～80	>80～90	>90～125	>125～150
≥30～100	75 mg	75 mg	75 mg	150 mg	150 mg	150 mg	150 mg	150 mg	300 mg	300 mg
>100～200	150 mg	150 mg	150 mg	300 mg	300 mg	300 mg	300 mg	300 mg	450 mg	600 mg
>200～300	150 mg	150 mg	225 mg	300 mg	300 mg	450 mg	450 mg	450 mg	600 mg	
>300～400	225 mg	225 mg	300 mg	450 mg	450 mg	450 mg	600 mg	600 mg		
>400～500	225 mg	300 mg	450 mg	450 mg	600 mg	600 mg				
>500～600	300 mg	300 mg	450 mg	600 mg	600 mg					
>600～700	300 mg		450 mg	600 mg						
>700～800	4週間毎投与の表に該当しない場合には2週間毎投与の表に従い投与すること									
>800～900										
>900～1,000										
>1,000～1,100										
>1,100～1,200										
>1,200～1,300										
>1,300～1,500										

2週間毎投与

投与前の血清中総IgE濃度（IU/mL）	体重（kg）									
	≥20～25	>25～30	>30～40	>40～50	>50～60	>60～70	>70～80	>80～90	>90～125	>125～150
≥30～100	2週間毎投与の表に該当しない場合には4週間毎投与の表に従い投与すること									
>100～200										
>200～300										375 mg
>300～400									450 mg	525 mg
>400～500							375 mg	375 mg	525 mg	600 mg
>500～600						375 mg	450 mg	450 mg	600 mg	
>600～700		225 mg			375 mg	450 mg	450 mg	525 mg		
>700～800	225 mg	225 mg	300 mg	375 mg	450 mg	450 mg	525 mg	600 mg		
>800～900	225 mg	225 mg	300 mg	375 mg	450 mg	525 mg	600 mg			
>900～1,000	225 mg	300 mg	375 mg	450 mg	525 mg	600 mg				
>1,000～1,100	225 mg	300 mg	375 mg	450 mg	600 mg	投与不可				
>1,100～1,200	300 mg	300 mg	450 mg	525 mg	600 mg					
>1,200～1,300	300 mg	375 mg	450 mg	525 mg						
>1,300～1,500	300 mg	375 mg	525 mg	600 mg						

投与量換算表では、本剤の臨床推奨用量である0.008mg/kg/［IU/mL］以上（2週間間隔皮下投与時）又は0.016mg/kg/［IU/mL］以上（4週間間隔皮下投与時）となるよう投与量が設定されている。

〈特発性の慢性蕁麻疹〉

通常、成人及び12歳以上の小児にはオマリズマブ（遺伝子組換え）として1回300mgを4週間毎に皮下に注射する。

7．用法及び用量に関連する注意

〈気管支喘息、季節性アレルギー性鼻炎〉

7.1 投与量換算表に該当しない患者への投与は行わないこと。

7.2 本剤投与中に大幅に体重が変化した場合には、本剤の臨床推奨用量が投与されない可能性があるので、投与量換算表に基づいて投与量並びに投与間隔を再設定すること。特に小児では、成長に伴う体重の増加に注意すること。

7.3 本剤投与によりIgEの消失半減期が延長し、血清中総IgE濃度が上昇するので本剤投与中に測定した血清中総IgE濃度による用法・用量の再設定は行わないこと。また、本剤投与中止後1年間は血清中総IgE濃度の上昇が持続する場合があるので、1年未満に投与を再開する場合は、最初の用量設定時に得られた血清中総IgE濃度に基づいて用量を設定すること。ただし、本剤の投与中断期間が1年以上の場合は、血清中総IgE濃度を再測定してもよい。［12.参照］

7.4 本剤投与中に喘息又は季節性アレルギー性鼻炎の症状の改善が認められた場合においても、投与量換算表により設定された投与量を変更しないこと。

〈気管支喘息〉

7.5 用法及び用量どおり、16週間使用しても効果が認められない場合には、漫然と投与を続けないよう注意すること。

〈季節性アレルギー性鼻炎〉

7.6 本剤投与が必要な季節性アレルギー性鼻炎に係る原因花粉抗原の飛散時期にのみ投与すること。なお、日本人を対象とした臨床試験において、本剤の12週以降の使用経験は無いため、12週以降も継続して投与する場合は、患者の状態を考慮し、その必要性を慎重に判断すること。また、症状発現初期に投与を開始することが望ましい。［15.1.5、17.1.5、18.2参照］

〈特発性の慢性蕁麻疹〉

7.7 日本人を対象とした臨床試験において、本剤の12週以降の使用経験は無いため、12週以降も継続して投与する場合は、患者の状態を考慮し、その必要性を慎重に判断すること。特に、用法及び用量どおり、12週間使用しても効果が認められない場合には、漫然と投与を続けないよう注意すること。［15.1.6、17.1.6参照］

8．重要な基本的注意

〈効能共通〉

8.1 本剤の投与は、各適応疾患の治療に精通している医師のもとで行うこと。

8.2 本剤投与後にショック、アナフィラキシーが発現する可能性があること、及びその徴候や症状について患者に十分説明し、異常が認められた場合には、速やかに担当医師に連絡するよう、患者を指導すること。［11.1.1、15.1.1参照］

8.3 本剤投与中に、好酸球性多発血管炎性肉芽腫症（Churg-Strauss症候群）があらわれることがあり、これらの多くは経口ステロイド剤の減量・中止時に発現している。本剤使用時は、好酸球数の推移及び発疹、肺症状の悪化（肺の浸潤等）、心臓合併症（心筋炎等）、ニューロパシー等の血管炎症状に注意すること。

8.4 本剤の投与中止により、通常、遊離IgE濃度及び症状が治療前の状態に戻る。

8.5 本剤投与中にめまい、疲労、失神、傾眠があらわれることがあるため、自動車の運転等危険を伴う機械の操作に従事する場合には十分に注意させること。

8.6 本剤はIgEと複合体を形成し、遊離IgEを減少させる。IgEは寄生虫感染に対する宿主防御機能に関与する因子の1つと考えられていることから、寄生虫感染のリスクが高い地域に旅行する場合には注意すること。

8.7 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。本剤投与中止・終了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。

〈気管支喘息、特発性の慢性蕁麻疹〉

8.8 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、医師の管理指導の下で実施すること。自己投与の適用後、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、医療施設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に患者に注意を促し、すべての器具の安全な廃棄方法に関する指導を行うと同時に、使用済みの注射器を廃棄する容器を提供すること。

〈気管支喘息〉

8.9 本剤は気管支拡張薬、ステロイド薬、ヒスタミンH_1受容体拮抗薬等と異なり、すでに起こっている発作や症状を速やかに軽減する薬剤ではないので、患者に十分説明しておく必要がある。

8.10 本剤を投与中、大発作をみた場合は気管支拡張薬あるいはステロイド薬を投与する必要がある。

8.11 長期ステロイド療法を受けている患者で、本剤投与によりステロイド薬の減量をはかる場合には十分な管理下で徐々に行うこと。

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

〈75mgシリンジ、150mgシリンジ〉

9.1.1 ラテックス過敏症の既往歴又は可能性のある患者

アレルギー反応を起こすことがあるので注意すること。注射針部分のカバーは、乾燥天然ゴム（ラテックス由来）を含む。

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。動物実験（サル）で本剤が胎盤を通過することが報告されている。

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。動物実験（サル）で乳汁中への移行が報告されている。

9.7 小児等

〈気管支喘息〉

9.7.1 低出生体重児、新生児、乳児又は6歳未満の幼児を対象とした臨床試験は実施していない。

9.7.2 6歳以上の小児を対象とした臨床試験において、頭痛、発熱、上腹部痛が多く認められている。

〈季節性アレルギー性鼻炎、特発性の慢性蕁麻疹〉

9.7.3 低出生体重児、新生児、乳児、幼児又は12歳未満の小児を対象とした臨床試験は実施していない。

9.8 高齢者

一般に生理機能（腎機能、肝機能、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 ショック、アナフィラキシー（頻度不明）

気管支痙攣、呼吸困難、血圧低下、失神、蕁麻疹、舌浮腫、口唇浮腫、咽・喉頭浮腫等があらわれることがある。本剤投与後2時間以内に発現することが多いが、2時間以上経過してから発現することもある。また、長期間の定期的投与後においても発現することがある。[8.2、15.1.1参照]

11.2 その他の副作用

	5%以上	1%～5%未満	1%未満	頻度不明
感染症及び寄生虫症	—	—	鼻咽頭炎	上気道感染、咽頭炎、副鼻腔炎、寄生虫感染、尿路感染
血液	—	—	血小板数減少	出血
神経系障害	—	頭痛	傾眠、めまい	錯感覚、失神
血管障害	—	—	潮紅	起立性低血圧
呼吸器、胸郭及び縦隔障害	—	—	—	咳嗽、アレルギー性気管支痙攣、喉頭浮腫
胃腸障害	—	—	消化不良、悪心	下痢、上腹部痛
過敏症	—	蕁麻疹	そう痒症、発疹	血管浮腫、血清病[注]
皮膚	—	—	—	光線過敏、脱毛
筋骨格系	—	—	四肢痛、筋骨格痛	関節痛、筋痛、関節腫脹
全身障害	—	—	熱感、疲労、腕の腫脹、発熱、けん怠感	体重増加、インフルエンザ様疾患
注射部位	紅斑、腫脹	そう痒感、疼痛、出血、熱感、硬結	発疹、腫瘤、浮腫、蕁麻疹、しびれ感、不快感	—

注）Ⅲ型過敏反応であり、関節炎及び関節痛、発疹（蕁麻疹又はその他の発疹）、発熱及びリンパ節腫脹を特徴とする。

12. 臨床検査結果に及ぼす影響

本剤は血中IgEと複合体を形成するため、IgEの消失半減期が延長し、血清中総IgE濃度が上昇する。従って、本剤投与中のIgE測定値を、気管支喘息及び季節性アレルギー性鼻炎の用法・用量の再設定には用いないこと。また、高IgE血症を示す疾患（アレルギー性気管支肺アスペルギルス症等）の診断やアレルギー性の喘息の治療効果の診断の根拠として用いないこと。[7.3参照]

14. 適用上の注意

14.1 薬剤投与前の注意

〈製剤共通〉

＊**14.1.1** 下記の投与液量一覧表を参考に、使用するシリンジ又はペンの本数を決定する。

投与液量一覧表

オマリズマブ（遺伝子組換え）投与量	必要シリンジ/ペン数の例（組み合わせはこの限りではない）			総投与液量
	75mgシリンジ/ペン	150mgシリンジ/ペン	300mgペン	
75mg	1本	—	—	0.5mL
150mg	—	1本	—	1.0mL
225mg	1本	1本	—	1.5mL
300mg	—	—	1本	2.0mL
375mg	1本	—	1本	2.5mL
450mg	—	1本	1本	3.0mL
525mg	1本	1本	1本	3.5mL
600mg	—	—	2本	4.0mL

＊**14.1.2** 投与する約30分前に冷蔵庫から取り出し、外箱に入れたまま室温（25℃以下）に戻すこと。室温に戻した後、速やかに使用しない場合は、再度冷蔵保存（2-8℃）することも可能だが、室温での保存は累積48時間を超えないこと。

〈75mgシリンジ、150mgシリンジ〉

14.1.3 針ガードで針が覆われてしまうのを防ぐため、使用前に針ガード作動クリップに触れないこと。

14.2 薬剤投与時の注意

14.2.1 外観に異常を認めた場合には使用しないこと。

14.2.2 投与直前に開封すること。

＊**14.2.3** 複数のシリンジ又はペンを使用する場合には、部位を分けて投与すること。

14.2.4 1回使用の製剤であるため、使用後は再使用せず廃棄すること。

15. その他の注意

15.1 臨床使用に基づく情報

15.1.1 国内臨床試験において、アナフィラキシーは報告されていないが、気管支喘息患者を対象とした海外臨床試験において報告されており、発現頻度は成人で0.1%（7例/5,367例）、小児で0.2%（1例/624例）であった。また、海外市販後の自発報告において、アナフィラキシー及びアナフィラキシーの可能性のある過敏症反応の発現頻度は、少なくとも0.2%と推定され、そのうち発現時間別では約30%が本剤投与2時間以降に発現しており、市販後データ及び海外文献報告において、投与回数別では約70%が本剤投与3回目以内に発現していた[1,2]。[8.2、11.1.1参照]

15.1.2 悪性腫瘍の発現頻度は、国内及び海外の無作為化プラセボ対照二重盲検臨床試験において、本剤群4,254例で4.14例/1,000人・年（14例/3,382人・年）、対照群3,178例で4.45例/1,000人・年（11例/2,474人・年）であった（発現頻度比：0.93［95%信頼区間：0.39、2.27］）。また、5年間の追跡調査を行った気管支喘息患者を対象とした海外の市販後観察研究においては、本剤群5,007例で16.01件/1,000人・年（295件/18,426人・年）、対照群2,829例で19.07件/1,000人・年（190件/9,963人・年）であった（発現頻度比：0.84［95%信頼区間：0.62、1.13］）。なお、本剤を悪性腫瘍のリスクが高い患者（例：高齢者、喫煙者）に使用した場合の影響は不明である。本剤のがん原性試験は、一般的にがん原性試験に使用されるマウス及びラットのIgEと結合しないことから、実施されていない。

15.1.3 動脈血栓塞栓イベントの発現頻度は、国内及び海外の投与期間8週間以上無作為化プラセボ対照二重盲検臨床試験において、本剤群3,342例で2.69例/1,000人・年（5例/1,856人・年）、対照群2,895例で2.38例/1,000人・年（4例/1,680人・年）であった（発現頻度比：1.13［95%信頼区間：0.24、5.71］）。内訳は、本剤群で心筋梗塞が2例、脳卒中、不安定狭心症、一過性脳虚血発作がそれぞれ1例、対照群で心血管死が3例、不安定狭心症が1例であった。また、5年間の追跡調査を行った気管支喘息患者を対象とした海外の市販後観察研究においては、本剤群5,007例で7.52件/1,000人・年（115件/15,286人・年）、対照群2,829例で5.12件/1,000人・年（51件/9,963人・年）であり、ベースラインの心血管危険因子で調整した多変量解析では、ハザード比1.32［95%信頼区間：0.91、1.91］であった。

15.1.4 気管支喘息患者を対象とした本剤の臨床試験は、国内成人臨床試験で48週間、国内小児臨床試験で24週間、海外成人臨床試験で5年間、海外小児臨床試験で3年間までの期間で実施されており、これらの期間を超えた本剤の長期投与時の安全性は確立していない。

15.1.5 スギ花粉症患者を対象とした本剤の臨床試験は、日本人の成人及び12歳以上の小児を対象として12週間の期間で実施されており、この期間を超えた本剤の長期投与時の安全性は確立していない。[7.6、17.1.5参照]

15.1.6 特発性の慢性蕁麻疹患者を対象とした本剤の臨床試験は、日本人の成人及び12歳以上の小児を含む臨床試験で12週間、海外の成人及び12歳以上の小児の臨床試験で最長24週間で実施されており、これらの期間を超えた本剤の長期投与時の安全性は確立していない。[7.7、17.1.6参照]

15.1.7 本剤投与により、抗オマリズマブ抗体が発現することがある。

15.2 非臨床試験に基づく情報

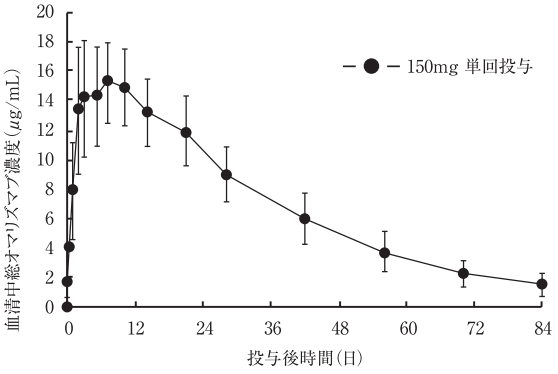
15.2.1 動物を用いた反復皮下投与毒性試験において、カニクイザルでは15mg/kg/週以上（幼若動物）及び30mg/kg/週以上（成熟動物）の群で、チンパンジーでは250mg/kg/週の群で血小板数の減少が報告されている。

16. 薬物動態

16.1 血中濃度

16.1.1 単回投与試験の成績

日本人健康成人男子19名（血清中総IgE濃度：32～96IU/mL、体重：50.5～69.8kg）に、オマリズマブ（遺伝子組換え）150mgを単回皮下投与した。その時の血清中オマリズマブ（遺伝子組換え）濃度推移及び薬物動態パラメータは次のとおりであった[3]。



血清中オマリズマブ（遺伝子組換え）濃度推移（平均値±標準偏差）

血清中オマリズマブ（遺伝子組換え）の薬物動態パラメータ（n=19）

投与量（mg）	T_{max}（日）	C_{max}（μg/mL）	$T_{1/2}$（日）	$AUC_{0\text{-}inf}$（日・μg/mL）	V_z/F（L）	CL/F（mL/日）
150	7［2～14］	16.7±2.7	21.0±3.5	642±134	7.25±1.33	242±45.4

T_{max}は中央値［範囲］、その他は平均値±標準偏差

16.1.2 母集団解析の成績

母集団解析の結果から、日本人及び外国人に投与量換算表に従ってオマリズマブ（遺伝子組換え）（日本人：75～375mg、外国人：75～600mg）を皮下投与した際の薬物動態及び遊離IgE濃度の抑制効果は同様であることが示された[4]。

17. 臨床成績

17.1 有効性及び安全性に関する試験

〈気管支喘息〉

17.1.1 国内第Ⅲ相試験（成人）

中等症から重症のアレルギー性喘息患者（高用量吸入ステロイド薬に加え、喘息治療薬1剤以上を併用してもコントロール不十分な患者）を対象としたプラセボ対照二重盲検比較試験において、本剤を既存治療に上乗せ投与した。朝のピークフローのベースライン値は本剤群（151例）323L/min、プラセボ群（164例）328L/minであり、最終評価時の平均改善量は本剤群で15.45L/min、プラセボ群で2.25L/min、群間差［95%信頼区間］は13.19L/min［5.93、20.46］と、プラセボ群に比して本剤群で有意に多かった（$p<0.001$、投与群、投与間隔及びベースライン値を共変量としたANCOVA）。

高用量の吸入ステロイド薬及び喘息治療薬を2剤以上併用もしくは経口ステロイド薬を併用しているにもかかわらず、喘息症状がある（毎日の喘息症状がある、週1回以上の夜間症状がある、% $FEV_{1.0}$が予測値の80%未満のいずれかを満たす）という条件に合致する部分集団（効能・効果に合致する部分集団）においては、朝のピークフローのベースライン値は本剤群（70例）308L/min、プラセボ群（91例）301L/minであり、最終評価時の平均改善量は本剤群で13.92L/min、プラセボ群で3.15L/min、群間差［95%信頼区間］は10.77L/min［1.49、20.04］でプラセボ群に比して本剤群で有意に多く（$p=0.023$、

投与群、投与間隔及びベースライン値を共変量としたANCOVA)、試験全体での結果とほぼ同様であった[5)]。
副作用発現頻度は本剤群で48.3%（73/151例）であった。主な副作用は、注射部位紅斑22.5%（34/151例）、注射部位そう痒感11.3%（17/151例）であった。

17.1.2 外国第Ⅲ相試験（成人）

重症持続型アレルギー性喘息患者（高用量吸入ステロイド薬に加え、長時間作用型β_2刺激薬を併用してもコントロール不十分な患者）を対象としたプラセボ対照二重盲検比較試験において、本剤を上乗せ投与した結果、治験薬投与期間（28週間）あたりの喘息増悪（全身性ステロイド薬による治療を必要とする喘息症状の悪化）の頻度は、本剤群（209例）0.68回、プラセボ群（210例）0.91回、群間比［95%信頼区間］は0.738［0.552、0.998］と、プラセボ群に比して本剤群で有意に低かった（p=0.042、投与群、投与間隔、実施国、喘息治療薬及びベースライン値を共変量としたポアソン回帰分析）[6)]。
副作用発現頻度は本剤群で11.8%（29/245例）であった。主な副作用は、悪心、注射部位紅斑、頭痛及びそう痒症各1.2%（3/245例）であった。

17.1.3 国内第Ⅲ相試験（小児）

最重症持続型の小児（6～15歳）アレルギー性喘息患者（吸入ステロイド薬（>200μg/day フルチカゾンプロピオン酸エステル又は相当量）に加え、喘息治療薬2剤以上を併用してもコントロール不十分な患者）を対象とした非対照非盲検試験において、本剤を38例に24週間上乗せ投与した。治験薬投与期間（24週間）終了時の血清中遊離IgE濃度（ng/mL）の幾何平均［95%信頼区間］は15.551［13.844、17.469］と、目標濃度の25ng/mL以下に抑制された。また、喘息増悪（吸入ステロイド薬の維持用量からの倍増を3日間以上必要とする、又は全身性ステロイド薬による治療を必要とする喘息症状の悪化）の頻度は、ベースライン（試験開始前1年間と試験中の観察期間を合わせた期間）の2.99回／患者・年に対して治験薬投与期間（24週間）では0.92回／患者・年であった。
副作用発現頻度は26.3%（10/38例）であった。主な副作用は、頭痛10.5%（4/38例）、注射部位疼痛7.9%（3/38例）、注射部位紅斑、注射部位腫脹及び蕁麻疹が各5.3%（2/38例）であった[7)]（小児承認時までの集計）。

17.1.4 外国第Ⅲ相試験（小児）

中等症～重症持続型の小児（6～11歳）アレルギー性喘息患者（吸入ステロイド薬（≥200μg/day　フルチカゾンプロピオン酸エステル又は相当量）単剤又は他の喘息治療薬を併用してもコントロール不十分な患者）を対象としたプラセボ対照二重盲検比較試験において、本剤を52週間上乗せ投与した。吸入ステロイド薬固定期間（24週間）あたりの喘息増悪（吸入ステロイド薬の維持用量からの倍増を3日間以上、又は全身性ステロイド薬による治療を3日間以上必要とする喘息症状の悪化）の頻度は、本剤群（384例）0.45回、プラセボ群（192例）0.64回、群間比［95%信頼区間］は0.693［0.553、0.903］（p=0.007）、治験薬投与期間（52週間）あたりの喘息増悪の頻度は、本剤群（384例）0.78回、プラセボ群（192例）1.36回、群間比［95%信頼区間］は0.573［0.453、0.725］（p<0.001）と、いずれもプラセボ群に比して本剤群で有意に低かった（投与群、投与間隔、実施国、喘息増悪歴を共変量としたポアソン回帰分析）。
吸入ステロイド薬（>200μg/day フルチカゾンプロピオン酸エステル又は相当量）及び喘息治療薬を2剤以上併用しているにもかかわらず、喘息症状がある（毎日の喘息症状がある、週1回以上の夜間症状がある、週1回以上の日常生活障害がある、のいずれかを満たす）という条件に合致する部分集団（効能・効果に合致する部分集団）においては、吸入ステロイド薬固定期間（24週間）あたりの喘息増悪の頻度は、本剤群（111例）0.73回、プラセボ群（48例）1.15回、群間比［95%信頼区間］は0.638［0.421、0.966］（p=0.034）、治験薬投与期間（52週間）あたりの喘息増悪の頻度は、本剤群（111例）1.29回、プラセボ群（48例）2.38回、群間比［95%信頼区間］は0.541［0.366、0.799］（p=0.002）と、いずれもプラセボ群に比して本剤群で有意に低く（投与群、投与間隔、喘息増悪歴を共変量としたポアソン回帰分析）、試験全体での結果とほぼ同様であった[8,9)]。
副作用発現頻度は、本剤群で6.9%（29/421例）であった。主な副作用は、頭痛1.7%（7/421例）、紅斑1.4%（6/421例）であった。

〈季節性アレルギー性鼻炎〉

17.1.5 国内第Ⅲ相試験

既存治療で鼻症状が効果不十分な12歳以上のスギ花粉症患者（前スギ花粉シーズンに鼻噴霧用ステロイドに加え、経口アレルギー性鼻炎治療薬※1剤以上を投与してもくしゃみ、鼻汁及び鼻閉のすべての症状が発現し、そのうち1つ以上の鼻症状スコア※※が3点以上の重症又は最重症の患者）を対象としたプラセボ対照二重盲検比較試験において、161例に本剤をフェキソフェナジン塩酸塩に上乗せ投与した。本剤投与期間は12週間であり、フェキソフェナジン塩酸塩は12週間を通して投与し、このうち4週間では鼻噴霧用フルチカゾンプロピオン酸エステルも投与した。症状ピーク期※※※のNasal Symptom Score※※※※（平均値±標準偏差）は、本剤群が3.65±1.56、プラセボ群が4.70±2.18であり、プラセボ群に比べて本剤群で低かった。投与群間差（本剤群－ プラセボ群、最小二乗平均値［95%CI］）は－1.03［－1.44、－0.62］であり、投与群間に有意な差が認められた（p < 0.001）。［5.2、7.6、15.1.5参照］

※第2世代ヒスタミンH_1受容体拮抗薬、ロイコトリエン受容体拮抗薬及びプロスタグランジンD_2・トロンボキサンA_2受容体拮抗薬
※※くしゃみ（0～4点）、鼻汁（0～4点）、及び鼻閉（0～4点）
※※※鼻噴霧用ステロイド併用期間の70%以上を含む、又は症状ピーク期の70%以上が鼻噴霧用ステロイド併用期間を含む、のいずれかを満たす1日のNasal symptom scoreの平均値の累積値が最大となる3週間以上の最短期間（2018年2月23日～3月24日）。
※※※※鼻症状スコアの合計（0～12点）

副作用発現頻度は本剤群で1.2%（2/161例）であった。主な副作用は、AST増加2例（1.2%）であった[10)]。

〈特発性の慢性蕁麻疹〉

17.1.6 国際共同第Ⅲ相試験

既存治療で効果不十分な12歳以上の特発性の慢性蕁麻疹患者（ヒスタミンH_1受容体拮抗薬で効果不十分な患者）を対象としたプラセボ対照二重盲検比較試験において、218例（日本人105例）に本剤をヒスタミンH_1受容体拮抗薬に上乗せ投与した。
プラセボ又は本剤150mg[注)]又は300mgを4週間隔で3回皮下投与した。12週後の週間そう痒スコア※のベースラインからの変化量、週間膨疹スコア※※のベースラインからの変化量及びUAS7※※※が0（以下、UAS7=0）となった患者の割合を次表に示す。［7.7、15.1.6参照］

（注）本剤の承認された用法及び用量は1回300mgである。）
※1週間のそう痒スコア（1日0～3）を累計したスコア。
※※1週間の膨疹スコア（1日0～3）を累計したスコア。
※※※7-day Urticaria Activity Score：1週間のそう痒スコア及び膨疹スコアを累計したスコア。

	300mg群	150mg群	プラセボ群	群間差［95%信頼区間］、p値	
				300mg群	150mg群
全体集団					
週間そう痒スコア	−10.22（73例）	−8.80（70例）	−6.51（74例）	−3.70［−5.31、−2.10］p<0.001[a)]	−2.29［−3.92、−0.65］p=0.006[a)]
週間膨疹スコア	−12.17（73例）	−10.04（70例）	−7.41（74例）	−4.76［−6.84、−2.67］[b)]	−2.63［−4.75、−0.50］[b)]
UAS7=0達成割合	35.6%（26/73例）	18.6%（13/70例）	4.1%（3/74例）		
日本人部分集団					
週間そう痒スコア	−9.54（35例）	−7.29（34例）	−5.17（36例）	−4.37［−6.77、−1.97］[c)]	−2.12［−4.54、0.30］[c)]
週間膨疹スコア	−12.06（35例）	−8.36（34例）	−5.77（36例）	−6.29［−9.41、−3.17］[c)]	−2.59［−5.74、0.55］[c)]
UAS7=0達成割合	31.4%（11/35例）	11.8%（4/34例）	2.8%（1/36例）		

a）国、投与群、週、投与群と週の交互作用を固定効果、被験者を変量効果、ベースライン値を共変量とする反復測定混合モデルを用いて検定。
b）国、投与群、週、投与群と週の交互作用を固定効果、被験者を変量効果、ベースライン値を共変量とする反復測定混合モデル。
c）投与群、週、投与群と週の交互作用を固定効果、被験者を変量効果、ベースライン値を共変量とする反復測定混合モデル。

副作用発現頻度は、300 mg群で9.6%（7/73例）、150mg群で8.5%（6/71例）であった。主な副作用は、頭痛300mg群2.7%（2/73例）、150mg群1.4%（1/71例）、鼻咽頭炎300mg群1.4%（1/73例）、150mg群1.4%（1/71例）であった[11)]。

18．薬効薬理

18.1 作用機序

本剤は、ヒト化抗ヒトIgEモノクローナル抗体であり、IgEと高親和性受容体（FcεRI）の結合を阻害することで、好塩基球、肥満細胞等の炎症細胞の活性化を抑制する。

18.2 IgEに対する阻害作用

本剤はヒトIgEとFcεRIの結合を競合的に阻害し、血清中遊離IgE濃度を減少させた。なお、本剤はすでにFcεRIと結合したIgEには結合しない[5,12,13)]。［7.6参照］

18.3 ヒスタミン遊離に対する効果

ブタクサ特異的IgEでの感作時に本剤を添加することにより、ブタクサ抗原刺激によるヒト好塩基球からのヒスタミン遊離が抑制された[13)]。

18.4 気道収縮に対する効果

気管支喘息患者において、抗原吸入による即時型喘息反応及び遅発型喘息反応が抑制された[14,15)]。

18.5 気道過敏性に対する効果

気管支喘息患者において、メサコリンに対する気道過敏性が改善した[16)]。

19．有効成分に関する理化学的知見

一般的名称

オマリズマブ（遺伝子組換え）

Omalizumab（Genetical Recombination）

分子量

約149,000

本質

ヒト化マウス抗ヒトIgEモノクローナル抗体に由来する軽鎖（$C_{1048}H_{1609}N_{278}O_{350}S_6$；分子量：23,895.03）と重鎖（$C_{2204}H_{3389}N_{588}O_{673}S_{15}$；分子量：49,372.00）をコードするDNAの導入によりチャイニーズハムスター卵巣細胞で産生される糖蛋白質

20．取扱い上の注意

外箱に入れたまま（遮光）の状態で、凍結を避けて冷蔵庫（2-8℃）で保管すること。

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

〈ゾレア皮下注75mgシリンジ〉

1本

〈ゾレア皮下注150mgシリンジ〉

1本

〈ゾレア皮下注75mgペン〉

1本

〈ゾレア皮下注150mgペン〉

1本

〈ゾレア皮下注300mgペン〉

1本

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24．文献請求先及び問い合わせ先

ノバルティスファーマ株式会社　ノバルティスダイレクト
〒105-6333　東京都港区虎ノ門1-23-1

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（祝日及び当社休日を除く）
www.novartis.co.jp

26．製造販売業者等

26.1 製造販売（輸入）

ノバルティス ファーマ株式会社
東京都港区虎ノ門１－２３－１

（08）

2024年10月改訂（第7版）
＊2024年8月改訂（第6版、効能変更）

日本標準商品分類番号
87229

ヒト化抗IL-5モノクローナル抗体
メポリズマブ（遺伝子組換え）製剤

貯法：2～8℃で保存
有効期間：36ヵ月

ヌーカラ皮下注100mgペン
ヌーカラ皮下注100mgシリンジ
小児用ヌーカラ皮下注40mgシリンジ

NUCALA solution for s.c. injection
NUCALA solution for s.c. injection for Pediatric

規制区分：
生物由来製品、
劇薬、
処方箋医薬品[注)]
注）注意－医師等の処方箋により使用すること

（一部）最適使用推進ガイドライン対象品目

	100mg ペン	100mg シリンジ	小児用 40mg シリンジ
承認番号	30200AMX00451	30200AMX00450	30400AMX00204
販売開始	2020 年 5 月		2022 年 11 月

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

販売名	ヌーカラ皮下注100mgペン	ヌーカラ皮下注100mgシリンジ	小児用ヌーカラ皮下注40mgシリンジ
有効成分	1ペン又は1シリンジ（1mL）中メポリズマブ（遺伝子組換え）100mg		1シリンジ（0.4mL）中メポリズマブ（遺伝子組換え） 40mg
添加剤	精製白糖 120.0mg リン酸水素二ナトリウム七水和物 4.16mg クエン酸水和物 0.95mg ポリソルベート80 0.20mg エデト酸ナトリウム水和物 0.019mg		精製白糖 48.0mg リン酸水素二ナトリウム七水和物 1.66mg クエン酸水和物 0.38mg ポリソルベート80 0.08mg エデト酸ナトリウム水和物 0.0074mg

本剤は、チャイニーズハムスター卵巣細胞を用いて製造される。メポリズマブ（遺伝子組換え）のセルバンクの培養に使用する培地成分の製造において、ブタ由来成分（カルボキシペプチダーゼB）及びウシの膵臓由来成分（トリプシン）を使用している。

3.2 製剤の性状

販売名	ヌーカラ皮下注100mgペン	ヌーカラ皮下注100mgシリンジ	小児用ヌーカラ皮下注40mgシリンジ
剤形・性状	無色～微黄色又は微褐色の液		
pH	6.0～6.6		
浸透圧	415～615mOsm/kg		

4．効能又は効果
100mgペン、100mgシリンジ
○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難治の患者に限る）
○既存治療で効果不十分な好酸球性多発血管炎性肉芽腫症
＊○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）[注)]
小児用40mgシリンジ
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難治の患者に限る）
注）最適使用推進ガイドライン対象

5．効能又は効果に関連する注意
〈気管支喘息〉
5.1 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。
5.2 投与前の血中好酸球数が多いほど本剤の気管支喘息増悪発現に対する抑制効果が大きい傾向が認められている。また、データは限られているが、投与前の血中好酸球数が少ない患者では、十分な気管支喘息増悪抑制効果が得られない可能性がある。本剤の作用機序及び臨床試験で認められた投与前の血中好酸球数と有効性の関係を十分に理解し、患者の血中好酸球数を考慮した上で、適応患者の選択を行うこと。[17.1.1、17.1.2参照]
5.3 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。
〈好酸球性多発血管炎性肉芽腫症〉
5.4 過去の治療において、全身性ステロイド薬による適切な治療を行っても、効果不十分な場合に、本剤を上乗せして投与を開始すること。
〈鼻茸を伴う慢性副鼻腔炎〉
＊5.5 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。[17.1.4参照]

6．用法及び用量
100mgペン、100mgシリンジ
〈気管支喘息〉
通常、成人及び12歳以上の小児にはメポリズマブ（遺伝子組換え）として1回100mgを4週間ごとに皮下に注射する。
〈好酸球性多発血管炎性肉芽腫症〉
通常、成人にはメポリズマブ（遺伝子組換え）として1回300mgを4週間ごとに皮下に注射する。
＊〈鼻茸を伴う慢性副鼻腔炎〉
通常、成人にはメポリズマブ（遺伝子組換え）として1回100mgを4週間ごとに皮下に注射する。
小児用40mgシリンジ
〈気管支喘息〉
通常、6歳以上12歳未満の小児にはメポリズマブ（遺伝子組換え）として1回40mgを4週間ごとに皮下に注射する。

7．用法及び用量に関連する注意
〈好酸球性多発血管炎性肉芽腫症〉
7.1 本剤とシクロホスファミドを併用投与した場合の安全性は確認されていない。[17.1.3参照]
〈鼻茸を伴う慢性副鼻腔炎〉
＊7.2 本剤による治療反応は、通常投与開始から24週までには得られる。24週までに治療反応が得られない場合は、漫然と投与を続けないよう注意すること。

8．重要な基本的注意
8.1 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。
8.2 本剤はヒトインターロイキン-5（IL-5）と結合し、IL-5の機能を阻害することにより血中好酸球数を減少させる。好酸球は一部の寄生虫（蠕虫）感染に対する免疫応答に関与している可能性がある。患者が本剤投与中に蠕虫類に感染し、抗蠕虫薬に

よる治療が無効な場合には、本剤投与の一時中止を考慮すること。[9.1.1参照]

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 本剤の投与期間中に喘息に関連した事象及び喘息の悪化が現れることがある。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、医師の診察を受けるよう患者に指導すること。

＊**8.5** 本剤の投与によって合併する他の好酸球関連疾患の症状が変化する可能性があり、当該好酸球関連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。本剤の投与中止後の疾患管理も含めて、本剤投与中から、合併する好酸球関連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。

8.6 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下で投与を行うこと。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又はその保護者が理解し、患者又はその保護者自ら確実に投与できることを確認した上で、医師の管理指導の下で実施すること。自己投与の適用後、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し医療施設に連絡するよう患者又はその保護者に指導し、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、使用済みの注射器を再使用しないように患者又はその保護者に注意を促し、安全な廃棄方法について指導すること。

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 蠕虫類に感染している患者

本剤投与開始前に蠕虫感染を治療すること。[8.2参照]

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。サルではメポリズマブが胎盤を通過することが報告されている。

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。サルではメポリズマブが乳汁中へわずかに移行することが報告されている。

9.7 小児等

〈気管支喘息〉

9.7.1 6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。

＊**〈好酸球性多発血管炎性肉芽腫症、鼻茸を伴う慢性副鼻腔炎〉**

9.7.2 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

一般に、生理機能が低下している。

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

アナフィラキシー（頻度不明）

11.2 その他の副作用

		5%以上	1%以上5%未満	1%未満
＊	過敏症		過敏症反応（蕁麻疹、血管性浮腫、発疹、気管支痙攣、低血圧）	
	感染症			下気道感染症、咽頭炎、尿路感染
	精神神経系	頭痛		
	呼吸器			鼻閉
＊	胃腸障害			上腹部痛
	皮膚			湿疹
	筋骨格系			背部痛
	全身障害			発熱
	投与部位	注射部位反応（疼痛、紅斑、腫脹、そう痒、灼熱感）		

14. 適用上の注意

14.1 薬剤交付時の注意

患者又はその保護者には本剤に添付の使用説明書を渡し、使用方法を指導すること。

14.2 薬剤投与前の注意

14.2.1 投与前に室温で最低30分放置する。

14.2.2 開封後、8時間以内に投与する。8時間以内に投与しなかった場合は廃棄すること。

14.3 薬剤投与時の注意

〈効能共通〉

14.3.1 注射部位は上腕部、大腿部又は腹部とすること。

14.3.2 本剤は1回使用の製剤であり、1回に全量を使用し再使用しないこと。使用後は針が格納されるため、分解しないこと。

〈好酸球性多発血管炎性肉芽腫症〉

14.3.3 100mgずつ3ヵ所に分けて投与し、各注射部位は5cm以上離すこと。

16. 薬物動態

16.1 血中濃度

16.1.1 健康成人

健康成人にヌーカラ皮下注100mgシリンジ及びヌーカラ皮下注100mgペンをそれぞれ単回皮下投与した時の血漿中メポリズマブ濃度推移を図1に、薬物動態パラメータを表1に示す（外国人データ）。

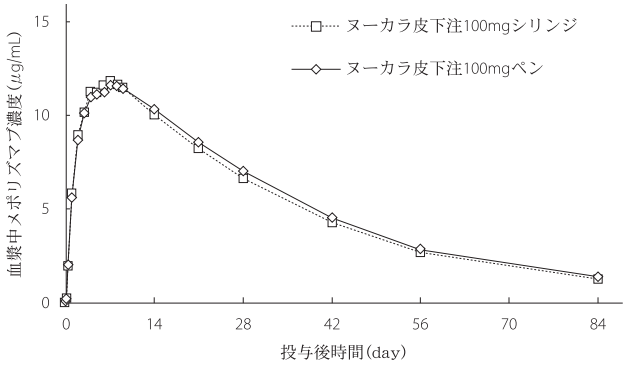


図1 健康成人にメポリズマブ100mgを単回皮下投与した時の血漿中メポリズマブ濃度推移（平均値）

表1 健康成人にメポリズマブ100mgを単回皮下投与した時の薬物動態パラメータ

薬物動態パラメータ	ヌーカラ皮下注100mgシリンジ（80例）	ヌーカラ皮下注100mgペン（79例）
$AUC_{0\text{-}t}$（μg・day/mL）	432.45（117.841）	446.76（101.053）
Cmax（μg/mL）	12.55（3.427）	12.40（3.094）
tmax[注1)]（日）	7.06（1.9-14.0）	7.05（2.9-21.0）
$t_{1/2}$（日）	22.40（4.843）	22.90（4.896）

平均値（SD）

注1）中央値（範囲）

16.1.2 重症喘息患者

(1) 成人及び12歳以上の小児

重症喘息患者にメポリズマブ100mgを4週間ごとに皮下投与した時の定常状態における薬物動態パラメータの母集団薬物動態解析に基づく推定値を表2に示す。

表2 重症喘息患者にメポリズマブ100mgを皮下投与した時の定常状態における薬物動態パラメータ（母集団薬物動態解析に基づく推定値）

薬物動態パラメータ	日本人（16例）	外国人（175例）
Cmax ss（ng/mL）	20048.5（5513.72）	17162.3（5014.53）
AUC ss（μg・day/mL）	405.9（145.78）	359.1（121.66）

平均値（SD）

(2) 6歳以上12歳未満の小児

6～11歳の小児重症喘息患者にメポリズマブ40mg又は100mg[注]を4週間ごとに皮下投与した時の薬物動態パラメータの母集団薬物動態解析に基づく推定値を表3に示す。

表3　6～11歳の小児重症喘息患者にメポリズマブ40mg又は100mgを皮下投与した時の薬物動態パラメータ（母集団薬物動態解析に基づく推定値）

用法・用量[注1)]	薬物動態パラメータ	日本人	外国人
40mg	Cmax[注2)]（μg/mL）	16.50（2.39）（6例）	18.20（2.25）（17例）
	AUC ss（μg・day/mL）	411.92（72.94）（6例）	478.03（80.99）（20例）
100mg	Cmax[注2)]（μg/mL）	30.50（1例）	27.06（4.08）（9例）
	AUC ss（μg・day/mL）	748.87（1例）	675.78（140.53）（9例）

平均値（SD）

注1）体重が40kg未満の患者に対してはメポリズマブ40mgを、40kg以上の患者に対してはメポリズマブ100mgを4週間ごとに投与した。なお、本剤の承認用量は6歳以上12歳未満の小児気管支喘息では40mgである。

注2）メポリズマブ40mg又は100mgを4週間ごとに3回皮下投与した後のCmax

16.1.3 好酸球性多発血管炎性肉芽腫症患者

好酸球性多発血管炎性肉芽腫症患者にメポリズマブ300mgを4週間ごとに皮下投与した時の定常状態における血漿中メポリズマブ濃度を表4に示す。

表4　好酸球性多発血管炎性肉芽腫症患者にメポリズマブ300mgを皮下投与した時の定常状態における血漿中メポリズマブ濃度（μg/mL）

	投与28週目（トラフ値）	投与29週目
全体集団	32.2（9.98）（66例）	45.5（8.81）（45例）
日本人集団	31.1（6.75） 26.4，28.2，38.9 （3例）	52.0（6.25） 48.0，48.7，59.2 （3例）

上段：平均値（SD）、中段：各症例の血漿中メポリズマブ濃度（日本人集団のみ）、下段：（例数）

＊16.1.4 鼻茸を伴う慢性副鼻腔炎患者

鼻茸を伴う慢性副鼻腔炎患者にメポリズマブ100mgを4週間ごとに皮下投与した時の定常状態における薬物動態パラメータの母集団薬物動態解析に基づく推定値を表5に示す。

表5　鼻茸を伴う慢性副鼻腔炎患者にメポリズマブ100mgを皮下投与した時の定常状態における薬物動態パラメータ（母集団薬物動態解析に基づく推定値）

薬物動態パラメータ	日本人（41例）	外国人（15例）
Cmax ss（μg/mL）	17.39（2.94）	17.44（5.86）
AUC ss（μg・day/mL）	371.48（71.75）	382.37（138.57）

平均値（SD）

16.1.5 相対的バイオアベイラビリティ

健康成人にヌーカラ皮下注100mgシリンジ、ヌーカラ皮下注100mgペン及び凍結乾燥注射剤100mgをそれぞれ単回皮下投与した[1)]。その結果、ヌーカラ皮下注100mgシリンジ及びヌーカラ皮下注100mgペンの最高血漿中濃度（Cmax）及び最終測定時点までの血漿中濃度－時間曲線下面積（$AUC_{0\text{-}t}$）の凍結乾燥注射剤100mgに対する比（90%信頼区間）は表6の通りであり、90%信頼区間はいずれも生物学的同等性の基準である0.8～1.25の範囲内であった（外国人データ）。

表6　健康成人にヌーカラ皮下注100mgシリンジ、ヌーカラ皮下注100mgペンを単回皮下投与した時の凍結乾燥注射剤100mgに対する薬物動態パラメータの比

	Cmax	$AUC_{0\text{-}t}$
ヌーカラ皮下注100mgシリンジ	1.06（0.99，1.12）	1.04（0.97，1.12）
ヌーカラ皮下注100mgペン	1.04（0.98，1.11）	1.08（1.01，1.15）

幾何平均値の比（90%信頼区間）

16.2 吸収

健康成人にメポリズマブ250mg[注]を上腕部に単回皮下投与した時の絶対的バイオアベイラビリティは75%（90%信頼区間：65.6，86.4）であった。上腕部、大腿部又は腹部に単回皮下投与した時、投与部位間の絶対的バイオアベイラビリティの差は小さかった（外国人データ）。

16.4 代謝

メポリズマブはヒト化IgG1モノクローナル抗体であり、体内に広く分布する蛋白質分解酵素で分解されると推定される。

注）本剤の承認用量は気管支喘息では成人及び12歳以上の小児で100mg、6歳以上12歳未満の小児で40mg、鼻茸を伴う慢性副鼻腔炎では100mg、好酸球性多発血管炎性肉芽腫症では300mgである。

17．臨床成績

17.1 有効性及び安全性に関する試験

〈気管支喘息〉

17.1.1 国際共同第Ⅲ相試験（成人及び12歳以上の小児）

12歳以上の重症喘息患者（高用量の吸入ステロイド薬及びその他の長期管理薬を併用しているが喘息増悪をきたす患者で、血中好酸球数が試験開始時に150/μL以上の患者、又は過去12ヵ月間に300/μL以上が認められた患者）576例（日本人患者50例を含む）を対象にメポリズマブ凍結乾燥注射剤を用いて実施したプラセボ対照二重盲検比較試験において、既存治療に上乗せしてメポリズマブ100mgを4週間ごとに皮下投与した時の32週間の投与期間における喘息増悪（全身性ステロイド薬による治療、入院、又は救急外来受診を必要とする喘息症状の悪化）の頻度を評価した[2)]。その結果、喘息増悪の頻度はメポリズマブ100mg群において0.83回/年、プラセボ群において1.74回/年であり、メポリズマブ100mg群はプラセボ群に比し有意に増悪頻度が少なかった（表1）。また、組入れ時及び投与開始時における血中好酸球数別の部分集団解析結果は表2及び表3の通りであった。[5.2参照]

本試験の治験薬投与期間における副作用発現頻度は、メポリズマブ100mg群で20%（39/194例）であった。主な副作用は、注射部位反応7%（14/194例）、頭痛4%（8/194例）及び疲労2%（4/194例）であった。

表1　喘息増悪の頻度

	メポリズマブ100mg群	プラセボ群
症例数	194	191
喘息増悪発現例数（割合）、件数	64（0.33）、116	105（0.55）、216
喘息増悪の頻度（回/年）[注1)]	0.83	1.74
プラセボ群に対する比[注2)]［95%信頼区間[注1)]］、p値[注1)]	0.47［0.35，0.64］、p<0.001	

注1）投与期間の対数をオフセット変数、投与群、地理的地域、ベースライン時のFEV_1の予測値に対する割合、経口ステロイド薬の併用の有無及び治験開始前1年間における喘息増悪の頻度を共変量とし、負の2項確率分布を仮定した一般化線形モデル

注2）メポリズマブ100mg群/プラセボ群

表2　組入れ時（投与開始1～6週間前）における血中好酸球数別の喘息増悪の頻度

		メポリズマブ100mg群（194例）	プラセボ群（191例）
150/μL未満	症例数	35	21
	喘息増悪の頻度（回/年）[注1)]	1.20	1.31
	プラセボ群に対する比[注2)]［95%信頼区間[注1)]］	0.91［0.44，1.90］	
150/μL以上、300/μL未満	症例数	49	59
	喘息増悪の頻度（回/年）[注1)]	0.62	1.28
	プラセボ群に対する比[注2)]［95%信頼区間[注1)]］	0.48［0.27，0.86］	
300/μL以上、500/μL未満	症例数	45	48
	喘息増悪の頻度（回/年）[注1)]	0.78	1.63
	プラセボ群に対する比[注2)]［95%信頼区間[注1)]］	0.48［0.26，0.89］	
500/μL以上	症例数	61	60
	喘息増悪の頻度（回/年）[注1)]	0.47	2.26
	プラセボ群に対する比[注2)]［95%信頼区間[注1)]］	0.21［0.12，0.36］	

注1）投与期間の対数をオフセット変数、投与群、地理的地域、ベースライン時のFEV_1の予測値に対する割合、経口ステロイド薬の併用の有無及び治験開始前1年間における喘息増悪の頻度を共変量とし、負の2項確率分布を仮定した一般化線形モデル

注2）メポリズマブ100mg群/プラセボ群

表3　投与開始時における血中好酸球数別の喘息増悪の頻度

		メポリズマブ100mg群（194例）	プラセボ群（191例）
150/μL未満	症例数	39	32
	喘息増悪の頻度（回/年）[注1)]	1.15	1.92
	プラセボ群に対する比[注2)]［95%信頼区間[注1)]］	0.60［0.32，1.13］	
150/μL以上、300/μL未満	症例数	53	51
	喘息増悪の頻度（回/年）[注1)]	0.67	1.02
	プラセボ群に対する比[注2)]［95%信頼区間[注1)]］	0.66［0.34，1.29］	
300/μL以上、500/μL未満	症例数	34	40
	喘息増悪の頻度（回/年）[注1)]	0.80	1.66
	プラセボ群に対する比[注2)]［95%信頼区間[注1)]］	0.48［0.23，1.00］	

		メポリズマブ100mg群（194例）	プラセボ群（191例）
500/μL以上	症例数	66	66
	喘息増悪の頻度（回/年）[注1)]	0.54	2.11
	プラセボ群に対する比[注2)] [95%信頼区間[注1)]]	0.25 [0.15，0.43]	

注1）投与期間の対数をオフセット変数、投与群、地理的地域、ベースライン時のFEV_1の予測値に対する割合、経口ステロイド薬の併用の有無及び治験開始前1年間における喘息増悪の頻度を共変量とし、負の2項確率分布を仮定した一般化線形モデル

注2）メポリズマブ100mg群/プラセボ群

17.1.2 国際共同第Ⅱ相試験（6歳以上12歳未満の小児）

6～11歳の小児重症喘息患者（高用量の吸入ステロイド薬及びその他の長期管理薬を併用しているが喘息増悪をきたす患者で、血中好酸球数が試験開始時に150/μL以上の患者、又は過去12ヵ月間に300/μL以上が認められた患者）36例（日本人患者7例を含む）を対象に実施した非対照非盲検試験において、既存治療に上乗せしてメポリズマブ凍結乾燥注射剤[注1)]を4週間ごとに12週間皮下投与した。8週間の休薬後、30例（日本人患者7例を含む）を対象にメポリズマブ凍結乾燥注射剤[注2)]を52週間皮下投与した[3)]。52週間の投与期間における喘息増悪（全身性ステロイド薬による治療、入院、又は救急外来受診を必要とする喘息症状の悪化）の頻度（回/年［95%信頼区間］）は、試験開始前12ヵ月間の発現回数（平均値）[注3)]3.5回/年に対して1.09回/年［0.63，1.89］であった。[5.2参照]

52週間の投与期間における副作用発現頻度は、メポリズマブ凍結乾燥注射剤群全体で27%（8/30例）であった。主な副作用は、頭痛13%（4/30例）、上腹部痛10%（3/30例）及び発熱7%（2/30例）であった[注2)]。

注1）初回投与時に体重が40kg未満の患者（26例）に対してはメポリズマブ凍結乾燥注射剤40mgを、40kg以上の患者（10例）に対してはメポリズマブ凍結乾燥注射剤100mgを投与した。なお、本剤の承認用量は6歳以上12歳未満の小児では40mgである。

注2）8週間の休薬後に体重が40kg未満の患者（16例）に対してはメポリズマブ凍結乾燥注射剤40mgを、40kg以上の患者（10例）に対してはメポリズマブ凍結乾燥注射剤100mgを投与した。ただし、来院ごとに体重を測定し、体重が40kgを超えた患者（4例）には、以降の投与量を100mgとした。

注3）全身性ステロイド薬による治療を必要とする喘息増悪の回数と定義した。

〈好酸球性多発血管炎性肉芽腫症〉

17.1.3 国際共同第Ⅲ相試験（18歳以上の成人）

18歳以上の再燃又は難治性の好酸球性多発血管炎性肉芽腫症患者136例（日本人患者6例を含む）を対象にメポリズマブ凍結乾燥注射剤を用いて実施したプラセボ対照二重盲検比較試験において、経口ステロイド薬（プレドニゾロン換算で7.5～50mg/日）[注1)]に追加[注2)]してメポリズマブ300mgを4週間ごとに52週間皮下投与した[4)]。その結果、プラセボ群に比べメポリズマブ300mg群で累積寛解維持期間が有意に長く（表4）、また投与36週時及び48週時の両時点において寛解状態にあった症例の割合は有意に高かった（表5）。投与期間最後の4週間における経口ステロイド薬の平均1日用量は、メポリズマブ300mg群でプラセボ群よりも有意に低く、0mgとなった症例はメポリズマブ300mg群18%（12/68例）、プラセボ群3%（2/68例）であった。[7.1参照]

本試験の治験薬投与期間及び後観察期間（8週間）における副作用発現頻度は、メポリズマブ300mg群で51%（35/68例）であった。主な副作用は、注射部位反応10%（7/68例）、頭痛7%（5/68例）、無力症及び気道感染各6%（各4/68例）であった。

注1）経口ステロイド薬は、医師の判断で投与開始4週以降に適宜減量することと設定した。

注2）免疫抑制剤（シクロホスファミドを除く）は、併用可能とされた。

表4　累積寛解維持期間

	メポリズマブ300mg群（68例）	プラセボ群（68例）
累積寛解維持期間[注1)]別の症例数（割合）		
0週	32（47%）	55（81%）
0週超～12週未満	8（12%）	8（12%）
12週～24週未満	9（13%）	3（4%）
24週～36週未満	10（15%）	0
36週以上	9（13%）	2（3%）
プラセボ群に対するオッズ比[注2)] [95%信頼区間][注3)] p値[注3)]	5.91 [2.68，13.03] p<0.001	

注1）52週間の投与期間のうちバーミンガム血管炎活動性スコア（BVAS）が0、かつ経口ステロイド薬の平均1日用量が4mg以下の寛解状態にあった週数の累積期間

注2）メポリズマブ300mg群/プラセボ群

注3）ベースライン時の経口ステロイド薬の平均1日用量、BVAS、治療群及び地域を共変量とした順序カテゴリカルデータに対する比例オッズ回帰モデル

表5　投与36週時及び48週時の両時点で寛解状態であった症例の割合

	メポリズマブ300mg群（68例）	プラセボ群（68例）
寛解状態であった症例数（割合）[注1)]	22（32%）	2（3%）
プラセボ群に対するオッズ比[注2)] [95%信頼区間][注3)] p値[注3)]	16.74 [3.61，77.56] p<0.001	

注1）BVASが0、かつ経口ステロイド薬の1日用量が4mg以下の場合を寛解と定義し、投与36週時及び48週時の両時点で寛解状態であった症例の割合

注2）メポリズマブ300mg群/プラセボ群

注3）ベースライン時の経口ステロイド薬の平均1日用量、BVAS、治療群及び地域を共変量としたロジスティック回帰モデル

〈鼻茸を伴う慢性副鼻腔炎〉

＊17.1.4 国際共同第Ⅲ相試験（18歳以上の成人）

手術又は全身性ステロイド薬の投与によっても効果不十分[注1)]な、18歳以上の鼻茸を伴う慢性副鼻腔炎患者163例（日本人患者85例を含む）を対象にメポリズマブ液剤を用いて実施したプラセボ対照二重盲検比較試験において、標準治療[注2)]に追加してメポリズマブ100mgを4週間ごとに52週間皮下投与した。主要評価項目（co-primary endpoint）のうち、投与52週時の鼻茸スコアのベースラインからの変化量ではメポリズマブ100mg群とプラセボ群との対比較において統計学的な有意差は認められなかったが、投与52週時の直前4週間における鼻閉VAS症状スコアの平均値のベースラインからの変化量については統計学的に有意な差が認められた。投与52週時の有効性評価項目の結果を表6に示す。[5.5 参照]

52週間の投与期間における副作用発現頻度は、メポリズマブ100mg群で3%（2/80例）であった。すべての副作用の発現頻度は2%未満（1/80例）であり、頭痛、顔面痛、疼痛、咳嗽、発声障害、口腔咽頭痛、アラニンアミノトランスフェラーゼ増加、骨痛であった。

注1）鼻手術歴を有する、及び/又は鼻茸の治療のため過去2年以内に3日以上連続の全身性ステロイド薬投与がある、及び/又は全身性ステロイド薬に対する医学的禁忌/不耐性がある患者で、両側鼻茸スコアが5以上（各鼻腔スコアは2以上）、かつ鼻閉VAS症状スコアが5を超える。加えて、JESRECスコア11以上であること、血中好酸球数が2%超5%以下であると確認された患者については気管支喘息、アスピリン不耐症又は非ステロイド性抗炎症薬アレルギーの合併が必要であり、血中好酸球数が5%超の患者についてはCT陰影が篩骨洞≥上顎洞の場合、前出の合併を必要としない。

注2）各国の診療方針に応じて、鼻腔内ステロイド（INCS）、生理食塩液による鼻腔内洗浄、全身性ステロイド薬及び/又は抗生物質の短期投与等

表6　投与52週時におけるベースラインからの変化量の調整平均及び群間差

		メポリズマブ100mg群（80例）	プラセボ群（83例）
鼻茸スコア[注1)]	投与前[注2)]	5.9 (1.27)	6.1 (1.25)
	変化量[注3)]	−0.62 (0.164)	−0.19 (0.164)
	プラセボ群との差 [95%信頼区間][注4)] p値[注4)]	−0.43 [−0.89，0.03] 0.067	
鼻閉VAS症状スコア[注1)]	投与前[注2)]	8.60 (1.249)	8.59 (1.260)
	変化量[注3)]	−3.23 (0.336)	−1.80 (0.333)
	プラセボ群との差 [95%信頼区間][注4)] p値[注4)]	−1.43 [−2.37，−0.50] 0.003	
LMK-CTスコア[注1)]	投与前[注2)]	20.3 (3.25)	20.7 (3.44)
	変化量[注3)]	−3.52 (0.449)	−1.88 (0.452)
	プラセボ群との差 [95%信頼区間][注4)]	−1.63 [−2.90，−0.37]	
SNOT-22総スコア[注1)]	投与前[注2)]	56.9 (18.94)	55.6 (20.22)
	変化量[注3)]	−18.27 (2.889)	−7.65 (2.869)
	プラセボ群との差 [95%信頼区間][注4)]	−10.63 [−18.68，−2.57]	

注1）鼻茸スコア（0-8点）；鼻閉VAS症状スコア（0-10点）；LMK-CTスコア（0-24点）；SNOT-22総スコア（0-110点）
鼻茸スコア、鼻閉VAS症状スコア、LMK-CTスコア及びSNOT-22総スコアはスコアの減少が改善を意味する。なお、鼻茸スコア及び鼻閉VAS症状スコアが主要評価項目（co-primary endpoint）である。
注2）平均値（SD）
注3）投与52週時（鼻閉VAS症状スコアは投与52週時の直前4週間）における調整平均（SE）
注4）投与群、ベースライン値、ベースラインの血中好酸球数の対数値、標準治療としてのINCS使用、国及び時点を共変量とし、ベースライン値と時点及び投与群と時点の交互作用を考慮したMMRM（反復測定混合モデル解析）

18．薬効薬理

18.1 作用機序

メポリズマブはヒトインターロイキン-5（IL-5）に対して特異的に結合し、好酸球の細胞表面に発現しているIL-5受容体α鎖へのIL-5結合を阻害することにより、IL-5の好酸球増殖作用を抑制する。

＊18.2 好酸球に対する作用

メポリズマブの投与により、カニクイザルのアスカリス抗原誘発喘息モデルにおいて血中及び気管支肺胞洗浄液中の好酸球数が減少した[6]。メポリズマブの投与により、重症喘息患者において血中好酸球数及び誘発喀痰中好酸球比率が減少した[2),3),7),8)]。また、メポリズマブの投与により、好酸球性多発血管炎性肉芽腫症患者及び鼻茸を伴う慢性副鼻腔炎患者において血中好酸球数が減少した[4),5)]。

19．有効成分に関する理化学的知見

一般的名称：メポリズマブ（遺伝子組換え）
Mepolizumab（Genetical Recombination）
本　　質：メポリズマブは、遺伝子組換えヒト化モノクローナル抗体であり、マウス抗ヒトインターロイキン-5抗体の相補性決定部、並びにヒトIgG1のフレームワーク部及び定常部からなる。メポリズマブは、チャイニーズハムスター卵巣細胞により産生される。メポリズマブは、449個のアミノ酸残基からなるH鎖（γ1鎖）2本及び220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149,000）である。
分　子　式：$C_{6476}H_{10084}N_{1732}O_{2028}S_{46}$（糖鎖部分を含まない）
分　子　量：約149,000

20．取扱い上の注意

凍結を避けて保存すること。冷蔵庫から取り出した場合は、室温（30℃以下）で外箱に入れたまま保存し、7日以内に使用すること。また、外箱開封後は遮光して保存すること。

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

〈ヌーカラ皮下注100mgペン〉
1mL［1ペン］
〈ヌーカラ皮下注100mgシリンジ〉
1mL［1シリンジ］
〈小児用ヌーカラ皮下注40mgシリンジ〉
0.4mL［1シリンジ］

23．主要文献

1）Shabbir S. et al. Clin Pharmacol Drug Dev. 2020；9：375-85
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6）Hart TK, et al.：J Allergy Clin Immunol. 2001；108：250-7
7）Bel E, et al.：N Engl J Med. 2014；371（13）：1189-97
8）Pavord ID, et al.：Lancet. 2012；380：651-9

24．文献請求先及び問い合わせ先

グラクソ・スミスクライン株式会社
東京都港区赤坂1-8-1
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TEL：0120-561-007（9：00～17：45/土日祝日及び当社休業日を除く）
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26．製造販売業者等

26.1 製造販売元

グラクソ・スミスクライン株式会社
東京都港区赤坂1－8－1

**2024年3月改訂（第2版、用法変更、用量変更）
*2021年1月改訂（第1版）

日本標準商品分類番号
87229

ヒト化抗IL-5受容体αモノクローナル抗体製剤
ベンラリズマブ（遺伝子組換え）製剤

貯　　法：2～8℃に保存
有効期間：36箇月

ファセンラ® 皮下注30mgシリンジ
**ファセンラ® 皮下注10mgシリンジ

**Fasenra® Subcutaneous Injection 10 mg・30 mg Syringe

生物由来製品、劇薬、処方箋医薬品注）

注）注意－医師等の処方箋により使用すること

		30mgシリンジ	10mgシリンジ
**	承認番号	23000AMX00016	30600AMX00129
	販売開始	2018年4月	2024年6月

2. 禁忌（次の患者には投与しないこと）
2.1 本剤及び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

	販売名	ファセンラ皮下注30mgシリンジ	ファセンラ皮下注10mgシリンジ
**	有効成分	1シリンジ（1mL）中 ベンラリズマブ（遺伝子組換え） 30mg	1シリンジ（0.5mL）中 ベンラリズマブ（遺伝子組換え） 10mg
**	添加剤	L-ヒスチジン　1.4mg、 L-ヒスチジン塩酸塩水和物　2.3mg、 トレハロース水和物　95mg、 ポリソルベート20　0.06mg	L-ヒスチジン　0.7mg、 L-ヒスチジン塩酸塩水和物　1.2mg、 トレハロース水和物　47mg、 ポリソルベート20　0.03mg

本剤の有効成分ベンラリズマブ（遺伝子組換え）は、チャイニーズハムスター卵巣細胞で産生される。ベンラリズマブ（遺伝子組換え）のセルバンクの作製に使用する培地成分の製造において、ブタ由来成分（トリプシン）を使用している。

**3.2 製剤の性状

	販売名	ファセンラ皮下注30mgシリンジ	ファセンラ皮下注10mgシリンジ
	剤形	注射剤（プレフィルドシリンジ）	
	色・性状	無色から黄色の澄明又は乳白光を呈する液。 半透明から白色の微粒子を認めることがある。	
	pH	5.5～6.5	
	浸透圧比	約1（生理食塩液に対する比）	

4. 効能又は効果
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難治の患者に限る）

5. 効能又は効果に関連する注意
5.1 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。

5.2 投与前の血中好酸球数が多いほど本剤の気管支喘息増悪発現に対する抑制効果が大きい傾向が認められている。また、データは限られているが、投与前の血中好酸球数が少ない患者では、十分な気管支喘息増悪抑制効果が得られない可能性がある。本剤の作用機序及び臨床試験で認められた投与前の血中好酸球数と有効性の関係を十分に理解し、患者の血中好酸球数を考慮した上で、適応患者の選択を行うこと。[17.1.1参照]

5.3 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ため、急性の発作に対しては使用しないこと。

**6. 用法及び用量
〈ファセンラ皮下注30mgシリンジ〉
通常、成人、12歳以上の小児及び体重35kg以上の6歳以上12歳未満の小児にはベンラリズマブ（遺伝子組換え）として1回30mgを、初回、4週後、8週後に皮下に注射し、以降、8週間隔で皮下に注射する。

〈ファセンラ皮下注10mgシリンジ〉
通常、体重35kg未満の6歳以上12歳未満の小児にはベンラリズマブ（遺伝子組換え）として1回10mgを、初回、4週後、8週後に皮下に注射し、以降、8週間隔で皮下に注射する。

**7. 用法及び用量に関連する注意
10mgシリンジと30mgシリンジの生物学的同等性試験は実施していないため、30mgを投与する際には10mgシリンジを使用しないこと。

8. 重要な基本的注意
8.1 本剤の投与は、気管支喘息の治療に精通している医師のもとで行うこと。

8.2 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に患者に指導すること。

8.3 本剤の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 本剤はヒトインターロイキン-5（IL-5）受容体αサブユニットと結合することにより、好酸球数を減少させる。好酸球は一部の寄生虫（蠕虫）感染に対する免疫応答に関与している可能性がある。患者が本剤投与中に感染し、抗寄生虫薬による治療が無効な場合には、本剤投与の一時中止を考慮すること。[9.1.1参照]

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 寄生虫に感染している患者
本剤の投与開始前に寄生虫感染を治療すること。[8.4参照]

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のみ投与すること。本剤はモノクローナル抗体であり、動物実験（カニクイザル）において本剤は胎盤を通過することが報告されており、妊娠中のカニクイザルにおける曝露量が臨床投与量における曝露量の99.0倍であったときに、出生児で末梢血好酸球の減少が認められたが、出生後180日までに回復した。

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。本剤の乳汁中への移行は不明である。

**9.7 小児等
6歳未満の幼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
重篤な過敏症（頻度不明）
アナフィラキシー（蕁麻疹、血管浮腫、喉頭浮腫、アナフィラキシー反応等）等の重篤な過敏症があらわれることがある。また、過敏症反応の発現が遅れて認められることがある。

11.2 その他の副作用

	1%以上10%未満	0.1%以上1%未満	頻度不明
精神神経系	頭痛		
感染症			咽頭炎（咽頭炎、細菌性咽頭炎、ウイルス性咽頭炎、及びレンサ球菌性咽頭炎）
全身障害	発熱		
投与部位	注射部位反応（疼痛、紅斑、そう痒感、丘疹等）		
過敏症		過敏症反応（蕁麻疹、丘疹状蕁麻疹、及び発疹）	

14. 適用上の注意

14.1 薬剤投与前の注意

**14.1.1 投与30分前に冷蔵庫から取り出し、本剤を外箱に入れたままの状態で室温に戻しておくことが望ましい。

**14.1.2 使用前に不溶性異物や変色がないことを目視により確認すること。不溶性異物又は変色が認められる場合は使用しないこと。

14.2 薬剤投与時の注意

14.2.1 皮膚に圧痛、挫傷、紅斑、硬化がある部位には使用しないこと。

14.2.2 投与部位は、上腕部、大腿部又は腹部とすること。同一箇所へ繰り返し注射することは避け、投与毎に注射部位を変えること。

14.2.3 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

重症喘息患者を対象とした第III相国際共同臨床試験（SIROCCO試験及びCALIMA試験）において、本剤の成人における承認用法・用量で投与を受けた患者の14.9%（122/820例）に抗ベンラリズマブ抗体が認められ、12.0%（98/820例）に中和抗体が認められた。

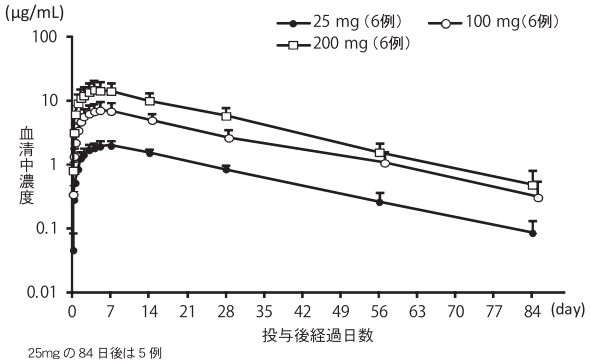
小児の重症喘息患者を対象として薬物動態、薬力学及び長期安全性を評価した第III相国際共同試験（TATE試験）において、6～14歳の患者の13.3%（4/30例）に抗ベンラリズマブ抗体が認められ、4例全てに中和抗体が認められた。抗ベンラリズマブ抗体陽性となった一部の患者では、血清中ベンラリズマブ濃度の低下及び本剤投与後に減少した血中好酸球数の増加が認められた。なお、抗ベンラリズマブ抗体の発現による本剤の有効性及び安全性に対する影響を示唆する成績は得られていない[1),2)]。

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25、100及び200mg[注)]を単回皮下投与したときの血清中濃度推移及び薬物動態パラメータは下記のとおりである[3)]。



25mgの84日後は5例

図1　日本人健康成人における血清中濃度推移（平均値+標準偏差）

表1　日本人健康成人における単回皮下投与時の薬物動態パラメータ

投与量	25mg（6例）	100mg（6例）	200mg（6例）
t_{max}（day）	7.00（4.00, 7.00）	5.00（4.00, 7.00）	4.00（4.00, 7.00）
C_{max}（μg/mL）	1.99±0.34	7.17±2.41	15.0±5.4
$AUC_{0\text{-}t}$（μg・day/mL）	59.10±9.80	203.46±68.78	408.47±131.47
$AUC_{0\text{-}\infty}$（μg・day/mL）	61.33±10.12	211.92±76.02	420.13±136.69
$t_{1/2}$（day）	15.6±3.0	17.4±3.0	15.6±2.6
CL/F（mL/day）	417.68±73.55	528.99±205.52	523.79±180.38
Vz/F（mL）	9,228.1 ±1,299.5	12,930.5 ±4,709.3	11,779.6 ±4,695.4

平均値±標準偏差（t_{max}は中央値（最小値, 最大値））

注）本剤の成人における承認用量は1回30mgである。

日本人小児喘息患者に本剤10及び30mgを単回皮下投与したときの血清中濃度推移及び薬物動態パラメータは下記のとおりである[2)]。

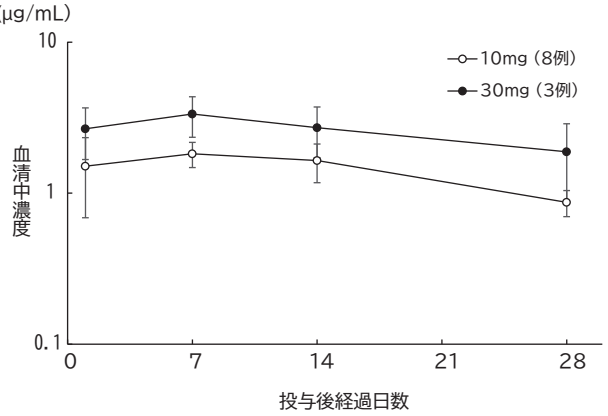


図2　日本人小児喘息患者における血清中濃度推移（平均値±標準偏差）

表2　日本人小児喘息患者における単回皮下投与時の薬物動態パラメータ

投与量	10mg（8例）	30mg（3例）
t_{max}（day）	6.92（0.93, 14.95）	7.94（7.26, 8.13）
C_{max}（μg/mL）	2.02±0.53	3.35±0.76
$AUC_{0\text{-}28}$（μg・day/mL）	39.60±5.49	72.16±21.53

平均値±標準偏差（t_{max}は中央値（最小値, 最大値））、$AUC_{0\text{-}28}$の例数は10mg群5例及び30mg群2例

**16.1.2 反復投与[4),5)]

第III相国際共同試験（CALIMA試験）において、本剤の成人における承認用法・用量で投与を受けた喘息患者（日本人患者を含む）の投与開始後16週及び48週の血清中トラフ濃度（平均値±標準偏差、以下同様）は、それぞれ412±330ng/mL（377例）及び326±267ng/mL（337例）であった。これらの患者のうち、日本人集団における投与開始後16週及び48週の血清中トラフ濃度は、それぞれ452±324ng/mL（26例）及び392±326ng/mL（26例）であった。

16.2 吸収

母集団薬物動態解析の結果、上腕部への皮下投与時の絶対的バイオアベイラビリティは58.9%と推定された[6)]。

16.4 代謝

ベンラリズマブはヒト化IgG1モノクローナル抗体であり、肝臓以外にも広く生体に存在するタンパク質分解機構により消失すると推定される[6)]。

17. 臨床成績

17.1 有効性及び安全性に関する試験

17.1.1 第III相国際共同試験（CALIMA試験）[4),5),7)]（成人及び12歳以上の小児）

中用量又は高用量の吸入ステロイド（ICS）及び長時間作用性β_2刺激薬（LABA）で治療してもコントロール不良の成人又は小児（12歳以上、海外のみ）喘息患者1,306例（日本人患者83例を含む）を対象としたランダム化、プラセボ対照、二重盲検、並行群間比較国際共同試験を実施した。中用量又は高用量ICS/LABAの併用下で、本剤30mg又はプラセボを、4週に1回（Q4W）、又は最初の3回は4週に1回、以降8週に1回（Q8W）、56週間皮下投与した。有効性の主要解析対象集団である高用量ICS/LABAを使用しているベースラインの血中好酸球数が300/μL以上の被験者において、主要評価項目である年間喘息増悪率（モデル調整済み）は、本剤Q8W群、プラセボ群でそれぞれ0.66、0.93であり、プラセボ群と比較して本剤Q8W群で有意に低下した（表3）。

表3　年間喘息増悪率（高用量ICSを使用しているベースラインの血中好酸球数300/μL以上の集団）

	CALIMA試験		参考：SIROCCO試験[注)8)]	
	本剤30mg Q8W群（239例）	プラセボ群（248例）	本剤30mg Q8W群（267例）	プラセボ群（267例）
喘息増悪発現件数（回）	163	270	156	365
総観察期間（人・年）	245.4	261.2	236.1	238.2
年間喘息増悪率（回/人・年）	0.66	1.03	0.66	1.53
年間喘息増悪率[a)]（回/人・年）[95%信頼区間]	0.66 [0.54, 0.82]	0.93 [0.77, 1.12]	0.65 [0.53, 0.80]	1.33 [1.12, 1.58]
プラセボ群との比[a)] [95%信頼区間] p値[a),b)]	0.72 [0.54, 0.95] p=0.019	−	0.49 [0.37, 0.64] p<0.001	−

注）CALIMA試験と同様の対象患者及びデザイン（ただし高用量ICS/LABA併用患者を対象、投与期間は48週間）で実施された海外臨床試験

a)投与群、地域、治験参加前1年間の喘息増悪回数、継続的な経口ステロイド薬の使用の有無を共変量として含む負の二項回帰モデル

b)有意水準は両側4%、検定の多重性はHochbergの方法により調整

有効性の主要解析対象集団のうち、日本人集団における年間喘息増悪率の解析結果を表4に示した。

表4　日本人集団における年間喘息増悪率（高用量ICSを使用しているベースラインの血中好酸球数300/μL以上の集団）

	CALIMA試験	
	本剤30mg Q8W群（15例）	プラセボ群（16例）
喘息増悪発現件数（回）	6	48
総観察期間（人・年）	14.6	16.7
年間喘息増悪率（回/人・年）	0.41	2.87
年間喘息増悪率[a)]（回/人・年）[95%信頼区間]	0.42 [0.15, 1.18]	2.45 [1.23, 4.89]
プラセボ群との比[a)] [95%信頼区間]	0.17 [0.05, 0.60]	−

a)投与群、治験参加前1年間の喘息増悪回数、継続的な経口ステロイド薬の使用の有無を共変量として含む負の二項回帰モデル

また、ベースラインの血中好酸球数別の年間喘息増悪率の部分集団別解析結果は表5のとおりであった。[5.2参照]

表5　ベースラインの血中好酸球数別の年間喘息増悪率のプラセボ群との比（高用量ICSを使用している集団）

		CALIMA試験	参考：SIROCCO試験[9)]
		本剤30mg Q8W群	本剤30mg Q8W群
150/μL未満	症例数（本剤/プラセボ）	50/43	55/79
	プラセボ群との比[a)] [95%信頼区間]	0.65 [0.36, 1.17]	0.70 [0.42, 1.18]
150/μL以上、300/μL未満	症例数（本剤/プラセボ）	73/77	74/60
	プラセボ群との比[a)] [95%信頼区間]	0.57 [0.35, 0.93]	0.99 [0.60, 1.62]
300/μL以上、450/μL未満	症例数（本剤/プラセボ）	85/99	116/106
	プラセボ群との比[a)] [95%信頼区間]	0.89 [0.57, 1.39]	0.57 [0.38, 0.86]
450/μL以上	症例数（本剤/プラセボ）	151/148	147/158
	プラセボ群との比[a)] [95%信頼区間]	0.61 [0.43, 0.86]	0.42 [0.29, 0.59]

a)投与群、地域、治験参加前1年間の喘息増悪回数、継続的な経口ステロイド薬の使用の有無、ベースラインの血中好酸球数カテゴリ、投与群とベースラインの血中好酸球数カテゴリの交互作用を共変量として含む負の二項回帰モデル

本剤30mg Q8W群における副作用発現頻度は12.6%（54/428例）であり、主な副作用は、頭痛1.4%（6/428例）、次いで発熱1.2%（5/428例）であった。

**17.1.2 第III相国際共同試験（TATE試験）[2)]（6歳以上14歳以下の小児）

血中好酸球数が試験開始時に150/μL以上、かつ中用量又は高用量ICS及びLABA等のその他の長期管理薬で治療しても喘息増悪をきたす6～11歳（6～14歳、日本のみ）の小児喘息患者30例（日本人患者11例を含む）を対象とした非盲検、並行群間国際共同試験を実施した[注1)]。中用量又は高用量のICS及びその他の長期管理薬併用下で、本剤10又は30mg[注2)]を、最初の3回は4週に1回（Q4W）、以降の4回は8週に1回（Q8W）、48週間皮下投与した。6～14歳の患者における副作用発現頻度は13.3%（4/30例）であり、報告された副作用は頭痛、疲労、注射部位反応及び消化不良が各3.3%（1/30例）であった。

注1）本試験の目的は、ベンラリズマブ皮下投与時の薬物動態、薬力学及び長期安全性の評価であった。

注2）体重が35kg未満の6～11歳の患者には本剤10mgを投与した。体重が35kg以上の6～11歳の患者又は12～14歳の患者には本剤30mgを投与した。

18. 薬効薬理

18.1 作用機序

本剤は、ヒトインターロイキン-5受容体αサブユニット（IL-5Rα）に特異的かつ高親和性で結合（解離定数：16pM）[10)]する、フコース欠損型ヒト化免疫グロブリンGサブクラス1、κ型アイソタイプ（IgG1κ）モノクローナル抗体である。

18.2 アポトーシス誘導作用

本剤は、Fcドメインのフコース欠損により、ナチュラルキラー細胞等のエフェクター細胞上のFcγRIIIaに高い親和性（解離定数：45.5nM）[11)]を示すために抗体依存性細胞傷害活性が増強され、IL-5Rαを発現する好酸球及び好塩基球のアポトーシスを誘導する[11),12)]。

**18.3 血中好酸球の除去作用

第III相国際共同試験（SIROCCO試験及びCALIMA試験）で、成人における承認用法・用量で本剤を皮下投与したとき、血中好酸球の低下が認められた[7),8)]。同様の血中好酸球の低下が、第III相国際共同試験（TATE試験）で、6～14歳の小児における承認用法・用量で本剤を皮下投与したときにも認められた[2)]。

19. 有効成分に関する理化学的知見

一般的名称

ベンラリズマブ(遺伝子組換え)

Benralizumab (Genetical Recombination)

本質

ベンラリズマブは、遺伝子組換えヒト化モノクローナル抗体であり、マウス抗ヒトインターロイキン-5受容体αサブユニット抗体の相補性決定部、並びにヒトIgG1のフレームワーク部及び定常部からなる。ベンラリズマブは、糖タンパク質6-α-Lフコース転移酵素が欠損したチャイニーズハムスター卵巣細胞により産生される。ベンラリズマブは、451個のアミノ酸残基からなるH鎖(γ1鎖)2本及び214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148,000)である。

20. 取扱い上の注意

20.1 本剤は激しく振とうしないこと。

20.2 本剤は凍結を避け、凍結した場合は使用しないこと。

20.3 光曝露を避けるため、本剤は外箱に入れて保存すること。

****20.4** 冷蔵庫から出した後は30℃以下で保存し、14日以内に使用すること。

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

〈ファセンラ皮下注30mgシリンジ〉

1mL[1キット(注射針(29G)付きプレフィルドシリンジ×1)]

〈ファセンラ皮下注10mgシリンジ〉

0.5mL[1キット(注射針(29G)付きプレフィルドシリンジ×1)]

**23. 主要文献

1)社内資料：Integrated Summary of Immunogenicity

2)社内資料：D3250C00025(TATE試験)(2024年3月26日承認、CTD 2.7.6.2.1)

3)社内資料：4563-002試験(2018年1月19日承認、CTD 2.7.6.2)

4)社内資料：D3250C00018(CALIMA試験)(2018年1月19日承認、CTD 2.7.6.8)

5)社内資料：D3250C00018(CALIMA試験)部分集団解析(日本人データ)(2018年1月19日承認、CTD 2.7.3.3)

6)社内資料：Benralizumab Population Pharmacokinetic Analysis.(2018年1月19日承認、CTD 2.7.2.3)

7)FitzGerald JM, et al. Lancet. 2016;388:2128-41.

8)Bleecker ER, et al. Lancet. 2016;388:2115-27.

9)社内資料：D3250C00017(SIROCCO試験)治験総括報告書

10)社内資料：組換えヒトIL-5Rαに対するベンラリズマブの結合親和性(2018年1月19日承認、CTD 2.6.2.3)

11)Kolbeck R, et al. J Allergy Clin Immunol. 2010;125(6):1344-53.

12)社内資料：ヒト好酸球に対するベンラリズマブのADCCを介したアポトーシス誘導(2018年1月19日承認、CTD 2.6.2.3)

24. 文献請求先及び問い合わせ先

アストラゼネカ株式会社　メディカルインフォメーションセンター

〒530-0011 大阪市北区大深町3番1号

TEL 0120-189-115

https://www.astrazeneca.co.jp

26. 製造販売業者等

26.1 製造販売元

アストラゼネカ株式会社

大阪市北区大深町3番1号

Ⓡ：アストラゼネカグループの登録商標です。

Ⓒ AstraZeneca 2018

AstraZeneca

※　最新の添付文書を参照すること。

添付文書（案）

（下線部：修正箇所）
20xx 年 X 月改訂（第 X 版）
貯法：凍結を避け、2～8℃にて保存
有効期間：36 箇月
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

日本標準商品分類番号
87449

	300mg ペン	300mg シリンジ	200mg ペン	200mg シリンジ
承認番号	30200AMX00926	23000AMX00015	30700AMX00125	30500AMX00261
販売開始	2020 年 11 月	2018 年 4 月	2025 年 11 月	2023 年 12 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

デュピクセント皮下注 300mg ペン
デュピクセント皮下注 300mg シリンジ
デュピクセント皮下注 200mg ペン
デュピクセント皮下注 200mg シリンジ

DUPIXENT® S.C. Injection

（一部）最適使用推進ガイドライン対象品目

DUPIXENT
sanofi REGENERON

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

販売名		デュピクセント皮下注			
		300mg ペン	300mg シリンジ	200mg ペン	200mg シリンジ
成分		1 製剤（2mL）中の分量		1 製剤（1.14mL）中の分量	
有効成分	デュピルマブ（遺伝子組換え）注 1）	300mg		200mg	
添加剤	L-ヒスチジン	5.4mg		3.10mg	
	L-ヒスチジン塩酸塩水和物	1.0mg		0.60mg	
	L-アルギニン塩酸塩	10.5mg		12.01mg	
	酢酸ナトリウム水和物	2.6mg		1.50mg	
	氷酢酸	0.3mg		0.19mg	
	精製白糖	100mg		57.00mg	
	ポリソルベート 80	4mg		2.28mg	

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。

3.2 製剤の性状

販売名	デュピクセント皮下注			
	300mg ペン	300mg シリンジ	200mg ペン	200mg シリンジ
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

300mg ペン、300mg シリンジ
既存治療で効果不十分な下記皮膚疾患
- ○ アトピー性皮膚炎注）
- ○ 結節性痒疹
- ○ 特発性の慢性蕁麻疹
- ○ 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）注）
- ○慢性閉塞性肺疾患（既存治療で効果不十分な患者に限る）注）
- ○ 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）注）

200mg ペン、200mg シリンジ
既存治療で効果不十分な下記皮膚疾患
- ○ アトピー性皮膚炎注）
- ○ 特発性の慢性蕁麻疹
- ○ 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）注）

注）最適使用推進ガイドライン対象

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。［17.1.1-17.1.3 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。

〈結節性痒疹〉

5.4 「17. 臨床成績」の項の内容を熟知し、臨床試験に組み入れられた患者の背景を十分に理解した上で、本剤はステロイド外用剤等による治療を施行しても、痒疹結節を主体とする病変が多発し、複数の部位に及ぶ患者に用いること。［17.1.4 参照］

5.5 最新の診療ガイドライン等を参考に、臨床症状及び全身検索に基づいて他の皮膚疾患との鑑別を行うこと。

〈特発性の慢性蕁麻疹〉

5.6 食物、物理的刺激等の蕁麻疹の症状を誘発する原因が特定されず、ヒスタミン H_1 受容体拮抗薬の増量等の適切な治療を行っても、日常生活に支障をきたすほどの痒みを伴う膨疹が繰り返して継続的に認められる場合に本剤を追加して投与すること。［17.1.5 参照］

〈気管支喘息〉

5.7 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。

5.8 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。[17.1.6-17.1.8 参照]

5.9 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。

〈慢性閉塞性肺疾患〉

5.10 最新のガイドライン等を参考に、長時間作用性β_2刺激薬（LABA）、長時間作用性抗コリン薬（LAMA）及び吸入ステロイド薬（吸入ステロイド薬が禁忌の場合はLABA及びLAMA）の併用療法で全身性ステロイド薬の投与等が必要な増悪をきたす患者に本剤を追加して投与すること。

5.11 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、慢性閉塞性肺疾患の病態に関与する2型炎症反応を抑制することから、本剤投与前の2型炎症に関連するバイオマーカー（血中好酸球数等）を考慮した上で、適応患者の選択を行うこと。[17.1.9 参照]

5.12 本剤は慢性閉塞性肺疾患の症状の長期管理に用いること。本剤は慢性閉塞性肺疾患の増悪時における急性期治療を目的として使用する薬剤ではない。

〈鼻茸を伴う慢性副鼻腔炎〉

5.13 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。

通常、生後6カ月以上の小児にはデュピルマブ（遺伝子組換え）として体重に応じて以下を皮下投与する。

5kg以上15kg未満：1回200mgを4週間隔
15kg以上30kg未満：1回300mgを4週間隔
30kg以上60kg未満：初回に400mg、その後は1回200mgを2週間隔
60kg以上：初回に600mg、その後は1回300mgを2週間隔

〈結節性痒疹〉

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。

〈特発性の慢性蕁麻疹〉

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。

通常、12歳以上の小児にはデュピルマブ（遺伝子組換え）として体重に応じて以下を皮下投与する。

30kg以上60kg未満：初回に400mg、その後は1回200mgを2週間隔
60kg以上：初回に600mg、その後は1回300mgを2週間隔

〈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。

通常、6歳以上12歳未満の小児にはデュピルマブ（遺伝子組換え）として体重に応じて以下を皮下投与する。

15kg以上30kg未満：1回300mgを4週間隔
30kg以上：1回200mgを2週間隔

〈慢性閉塞性肺疾患〉

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。

〈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。

〈アトピー性皮膚炎、特発性の慢性蕁麻疹、気管支喘息〉

7.2 200mgシリンジ又は200mgペンと300mgシリンジ又は300mgペンの生物学的同等性試験は実施していないため、600mgを投与する際には200mgシリンジ又は200mgペンを使用しないこと。

〈特発性の慢性蕁麻疹〉

7.3 臨床試験において、本剤の24週以降の使用経験は無いため、24週以降も継続して投与する場合は、患者の状態を考慮し、その必要性を慎重に判断すること。特に、用法及び用量どおり、24週間使用しても効果が認められない場合には、漫然と投与を続けないよう注意すること。[17.1.5 参照]

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 好酸球増加症があらわれることがあり、特に喘息治療中の患者では好酸球性肺炎、好酸球性多発血管炎性肉芽腫症等の臨床症状を伴う好酸球増加症の発現も認められている。これらは経口ステロイド薬の減量・中止時以外にも認められている。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。[11.1.2 参照]

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又はその保護者が理解し、患者自ら又はその保護者が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又はその保護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又はその保護者に注意を促し、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、慢性閉塞性肺疾患〉

8.9 本剤の投与開始後に症状がコントロール不良又は悪化した場合には、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〉

低出生体重児、新生児及び生後 6 カ月未満の乳児を対象とした臨床試験は実施していない。

〈結節性痒疹、慢性閉塞性肺疾患、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。

〈特発性の慢性蕁麻疹〉

6 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。臨床試験において、6 歳以上 12 歳未満の小児に対する投与経験は極めて限られている。

〈気管支喘息〉

~~12~~6 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。

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、血管性浮腫等があらわれる可能性がある。[8.2 参照]

11.1.2 好酸球増加症（0.9%）

喘息治療中の患者では、好酸球性肺炎（0.1%未満）や好酸球性多発血管炎性肉芽腫症（頻度不明）も報告されている。[8.4 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、口腔ヘルペス、単純ヘルペス	蟯虫症
眼障害		アレルギー性結膜炎、眼瞼炎、眼乾燥	眼そう痒症、角膜炎、潰瘍性角膜炎
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、注射部位疼痛、注射部位硬結、注射部位内出血、注射部位発疹、注射部位皮膚炎	
神経系障害		頭痛	
皮膚および皮下組織障害		発疹	
その他		発熱、関節痛	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 300mg シリンジ及び 300mg ペンは 45 分以上、200mg シリンジ及び 200mg ペンは 30 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。

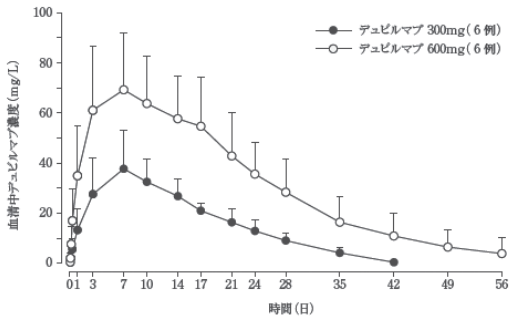
14.2 薬剤投与時の注意
14.2.1 皮下注射は腹部、大腿部又は上腕部に行うこと。腹部へ投与する場合は、へその周り 5cm を外して投与すること。注射部位反応が報告されているので、同一箇所へ繰り返し注射することは避けること。
14.2.2 正常な皮膚の部位に注射すること。皮膚が敏感な部位、皮膚に損傷、打撲や傷のある部位、アトピー性皮膚炎の強い炎症を伴う部位には注射しないこと。
14.2.3 皮膚及び皮下組織の薄い患者に投与する際にはシリンジ製剤を用いること。
14.2.4 他の薬剤と混合しないこと。
14.2.5 本剤は 1 回で全量を使用する製剤であり、再使用しないこと。

15. その他の注意
15.1 臨床使用に基づく情報
本剤を投与したときの抗薬物抗体（ADA）陽性反応発現割合、持続する ADA 陽性反応発現割合及び中和抗体陽性反応発現割合は下表のとおりであった。なお、プラセボ群の ADA 陽性反応発現割合、持続する ADA 陽性反応発現割合及び中和抗体陽性発現割合は、それぞれ約 4%、約 2%及び約 1%であった。高抗体価（10,000 超）の ADA の発現例（発現頻度 1%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。

ADA 陽性反応発現割合、持続する ADA 陽性反応発現割合及び中和抗体陽性反応発現割合

効能		ADA 陽性反応発現割合	持続する ADA 陽性反応発現割合	中和抗体陽性反応発現割合
アトピー性皮膚炎	成人	約 6%	約 2%	約 1%
	12～17 歳	約 16%	約 3%	約 5%
	生後 6 カ月～11 歳	約 2%	0%	約 1%
結節性痒疹		約 8%	約 1%	約 3%
特発性の慢性蕁麻疹		約 7%	約 1%	約 2%
気管支喘息	12 歳以上	約 5%	約 2%	約 2%
	6～11 歳	約 6%	約 3%	約 2%
慢性閉塞性肺疾患		約 8%	約 3%	約 3%
鼻茸を伴う慢性副鼻腔炎		約 5%	約 2%	約 3%

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清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清中濃度推移

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_{last}（mg・day/L）	$t_{1/2z}$ 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）血清中薬物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（成人）
アトピー性皮膚炎、結節性痒疹、特発性の慢性蕁麻疹、気管支喘息、慢性閉塞性肺疾患及び鼻茸を伴う慢性副鼻腔炎患者に本剤 300mg を隔週で反復投与したときのデュピルマブのトラフ濃度（平均値±標準偏差）を効能別に示す[2),6)-8),11),12)]（日本人及び外国人データ）。

デュピルマブのトラフ濃度

効能	例数（名）	トラフ濃度（mg/L）	週
アトピー性皮膚炎	219	73.3±40.0	16
結節性痒疹	65	60.2±34.7	24
特発性の慢性蕁麻疹	62	63.5±34.2	24
気管支喘息	544	69.0±37.8	24
慢性閉塞性肺疾患	427	62.1±34.4	24
鼻茸を伴う慢性副鼻腔炎	142	80.2±35.3	24

16.1.3 反復投与（小児）
小児のアトピー性皮膚炎患者及び気管支喘息患者に本剤を反復投与したときのデュピルマブのトラフ濃度（平均値±標準偏差）を示す[5),10)]（日本人データ）。

デュピルマブのトラフ濃度

体重	用量	例数（名）	トラフ濃度（mg/L）	週
アトピー性皮膚炎				
60 kg 以上	300mg Q2W	3	90.1±26.2	16
30 kg 以上 60 kg 未満	200mg Q2W	14	62.5±29.7	16
15 kg 以上 30 kg 未満	300mg Q4W	7	86.6±29.9	16
5 kg 以上 15 kg 未満	200mg Q4W	3	95.7±38.6	16

気管支喘息				
15 kg 以上 30 kg 以下	300mg Q4W	3	55.2±14.6	24
30 kg 超	200mg Q2W	6	98.3±18.1	24

Q2W：2 週に 1 回投与、Q4W：4 週に 1 回投与

16.1.4 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清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、結節性痒疹、特発性の慢性蕁麻疹、気管支喘息、慢性閉塞性肺疾患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（成人）

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、ステロイド外用剤に上乗せして本剤 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（成人）

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5),注6)]
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7)]	58.8 (60/102)	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7)]	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7)]	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）を因子として考慮した 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 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。［5.1 参照］

17.1.2 国際共同第Ⅲ相単独療法試験（成人）

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1)]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2)]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3)]。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。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4)]及び EASI-75 達成率[注5)]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 1）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 2）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 3）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 4）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 5）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（成人）

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 6), 注 7)]
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 8)]	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 8)]	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 6）地域及びベースライン時の重症度（IGA スコア 3 又は 4）を因子として考慮した Cochran-Mantel-Haenszel 検定（主要有効性評価項目についてのみ）
注 7）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 8）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 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。[5.1 参照]

17.1.3 国内第Ⅲ相試験（生後 6 カ月以上 18 歳未満の小児）
日本の分類でミディアムからストロングクラスのステロイド外用薬で効果不十分な、生後 6 カ月以上 18 歳未満の中等症から重症[注 1)]の日本人 AD 患者 62 例を対象に、ステロイド外用剤に上乗せしてベースライン時の体重に応じて以下の用法・用量で本剤又はプラセボを 16 週間、盲検下で投与した[注 2)]。
・ 体重 5kg 以上 15kg 未満：1 回 200mg を 4 週に 1 回（Q4W）
・ 体重 15kg 以上 30kg 未満：1 回 300mg を Q4W
・ 体重 30kg 以上 60kg 未満：投与 1 日目に初回用量 400mg、その後 200mg を Q2W
・ 体重 60kg 以上：投与 1 日目に初回用量 600mg、その後 300mg を Q2W
ベースライン時の EASI スコアは 25.2±6.8 であった。主要有効性評価項目とした投与後 16 週時点の EASI-75 達成率[注 3)]において、本剤群はプラセボ群に比べ統計的に有意な（P 値：0.0304）改善効果を示した[5)]。

注 1）IGA スコアが 3 以上、EASI スコアが 16 以上、体表面積に占める AD 病変の割合が 10%超、そう痒 NRS スコアの日内最大値の週平均が 4 点以上(12 歳以上 18 歳未満)、痒み NRS スコアの日内最悪値の週平均が 4 点以上（6 歳以上 12 歳未満)、又は掻破／痒み NRS スコアの日内最悪値の週平均が 4 点以上（生後 6 カ月以上 6 歳未満）
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）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・国内第Ⅲ相併用療法試験の成績（小児）

日本人集団	本剤群	プラセボ群	プラセボ群との差 [95%信頼区間] p 値[注 4)]
EASI-75 達成率	43.3 (13/30)	18.8 (6/32)	25.1 [3.26, 46.90] 0.0304

%（例数）
注 4）層別因子（ベースライン時で生後 6 カ月以上 6 歳未満、6 歳以上 12 歳未満かつ IGA スコアが 3、6 歳以上 12 歳未満かつ IGA スコアが 4、12 歳以上）を因子として考慮した Cochran-Mantel-Haenszel 検定

また、投与後 52 週時点（非盲検延長期）における本剤群の EASI-75 達成率は 62.9%であった。
投与 16 週までの本剤群での副作用は 16.7%（5/30 例)、プラセボ群では 9.4%（3/32 例）に認められ、本剤群の主な副作用はアレルギー性結膜炎 6.7%であった。[5.1 参照]

〈結節性痒疹〉
17.1.4 国際共同第Ⅲ相試験
日本の分類でウィークからベリーストロングのステロイド外用薬で効果不十分[注 1)]な、又はステロイド外用薬が推奨されない、18 歳以上の結節性痒疹[注 2)]患者 151 例（日本人患者 16 例を含む）を対象に、本剤 300mg を 2 週に 1 回（Q2W)、又はプラセボを 24 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。主要評価項目である投与後 24 週時点の WI-NRS スコア[注 3)]がベースラインから 4 点以上改善した患者の割合において、本剤群はプラセボ群に比べ統計的に有意な（P<0.0001）改善を示した[6)]。
注 1）ステロイド外用薬を 2 週間使用しても最悪のそう痒スコア（WI-NRS スコア）が週平均で 7 以上、両脚、両腕又は体幹の少なくとも 2 つの体表面領域に合計 20 か所以上の結節性痒疹の病変（IGA PN-S スコアが 3 又は 4 相当）を有する患者
注 2）次の所見に基づき診断；6 週間以上の持続する慢性そう痒がある、繰り返し掻く病歴又は徴候がある、多発性の限局性／全身性痒疹の結節性皮膚病変がある。

投与後 24 週時点の有効性の成績（ITT 集団）

評価項目	本剤群	プラセボ群	プラセボ群との差 [95%信頼区間] p 値[注 4)]
WI-NRS≧4 点改善達成率[注 3)]	60.0 (45/75)	18.4 (14/76)	42.7 (27.76, 57.72) <0.0001

評価項目	本剤群	プラセボ群	プラセボ群との差 [95%信頼区間] p 値[注4)]
IGA PN-S (0 又は 1) 達成率[注3)]	48.0 (36/75)	18.4 (14/76)	28.3 (13.41, 43.16)

注 3) WI-NRS スコア（0-10 点のスケールで評価される過去 24 時間の最悪のそう痒の程度の週平均）；IGA PN-S スコア（0-4 点のスケールで評価される結節性痒疹の病期に関する医師による全般評価）
WI-NRS スコア、IGA PN-S スコアはスコアの減少が改善を意味する。

注 4) アトピーの既往の有無、外用ステロイド薬又は外用カルシニューリン阻害薬の使用の有無、地域及びベースライン時の抗うつ薬使用の有無を因子として考慮した Cochran-Mantel-Haenszel 検定（主要有効性評価項目についてのみ表示）

本剤群での副作用は 14.7%（11/75 例）、プラセボ群では 13.3%（10/75 例）に認められ、本剤群の主な副作用は注射部位反応 4.0%であった。[5.4 参照]

〈特発性の慢性蕁麻疹〉

17.1.5 国際共同第Ⅲ相試験

第二世代ヒスタミン H_1 受容体拮抗薬の使用で効果不十分[注1)]な 6 歳以上の特発性の慢性蕁麻疹患者 138 例（12 歳以上の小児患者 4 名及び 6 歳以上 12 歳未満の小児患者 2 名[注2)]を含む、そのうち 12 名の日本人[いずれも成人]を含む）を対象に、本剤 300mg を 2 週に 1 回（成人及び 60 kg 以上の 12 歳以上の小児患者）又は本剤 200 mg を 2 週に 1 回（60 kg 未満の 12 歳以上の小児患者及び 30 kg 以上の 6 歳以上 12 歳未満の小児患者）、又はプラセボを 24 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（300mg を 2 週に 1 回の場合）又は 400mg（200mg を 2 週に 1 回の場合）の投与を行った。主要評価項目である投与 24 週時における 7 日間のそう痒重症度スコア（ISS7）のベースラインからの変化量（減少）において、本剤群はプラセボ群に比べ統計的に有意な（P＝0.0005）改善効果を示した[7)]。

注 1) ランダム化前の UAS7 及び ISS7 がそれぞれ 16 及び 8 以上を有するオマリズマブの投与歴のない患者

注 2) 6 歳以上 12 歳未満の小児患者はいずれも治験薬投与を早期に中止した

投与 24 週後の ISS7[注3)]の変化量（ITT 集団）

全体集団	本剤群	プラセボ群
ベースライン	16.10±3.98（70）	15.74±4.11（68）
投与 24 週後[注4)]	5.28±5.88（64）	8.06±6.64（53）
ベースラインからの変化量	-10.24[-12.03, -8.46]	-6.01[-7.85, -4.17]
プラセボ群との差[注5)] [95%信頼区間] p 値	-4.23 [-6.63, -1.84] 0.0005	

平均値±標準偏差（例数）又は最小二乗平均値[95%CI]

注 3) 0-3 点のスケールで評価される過去 24 時間のそう痒の程度を毎日同じ時間に記録して 7 日間合計したそう痒重症度スコア（範囲は 0～21）

注 4) 救済治療を受けた患者を含む実測値

注 5) 補完された完全データの各々についてベースライン値、投与群、ベースライン時の血管性浮腫の有無、および地域を共変量とした共分散分析により解析を行った。

本剤投与群での副作用は 14.3%（10/70 例）、プラセボ群では 23.5%（16/68 例）に認められ、本剤群の主な副作用は注射部位紅斑 4.3%、及び注射部位反応 4.3%であった。[5.6、7.3 参照]

〈気管支喘息〉

17.1.6 国際共同第Ⅲ相試験（成人及び 12 歳以上の小児）

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1)]（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 200mg[注2)]又は 300mg[注2)]、もしくはそれぞれと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3)]及び 12 週時点の FEV_1 の変化量[注4)]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[8)]。

注 1) 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 2) 投与開始時には初回用量としてそれぞれ 400mg 又は 600mg を投与

注 3) 52 週間の治験薬投与期間中における重度喘息増悪の年換算発生率

注 4) 投与開始後 12 週時点における気管支拡張薬投与前の FEV_1 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	300mg 群 (633 例)	プラセボ群 (321 例)
総観察期間（人・年）	612.5	313.2
喘息増悪発生件数 (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5)] (回/人・年) [95%信頼区間]	0.524 [0.450, 0.611]	0.970 [0.810, 1.160]
プラセボ群との比[注5)] [95%信頼区間] p 値[注5)]	0.540 [0.430, 0.680] <0.0001	
日本人部分集団	300mg 群 (41 例)	プラセボ群 (17 例)
総観察期間（人・年）	40.2	17.0
喘息増悪発生件数 (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5)] (回/人・年) [95%信頼区間]	0.309 [0.139, 0.687]	1.232 [0.502, 3.025]
プラセボ群との比[注5)] [95%信頼区間]	0.251 [0.072, 0.874]	

注 5) 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 FEV_1（L）の変化量（ITT 集団）

全体集団	300mg 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6)] [95%信頼区間] p 値[注6)]	0.13 [0.08, 0.18] <0.0001	
日本人部分集団	300mg 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6)]［95%信頼区間］	0.17［-0.04，0.37］	

平均値±標準偏差（例数）

注 6）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 週後までの年間重度喘息増悪発生率（ITT 集団）

マーカー	区分（ベースライン時）	重度喘息増悪の年間発生率		プラセボ群との比[注7)]［95%信頼区間］
		300mg 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 300/μL 未満	0.475（175）	0.845（95）	0.557［0.350，0.888］
	300/μL 以上 500/μL 未満	0.496（136）	1.393（68）	0.366［0.225，0.596］
	500/μL 以上	0.413（141）	1.486（74）	0.287［0.184，0.449］
FeNO	25ppb 未満	0.639（317）	0.863（144）	0.792［0.572，1.098］
	25ppb 以上 50ppb 未満	0.489（186）	1.183（97）	0.442［0.282，0.693］
	50ppb 以上	0.485（124）	1.444（75）	0.305［0.188，0.494］
総 IgE 濃度	61IU/mL 未満	0.681（149）	0.792（83）	0.817［0.511，1.307］
	61IU/mL 以上 167IU/mL 未満	0.535（156）	1.344（74）	0.420［0.275，0.641］
	167IU/mL 以上 449IU/mL 未満	0.616（164）	1.008（84）	0.685［0.424，1.106］
	449IU/mL 以上	0.402（157）	1.291（77）	0.375［0.232，0.606］

回/人・年（例数）

注 7）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

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 FEV_1（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8)]［95%信頼区間］
		300mg 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 300/μL 未満	0.22±0.45（168）	0.22±0.36（90）	-0.00［-0.10，0.10］
	300/μL 以上 500/μL 未満	0.36±0.39（131）	0.17±0.39（66）	0.18［0.07，0.30］
	500/μL 以上	0.50±0.45（135）	0.22±0.41（73）	0.30［0.19，0.42］
FeNO	25ppb 未満	0.20±0.37（309）	0.17±0.36（141）	0.03［-0.04，0.10］
	25ppb 以上 50ppb 未満	0.32±0.40（182）	0.18±0.37（94）	0.12［0.03，0.21］
	50ppb 以上	0.59±0.51（113）	0.20±0.48（73）	0.39［0.26，0.52］
総 IgE 濃度	61IU/mL 未満	0.21±0.36（143）	0.19±0.39（78）	0.05［-0.04，0.14］
	61IU/mL 以上 167IU/mL 未満	0.28±0.38（151）	0.23±0.40（73）	0.05［-0.05，0.15］
	167IU/mL 以上 449IU/mL 未満	0.34±0.47（156）	0.08±0.31（83）	0.26［0.15，0.36］
	449IU/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 8）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 FEV_1 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 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。［5.8 参照］

17.1.7 海外第Ⅲ相試験（6 歳以上 12 歳未満の小児）

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 6 歳以上 12 歳未満の気管支喘息患者 408 例[注1)]を対象に、既存治療の併用下で、ベースラインの体重に応じて本剤 100mg（体重 30kg 以下）又は 200mg（体重 30kg 超）[注2)]、もしくはそれぞれと対応するプラセボを Q2W で 52 週間投与した。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3)]で、本剤群はプラセボ群と比べて統計的に有意な効果を示した[9)]。

注 1）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 2）本剤を 6 歳以上 12 歳未満の小児気管支喘息患者に投与する場合の承認用法・用量は、300mg を Q4W 投与（体重 15kg 以上 30kg 未満）及び 200mg を Q2W 投与（体重 30kg 以上）である。

注 3）52 週間の治験薬投与期間中における重度喘息増悪の年換算発生率

投与 52 週後までの年間重度喘息増悪発生率（2 型炎症性喘息集団[注4)] 及び ITT 集団）

対象集団	2 型炎症性喘息集団		ITT 集団	
投与群	本剤群（236 例）	プラセボ群（114 例）	本剤群（273 例）	プラセボ群（135 例）
総観察期間（人・年）	229.6	112.7	266.0	133.9
喘息増悪発生件数（回）	82	81	92	86
年間増悪発生率[注5)]（回/人・年）［95%信頼区間］	0.305［0.223，0.416］	0.748［0.542，1.034］	0.278［0.208，0.372］	0.608［0.447，0.826］
プラセボ群との比[注5)]［95%信頼区間］ p 値[注5,6)]	0.407［0.274，0.605］ <0.0001		0.458［0.313，0.671］ -	

注 4）ベースライン時の血中好酸球数が 150/μL 以上又はベースライン時の FeNO が 20 ppb 以上の患者集団

注 5）投与群、年齢、ベースライン時の体重区分、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 FeNO 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現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

注 6）有意水準両側 5%

投与 12 週後の気管支拡張薬投与前 FEV_1 の予測値に対する割合のベースラインからの変化量及びバイオマーカーの区分別の投与 52 週後までの年間重度喘息増悪発生率は下表のとおりであった。

投与12週後の気管支拡張薬投与前FEV_1の予測値に対する割合のベースラインからの変化量（2型炎症性喘息集団[注7)]及びITT集団）

対象集団	2型炎症性喘息集団		ITT集団	
投与群	本剤群（236例）	プラセボ群（114例）	本剤群（273例）	プラセボ群（135例）
ベースライン	77.66±14.38（236）	78.36±14.51（114）	77.63±14.72（273）	78.98±14.74（135）
投与12週後	87.84±14.65（228）	83.25±15.49（111）	87.81±14.53（264）	83.80±15.36（132）
ベースラインからの変化量	10.26±16.07（228）	4.68±13.13（111）	10.30±16.41（264）	4.62±13.09（132）
プラセボ群との差[注8,9)]［95%信頼区間］	5.21［2.14, 8.27］		4.68［1.87, 7.49］	

平均値±標準偏差（例数）又は最小二乗平均値

注7）ベースライン時の血中好酸球数が150/μL以上又はベースライン時のFeNO が20 ppb以上の患者集団

注8)投与群、ベースラインの体重区分、地域、民族、ベースラインの好酸球数区分、ベースラインのFeNO区分、ベースラインのICS用量、評価時点、ベースライン値と評価時点の交互作用、ベースラインのFEV_1の予測値に対する割合及び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。

注9）有意水準両側5%

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

マーカー	区分（ベースライン時）	重度喘息増悪の年間発生率[注10)] 本剤群	重度喘息増悪の年間発生率[注10)] プラセボ群	プラセボ群との比[注10)]［95%信頼区間］
血中好酸球数	150/μL未満	0.178（50）	0.113（27）	1.568［0.509, 4.833］
	150/μL以上300/μL未満	0.297（48）	0.705（24）	0.422［0.205, 0.871］
	300/μL以上500/μL未満	0.205（49）	0.550（36）	0.373［0.169, 0.819］
	500/μL以上	0.249（126）	0.749（48）	0.332［0.177, 0.622］
FeNO	20ppb未満	0.274（124）	0.465（69）	0.591［0.338, 1.032］
	20ppb以上35ppb未満	0.292（63）	0.453（37）	0.646［0.290, 1.436］
	35ppb以上	0.215（78）	0.814（25）	0.264［0.134, 0.522］
総IgE濃度	100IU/mL未満	0.048（55）	0.101（36）	0.474［0.174, 1.288］
	100IU/mL以上	0.278（212）	0.660（97）	0.422［0.280, 0.635］

回/人・年（例数）

注10）投与群、年齢、ベースライン時の体重区分、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FeNO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

本剤群での副作用は21.8%（59／271例）、プラセボ群では15.7%（21/134例）に認められ、本剤群の主な副作用は注射部位紅斑12.9%、注射部位浮腫 10.3%、注射部位結節 6.3%であった。［5.8参照］

17.1.8 国内第Ⅲ相試験（6歳以上12歳未満の小児）

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6歳以上12歳未満の日本人気管支喘息患者[注1)]13例を対象に、既存治療の併用下で、ベースライン時の体重に応じて以下の用法・用量[注2)]で本剤を52週間投与した。

・体重15kg以上30kg未満：1回100mgをQ2W又は1回300mgをQ4W

・体重30kg以上：1回200mgをQ2W

主要有効性評価項目とした12週時点のFEV_1の予測値に対する割合のベースラインからの変化量[注3)]は下表のとおりであった[10)]。

注1)スクリーニング時の血中好酸球数が150/μL以上又はFeNO が20 ppb以上の患者を対象とし、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2）本剤を6歳以上12歳未満の小児気管支喘息患者に投与する場合の承認用法・用量は、300mgをQ4W投与（体重15kg以上30kg未満）及び200mgをQ2W投与（体重30kg以上）である。

注3）投与開始後12週時点における気管支拡張薬投与前のFEV_1の予測値に対する割合のベースラインからの変化量

投与12週後の気管支拡張薬投与前FEV_1の予測値に対する割合のベースラインからの変化量（ITT集団）

投与例／投与群	本剤（13例）	100mg Q2W群（3例）	300mg Q4W群（3例）	200mg Q2W群（7例）
ベースライン	87.00±8.01（13）	89.67±9.02（3）	83.67±5.51（3）	87.29±9.05（7）
投与12週後	94.08±6.33（13）	97.00±4.58（3）	89.67±2.52（3）	94.71±7.52（7）
ベースラインからの変化量［95%CI］	7.08±6.78（13）［2.98, 11.17］	7.33±4.51（3）［−3.87, 18.53］	6.00±4.36（3）［−4.83, 16.83］	7.43±8.83（7）［−0.74, 15.59］

平均値±標準偏差（例数）

投与52週後までの重度喘息増悪の発生状況は下表のとおりであった。

投与52週後までの重度喘息増悪の発生状況

投与例／投与群		本剤（13例）	100 mg Q2W群（3例）	300 mg Q4W群（3例）	200 mg Q2W群（7例）
総観察期間（人･年）		13.0	3.0	3.0	7.0
喘息増悪発生例数（%）	0回	10（76.9）	3（100）	2（66.7）	5（71.4）
	1回	1（7.7）	0	0	1（14.3）
	2回	1（7.7）	0	0	1（14.3）
	3回	1（7.7）	0	1（33.3）	0
	≧4回	0	0	0	0
年間増悪発現率（回/人･年）[注4)]		0.462	0	1.001	0.430

注4）喘息増悪発現件数は総観察期間で除した数値

副作用は30.8%（4/13例）に認められ、発熱（2例）、並びに口腔ヘルペス、好酸球増加症、注射部位紅斑及び注射部位硬結（各1例）であった。［5.8 参照］

〈慢性閉塞性肺疾患〉

17.1.9 国際共同第Ⅲ相試験

LABA、LAMA及び吸入ステロイド薬（吸入ステロイド薬が禁忌の場合はLABA及びLAMA）の併用療法で効果不十分[注1)]な、40歳以上の慢性閉塞性肺疾患患者931例（日本人患者13例を含む）を対象に、既存治療の併用下で、本剤300mgを2週に1回、又はプラセボを52週間投与した。主要評価項目である中等度又は重度の慢性閉塞性肺疾患増悪イベントの年間発現率[注2)]におい

て、本剤群はプラセボ群と比べて統計的に有意な効果を示した（P 値：0.0005）[11]。

注 1）気管支拡張薬投与後の FEV_1／努力肺活量比が 0.70 未満かつ気管支拡張薬投与後の FEV_1 が予測値の 30%超 70%以下の気流閉塞、組入れ前の 1 年以内に中等度の増悪が 2 回以上又は重度の増悪が 1 回以上かつ MRC 息切れスケールで Grade 2 以上、スクリーニング時の血中好酸球数が 300/μL 以上の患者

注 2）中等度の増悪は全身性ステロイド薬及び／又は抗菌薬の投与を必要とする増悪イベント、重度の増悪は入院若しくは救急治療部／救急処置室での 24 時間を超える観察を必要とする、又は死亡に至った増悪イベント

投与 52 週後までの中等度又は重度の慢性閉塞性肺疾患増悪イベントの年間発現率（ITT 集団）

	本剤 （463 例）	プラセボ群 （468 例）
総観察期間（人・年）	453.1	451.8
増悪発生件数（回）	296	422
年間増悪発生率[注3] （回/人・年）	0.65	0.93
年間増悪発生率[注4] （回/人・年） ［95.1%信頼区間］	0.788 ［0.655，0.949］	1.113 ［0.941，1.316］
プラセボ群との比[注5] ［95.1%信頼区間］ p 値[注5]	0.708 ［0.583，0.861］ 0.0005	

注 3）52 週間の治験薬投与期間中に発生した増悪イベントの総数を、52 週間の治療期間中に追跡された患者人年の総数で割ったもの

注 4）52 週間の治験薬投与期間中に発現した増悪イベントの総数を目的変数とし、投与群、地域、ICS 用量、スクリーニング時の喫煙状況、ベースライン時の疾患重症度、試験開始前 1 年以内の中等度から重度の COPD 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

注 5）有意水準両側 4.9%

気管支拡張薬投与前 FEV_1（L）の変化量（ITT 集団）

		本剤群	プラセボ群
ベースライン		1.28±0.45（462）	1.32±0.46（468）
投与 12 週後		1.43±0.55（444）	1.38±0.51（437）
	ベースラインからの変化量	0.14±0.37（444）	0.06±0.30（437）
	プラセボ群との差[注6] ［95%信頼区間］	0.080 ［0.038，0.122］	
投与 52 週後		1.44±0.57（421）	1.39±0.53（418）
	ベースラインからの変化量	0.14±0.39（421）	0.05±0.32（418）
	プラセボ群との差[注6] ［95%信頼区間］	0.076 ［0.031，0.121］	

平均値±標準偏差（例数）

注 6）12 週後又は 52 週後の気管支拡張薬投与前 FEV_1（L）の変化量を目的変数とし、投与群、年齢、性別、身長、地域、ICS 用量、スクリーニング時の喫煙状況、評価時点、投与群と評価時点の交互作用、ベースライン時の気管支拡張薬投与前 FEV_1、FEV_1 の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

本剤群での副作用は 7.5%（35/464 例）、プラセボ群では 3.9%（18/467 例）に認められ、本剤群で最も多く見られた副作用は注射部位反応 1.5%であった。［5.11 参照］

〈鼻茸を伴う慢性副鼻腔炎〉

17.1.10 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1]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 300mg 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）[12]。

注 1）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

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6] （295 例）	プラセボ群 （153 例）
投与後 24 週時点	鼻茸スコア[注2]	投与前[注3]	6.18	5.96
		変化量[注4]	-1.71	0.10
		プラセボ群との差［95%信頼区間］[注5]	-1.80 ［-2.10，-1.51］	
	鼻閉重症度[注2]	投与前[注3]	2.46	2.38
		変化量[注4]	-1.25	-0.38
		プラセボ群との差［95%信頼区間］[注5]	-0.87 ［-1.03，-0.71］	
	LMK スコア[注2]	投与前[注3]	18.12	17.65
		変化量[注4]	-5.21	-0.09
		プラセボ群との差［95%信頼区間］[注5]	-5.13 ［-5.80，-4.46］	
	UPSIT[注2]	投与前[注3]	13.53	13.78
		変化量[注4]	9.71	-0.81
		プラセボ群との差［95%信頼区間］[注5]	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 52 週時点	鼻茸スコア[注2]	投与前[注3]	6.07	6.29	5.96
		変化量[注4]	-2.24	-2.06	0.15
		プラセボ群との差［95%信頼区間］[注5]	-2.40 ［-2.77，-2.02］	-2.21 ［-2.59，-1.83］	
	鼻閉重症度[注2]	投与前[注3]	2.48	2.44	2.38
		変化量[注4]	-1.35	-1.48	-0.37
		プラセボ群との差［95%信頼区間］[注5]	-0.98 ［-1.17，-0.79］	-1.10 ［-1.29，-0.91］	
	LMK スコア[注2]	投与前[注3]	18.42	17.81	17.65
		変化量[注4]	-6.83	-5.60	0.11
		プラセボ群との差［95%信頼区間］[注5]	-6.94 ［-7.87，-6.01］	-5.71 ［-6.64，-4.77］	
	UPSIT[注2]	投与前[注3]	13.46	13.60	13.78
		変化量[注4]	9.53	9.99	-0.77
		プラセボ群との差	10.30 ［8.50，12.10］	10.76 ［8.95，12.57］	

		［95%信頼区間］ 注5)			

注2）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3）平均値
注4）調整平均
注5）WOCF法及び多重代入法を合わせた混成手法により、投与群、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6）Q2W群とQ2W-Q4W群の併合

本剤Q2W群での副作用は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。

17.1.11 国内第IV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1)]な、18歳以上の日本人の鼻茸を伴う慢性副鼻腔炎患者25例を対象に、鼻噴霧用ステロイド薬非併用下で本剤300mgを2週に1回、52週間投与した。なお、投与16週及び24週の両時点の鼻茸スコアがベースラインから2点以上改善した被験者では、投与24週以降、本剤300mgを4週に1回投与に変更することが許容された。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がベースラインから1点以上改善した被験者の割合は92.0%（23/25例）であった[13)]。

注1）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

ベースラインからの変化量

評価項目		本剤群（25例）
鼻茸スコア[注2)]	投与前	6.4±1.4
	投与24週時点の変化量[注3)]	-2.4±1.7
	投与52週時点の変化量[注3)]	-2.2±2.0[注4)]
鼻閉重症度[注2)]	投与前	2.7±0.6
	投与24週時点の変化量[注3)]	-1.6±1.1
	投与52週時点の変化量[注3)]	-1.8±1.2[注4)]
LMKスコア[注2)]	投与前	18.3±4.2
	投与24週時点の変化量[注3)]	-5.6±4.5
	投与52週時点の変化量[注3)]	-7.0±4.4[注4)]

平均値±標準偏差
注2）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）
スコアの減少が改善を意味する。
注3）WOCF法及び多重代入法を合わせた混成手法により解析した。
注4）投与24週以降、本剤300mgを4週に1回投与に変更した3例の成績を含む。

副作用は8%（2/25例）に認められ、頭部不快感（1件）、鼻痛（1件）及び注射部位紅斑（1件）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、結節性痒疹、特発性の慢性蕁麻疹、気管支喘息、慢性閉塞性肺疾患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[14)]。

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-4Rα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[14)]。

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-4Rα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[14)]。

19. 有効成分に関する理化学的知見
一般的名称：
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（γ4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 冷蔵庫から取り出した後は、外箱に入れたまま25℃以下で保存し、14日以内に使用すること。
20.2 外箱開封後は遮光して保存すること。
20.3 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
〈デュピクセント皮下注300mgペン〉
2mL×1本
〈デュピクセント皮下注300mgシリンジ〉
2mL×1本
〈デュピクセント皮下注200mgペン〉
1.14mL×1本
〈デュピクセント皮下注200mgシリンジ〉

1.14mL×1 本

23. 主要文献

1) 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）
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）
3) 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）
4) Simpson E L,et al.: N Engl J Med.2016; 375 (24) : 2335-48
5) 社内資料：生後 6 カ月以上 18 歳未満のアトピー性皮膚炎患者を対象とした国内第Ⅲ相併用療法試験（2023 年 9 月 25 日承認、審査報告書 p.8-11）
6) 社内資料：結節性痒疹患者を対象とした国際共同第Ⅲ相試験（2023 年 6 月 26 日承認、審査報告書 p.8-9）
7) 社内資料：特発性の慢性蕁麻疹患者を対象とした国際共同第Ⅲ相試験（2024 年 2 月 9 日承認、審査報告書 p.7-9）
8) 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）
9) 社内資料：6 歳以上 12 歳未満の気管支喘息患者を対象とした海外第Ⅲ相試験
10) 社内資料：6 歳以上 12 歳未満の気管支喘息患者を対象とした国内第Ⅲ相試験
11) 社内資料：慢性閉塞性肺疾患患者を対象とした国際共同第Ⅲ相試験（2025 年 3 月 27 日承認、審査報告書 p.8-10）
12) Bachert C,et al.: Lancet. 2019; 394 (10209) : 1638-50
13) 社内資料：鼻茸を伴う慢性副鼻腔炎患者を対象とした国内第Ⅳ相試験
14) 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

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26.2 販売提携

リジェネロン・ジャパン株式会社

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）

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）

[設定根拠]

本申請は現在承認されているデュピルマブの気管支喘息（喘息）に対する効能・効果に、6 歳以上 12 歳未満の小児に対する用法・用量の追加を目的としたものである。日本人小児喘息患者に対するデュピルマブの有効性及び安全性は、既存治療ではコントロール不良の中等症から重症の喘息を有する 6 歳以上 12 歳未満の小児患者を対象とした海外第 3 相試験（EFC14153 試験）、国際共同第 3 相試験（LTS14424 試験）main study 及び Japan substudy に基づき評価した。

EFC14153 試験はコントロール不良の持続型喘息を有する 6 歳以上 12 歳未満の小児を対象とした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、プラセボ対照、並行群間比較試験であった。デュピルマブは主要評価項目である重度喘息増悪の年間発生率をプラセボと比較して有意に低下させた。2 型炎症性喘息フェノタイプ集団では、多重性を調整した 52 週間のランダム化治験薬投与期間中の重度喘息増悪の年間発生率は、デュピルマブ群で 0.305、プラセボ群で 0.748 であり、プラセボに対する相対リスク減少は 59.3%であった（$p<0.0001$）。また、重要な副次有効性評価項目である Week 12 における気管支拡張薬投与前の FEV_1 の予測値に対する割合について、最小二乗平均のプラセボ群との差は、2 型炎症性喘息フェノタイプ集団で 5.21%（95%信頼区間［CI］：2.14%、8.27%、$p = 0.0009$）であった。肺機能の改善は迅速で、気管支拡張薬投与前の FEV_1 の予測値に対する割合への効果は投与開始後の最初の評価時点である Week 2 という早期に見られ、52 週間のランダム化治験薬投与期間を通して持続した。

LTS14424 試験 main study は、国際共同、多施設、非盲検、単群、1 年間投与試験であった。EFC14153 試験（先行試験）の完了後に最長 1 年間デュピルマブを継続投与された被験者における重度喘息増悪の発生率は低いことが示され、全曝露集団における重度喘息増悪の無調整年間発生率は 0.118 であった。デュピルマブ投与により、先行試験のベースラインと比較して肺機能の持続的な改善も示された。最大の解析対象集団では、先行試験の Week 2 において気管支拡張薬投与前の FEV_1 の予測値に対する割合の平均値がベースラインから＋10.01%改善し、デュピルマブ／デュピルマブ群ではその改善が 52 週間の治験薬投与期間にわたって持続した。

LTS14424 試験 Japan substudy は、コントロール不良の中等症から重症の喘息を有する 6 歳以上 12 歳未満の日本人小児患者を対象に、52 週間にわたるデュピルマブ皮下投与を評価する進行中の多施設、非盲検、単群、1 年間投与試験である。主要評価項目とした Week 12 における気管支拡張薬投与前の FEV_1 の予測値に対する割合のベースラインからの変化量の平均値は 7.92%であり、改善が認められた（表 1）。副次的評価項目である 52 週間の治験薬投与期間中の重度喘息増悪の無調整年間発生率は 0.556 であった（表 2）。

表 1 - 投与 12 週後の気管支拡張薬投与前%FEV_1 の変化量（ITT 集団）

日本人集団	本剤群 （13 例）
ベースライン	87.00%
投与 12 週後	94.92%
ベースラインからの変化量	7.92%

表 2 -投与 52 週後までの年間重度喘息増悪発生率（ITT 集団）

日本人集団	本剤群 （13 例）
総観察期間（人・年）*	10.7
喘息増悪発現件数（回）*	6
年間増悪発生頻度（回/人・年）	0.556

*: 52 週時のデータに基づき更新予定

LTS14424 試験 Japan substudy の結果から、EFC14153 試験及び LTS14424 試験 main study の結果との類似性が示され、6 歳以上 12 歳未満の小児喘息患者におけるデュピルマブの有効性が確認された。

2　「用法及び用量」（案）

通常、6 歳以上 12 歳未満の小児にはデュピルマブ（遺伝子組換え）として体重に応じて以下を皮下投与する。

15kg 以上 30kg 未満：1 回 300mg を 4 週間隔

30kg 以上：1 回 200mg を 2 週間隔

[設定根拠]

本申請における用法及び用量（案）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、小児喘息患者を対象とした海外第 3 相試験（EFC14153 試験）、国際共同第 3 相試験（LTS14424 試験）main study 及び Japan substudy 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　臨床試験で用いた用法及び用量

臨床試験におけるデュピルマブの用法・用量は、体重が 30 kg 超の小児に対しては、EFC14153 試験及び LTS14424 試験ともに 200 mg q2w 皮下投与であった。一方、体重が 30 kg 以下の小児に対しては、EFC14153 試験及び LTS14424 試験 main study の開始時は 100 mg q2w 皮下投与であったが、LTS14424 試験 main study では治験実施中に体重が 30 kg 以下の小児に対して 300 mg q4w 皮下投与が追加された。LTS14424 試験 Japan substudy では、LTS14424 試験 main study と同様の用法・用量を用いることとし、体重が 15 kg 以上 30 kg 以下の小児に対してはデュピルマブ 100 mg q2w 及び 300 mg q4w、体重が 30 kg 超の小児に対してはデュピルマブ 200 mg q2w を検討した。

2.2　6 歳以上 12 歳未満の小児喘息患者に対する用法及び用量の設定根拠

申請用法・用量は、臨床試験結果及び日本で既承認の小児 AD 患者に対するデュピルマブの用法・用量（体重 15 kg 以上 30 kg 未満の小児：300 mg q4w、体重 30 kg 以上 60 kg 未満の小児：200 mg q2w［初回用量 400 mg］）に基づいて選択された。LTS14424 試験 Japan substudy では、体重が 15 kg 以上 30 kg 以下の被験者に対して 300 mg q4w 及び 100 mg q2w の 2 つの用法・用量を評価したが、投与頻度の低減により患者の負担を軽減し、同じ年齢層／体重区分の AD 患者に対する承認用法・用量と一致させることで小児喘息患者の用法・用量の選択が複雑になることを回避し、また海外での現在の承認用法・用量と合わせるために、体重が 15 kg 以上 30 kg 未満の小児喘息患者に対する申請用法・用量を 300 mg q4w のみとした。

海外の一部の国／地域では、日本での申請用法・用量に加えて、体重が 15 kg 以上 30 kg 未満の小児に対し 100 mg q2w、体重が 30 kg 以上 60 kg 未満の小児に対し 300 mg q4w（米国では未承認）が承認された。なお、100 mg 製剤は世界全体で販売を中止し、対応する 100 mg q2w の用法・用量も承認を取り下げている。

2.2.1 海外での 6 歳以上 12 歳未満の小児喘息患者に対する用法及び用量の設定根拠

デュピルマブ 100 mg q2w 及び 200 mg q2w 投与は、EFC14153 試験及び LTS14424 試験 main study で認められた臨床的有効性及び安全性によって支持された。体重が 15 kg 以上 60 kg 未満の小児に対する 300 mg q4w 投与は、LTS14424 試験 main study の体重が 30 kg 以下の患者で観察された限られた臨床データ、6 歳以上 12 歳未満の小児喘息患者を対象とした Pop PK 解析及び E-R 解析、及び成人・思春期の喘息患者における PK、PK/PD 関係及び安全性プロファイルとともに、6 歳以上 12 歳未満の小児 AD 患者における 300 mg q4w 投与時の許容可能な安全性プロファイルによって支持された。300 mg q4w は、6 歳以上 12 歳未満の小児 AD 患者集団において許容可能な安全性及び有効性のプロファイルが示されており、AD に対する承認用法・用量に含まれている。

2.2.2 日本での 6 歳以上 12 歳未満の小児喘息患者に対する用法及び用量の設定根拠

LTS14424 試験 Japan substudy において、6 歳以上 12 歳未満の日本人小児喘息患者は、EFC14153 試験と同様の PK プロファイル、PD バイオマーカー反応（FeNO 及び血清中総 IgE）及び PK/PD 関係（気管支拡張薬投与前の FEV_1 の予測値に対する割合）を示した。このことより、6 歳以上 12 歳未満の日本人小児喘息患者に対する申請用法・用量を裏付けるために日本人以外の患者のデータを使用できることが支持された。

LTS14424 試験 Japan substudy では、デュピルマブ 200 mg q2w 及び 300 mg q4w 投与により、コントロール不良の喘息を有する 6 歳以上 12 歳未満の日本人小児患者において重度喘息増悪の年間発生率の顕著な低下、並びに肺機能及び喘息コントロール（ACQ-7-IA）の改善が示された。

また、コントロール不良の喘息を有する 6 歳以上 12 歳未満の日本人小児患者におけるデュピルマブ 200 mg q2w 及び 300 mg q4w 投与の忍容性は良好であり、許容可能な安全性プロファイルが示された。これは EFC14153 試験での結果とおおむね同様であった。体重が 15 kg 以上 30 kg 未満の小児に対する 300 mg q4w 投与を含むデュピルマブの安全性は、第 3 相 EFC16823 試験で喘息の合併症を有していた 6 歳以上 12 歳未満の日本人小児 AD 患者において確認されている。

2.3 結論

LTS14424 試験 Japan substudy では、デュピルマブ 200 mg q2w 及び 300 mg q4w 投与により、6 歳以上 12 歳未満の日本人小児喘息患者において有益な投与効果及び許容可能な安全性プロファイルが示された。また LTS14424 試験 Japan substudy で示された結果が EFC14153 試験とおおむね同様であり、6 歳以上 12 歳未満の日本人小児喘息患者に対する申請用法・用量を裏付けるために日本人以外の患者のデータを使用できることが支持されたことで、海外の承認用法・用量と同様のベネフィット・リスクプロファイルが日本人小児喘息患者においても示されることが期待できることから、上記の用法・用量とした。

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]

現行添付文書から変更はない。

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]

現行添付文書から変更はない。

5　効能又は効果に関連する注意

（省略）

〈気管支喘息〉

5.7　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。

5.8　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。［17.1.6-17.1.8 参照］

5.9　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。

（省略）

[設定根拠]

現行添付文書から変更はない。

7　用法及び用量に関連する注意

（省略）

〈アトピー性皮膚炎、特発性の慢性蕁麻疹、気管支喘息〉

7.3　200mg シリンジ又は 200mg ペンと 300mg シリンジ又は 300mg ペンの生物学的同等性試験は実施していないため、600mg を投与する際には 200mg シリンジ又は 200mg ペンを使用しないこと。

（省略）

[設定根拠]

7.3　気管支喘息でも 6 歳以上 12 歳未満の小児では 200 mg 製剤を用いることがあるため、当該注意事項の対象に気管支喘息を追加した。

その他は現行添付文書から変更はない。

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　好酸球増加症があらわれることがあり、特に喘息治療中の患者では好酸球性肺炎、好酸球性多発血管炎性肉芽腫症等の臨床症状を伴う好酸球増加症の発現も認められている。これらは経口ステロイド薬の減量・中止時以外にも認められている。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。［11.1.2 参照］

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又はその保護者が理解し、患者自ら又はその保護者が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又はその保護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又はその保護者に注意を促し、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〉

（省略）

〈気管支喘息、慢性閉塞性肺疾患〉

8.9　本剤の投与開始後に症状がコントロール不良又は悪化した場合には、医師の診療を受けるよう患者に指導すること。

（省略）

[設定根拠]

8.4　臨床症状を伴う好酸球増加症に関する注意として記載を修正した。

その他は現行添付文書から変更はない。

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

（省略）

〈気管支喘息〉
6 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。

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]

9.7　6 歳以上 12 歳未満の気管支喘息患者を対象とした臨床試験を実施したため、記載を修正した。
その他は現行添付文書から変更はない。

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、血管性浮腫等があらわれる可能性がある。［8.2 参照］

11.1.2 好酸球増加症（0.9%）
喘息治療中の患者では、好酸球性肺炎（0.1%未満）や好酸球性多発血管炎性肉芽腫症（頻度不明）も報告されている。［8.4 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、口腔ヘルペス、単純ヘルペス	蟯虫症
眼障害		アレルギー性結膜炎、眼瞼炎、眼乾燥	眼そう痒症、角膜炎、潰瘍性角膜炎
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、注射部位疼痛、注射部位硬結、注射部位内出血、注射部位発疹、注射部位皮膚炎	
神経系障害		頭痛	
皮膚および皮下組織障害		発疹	
その他		発熱、関節痛	血清病、血清病様反応

[設定根拠]

11.1　11.1.2 として好酸球増加症を追記した。

11.2　本剤の CCDS 及び 6 歳以上 12 歳未満の気管支喘息患者を対象とした臨床試験を加えた集計を踏まえ設定した。なお、好酸球増加症は 11.1.2 の追記に伴い削除した。

14　適用上の注意

14.1　薬剤投与前の注意
14.1.1 投与前に 300mg シリンジ及び 300mg ペンは 45 分以上、200mg シリンジ及び 200mg ペンは 30 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 皮膚及び皮下組織の薄い患者に投与する際にはシリンジ製剤を用いること。
14.2.4 他の薬剤と混合しないこと。
14.2.5 本剤は 1 回で全量を使用する製剤であり、再使用しないこと。

[設定根拠]
現行添付文書から変更はない。

15　その他の注意

15.1　臨床使用に基づく情報

本剤を投与したときの抗薬物抗体（ADA）陽性反応発現割合、持続する ADA 陽性反応発現割合及び中和抗体陽性反応発現割合は下表のとおりであった。なお、プラセボ群の ADA 陽性反応発現割合、持続する ADA 陽性反応発現割合及び中和抗体陽性発現割合は、それぞれ約 4%、約 2%及び約 1%であった。高抗体価（10,000 超）の ADA の発現例（発現頻度 1%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。

ADA 陽性反応発現割合、持続する ADA 陽性反応発現割合及び中和抗体陽性反応発現割合

効能		ADA 陽性反応発現割合	持続する ADA 陽性反応発現割合	中和抗体陽性反応発現割合
アトピー性皮膚炎	成人	約 6%	約 2%	約 1%
	12～17 歳	約 16%	約 3%	約 5%
	生後 6 カ月～11 歳	約 2%	0%	約 1%
結節性痒疹		約 8%	約 1%	約 3%
特発性の慢性蕁麻疹		約 7%	約 1%	約 2%
気管支喘息	12 歳以上	約 5%	約 2%	約 2%
	6～11 歳	約 6%	約 3%	約 2%
慢性閉塞性肺疾患		約 8%	約 3%	約 3%
鼻茸を伴う慢性副鼻腔炎		約 5%	約 2%	約 3%

[設定根拠]

小児気管支喘息患者における結果を追加し、表形式での提示に変更した。

サノフィ株式会社

デュピルマブ（遺伝子組換え）

1.10 毒薬・劇薬等の指定審査資料のまとめ（小児気管支喘息）

Total number of pages: 7

毒薬・劇薬等の指定審査資料のまとめ

現行

化学名・別名	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（γ4 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． （別名：デュピルマブ（遺伝子組換え））
構造式	別紙の通り
効能・効果	既存治療で効果不十分な下記皮膚疾患 アトピー性皮膚炎 結節性痒疹 特発性の慢性蕁麻疹 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） 慢性閉塞性肺疾患（既存治療で効果不十分な患者に限る） 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）
用法・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。 通常、生後 6 カ月以上の小児にはデュピルマブ（遺伝子組換え）として体重に応じて以下を皮下投与する。 5kg 以上 15kg 未満：1 回 200mg を 4 週間隔 15kg 以上 30kg 未満：1 回 300mg を 4 週間隔 30kg 以上 60kg 未満：初回に 400mg、その後は 1 回 200mg を 2 週間隔 60kg 以上：初回に 600mg、その後は 1 回 300mg を 2 週間隔 〈結節性痒疹〉 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。 〈特発性の慢性蕁麻疹〉

<table>
<tr><td></td><td>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。

通常、12 歳以上の小児にはデュピルマブ（遺伝子組換え）として体重に応じて以下を皮下投与する。

30kg 以上 60kg 未満：初回に 400mg、その後は 1 回 200mg を 2 週間隔

60kg 以上：初回に 600mg、その後は 1 回 300mg を 2 週間隔

〈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。

〈慢性閉塞性肺疾患〉

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。

〈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。</td></tr>
<tr><td>劇薬等の指定</td><td>劇薬（原体、製剤）、生物由来製品、処方箋医薬品</td></tr>
<tr><td>市販名及び有効成分・分量</td><td>原体：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、同皮下注 300mg ペン
1 製剤（2.0mL）中にデュピルマブ（遺伝子組換え）300mg 含有
デュピクセント皮下注 200mg シリンジ、同皮下注 200mg ペン
1 製剤（1.14mL）中にデュピルマブ（遺伝子組換え）200mg 含有</td></tr>
<tr><td>毒性</td><td>デュピルマブはヒト IL-4Rα への特異性が高く、サル IL-4Rα への親和性が低いため、サル相同抗体 REGN646 を用いて毒性を評価した。

急性（反復投与試験の初回投与時の成績を参考にした）：
<table>
<tr><td>動物種</td><td>投与経路（評価に用いた試験）</td><td>概略の致死量（mg/kg）</td></tr>
<tr><td rowspan="2">サル</td><td>静脈内（5 週間反復投与試験）</td><td>> 100</td></tr>
<tr><td>皮下（13 週間反復投与試験）</td><td>> 100</td></tr>
</table>
亜急性：
<table>
<tr><td>動物種</td><td>投与期間</td><td>投与経路</td><td>投与量
（mg/kg/週）</td><td>無毒性量
（mg/kg/週）</td><td>主な所見</td></tr>
<tr><td rowspan="2">サル</td><td>5 週間
(1 回/週)</td><td>静脈内</td><td>0, 1, 5, 25, 100</td><td>100</td><td rowspan="2">REGN646 に関連した毒性変化は認められなかった。</td></tr>
<tr><td>13 週間
(1 回/週)</td><td>皮下</td><td>0, 1, 5, 25, 100</td><td>100</td></tr>
</table></td></tr>
</table>

<table>
<tr><td></td><td>
慢性：
<table>
<tr><th>動物種</th><th>投与期間</th><th>投与経路</th><th>投与量
（mg/kg/週）</th><th>無毒性量
（mg/kg/週）</th><th>主な所見</th></tr>
<tr><td rowspan="2">サル</td><td rowspan="2">26 週間(1回/週)</td><td>皮下</td><td>0, 25, 100</td><td>100</td><td rowspan="2">REGN646に関連した毒性変化は認められなかった。</td></tr>
<tr><td>静脈内</td><td>0, 25</td><td>10025</td></tr>
</table>
</td></tr>
<tr><td>副作用</td><td>
アトピー性皮膚炎患者を対象とした国際共同試験 3 試験で本剤 300mg を 2 週に 1 回投与された 403 例（日本人を含む）において、副作用は 123 例（30.5%）に発現し、主な副作用は、注射部位反応 29 例（7.2%）、頭痛 12 例（3.0%）、アレルギー性結膜炎 7 例（1.7%）であった。

小児のアトピー性皮膚炎患者を対象とした国内試験で体重に応じて本剤 200mg 又は 300mg を 2 週に 1 回あるいは 4 週に 1 回投与された 30 例において、副作用は 5 例（16.7%）に発現し、主な副作用はアレルギー性結膜炎 2 例（6.7%）であった。

結節性痒疹患者を対象とした国際共同試験で本剤 300mg を 2 週に 1 回投与された 75 例（日本人を含む）において、副作用は 11 例（14.7%）に発現し、主な副作用は注射部位反応 3 例（4.0%）であった。特発性の慢性蕁麻疹患者を対象とした国際共同試験で本剤 300mg 又は 200mg を 2 週に 1 回投与された 70 例（日本人を含む）において、副作用は 10 例（14.3%）に発現し、主な副作用は注射部位反応 3 例（4.3%）であった。

気管支喘息患者を対象とした国際共同試験 2 試験で本剤 300mg を 2 週に 1 回投与された 788 例（日本人を含む）において、副作用は 192 例（24.4%）に発現し、主な副作用は、注射部位紅斑 127 例（16.1%）、注射部位浮腫 44 例（5.6%）、注射部位そう痒感 42 例（5.3%）であった。

慢性閉塞性肺疾患を対象とした国際共同試験で本剤 300mg を 2 週に 1 回投与された 464 例（日本人を含む）において、副作用は 35 例（7.5%）に発現し、最も多く見られた副作用は注射部位反応 7 例（1.5%）であった。

鼻茸を伴う難治性慢性副鼻腔炎患者を対象とした国際共同試験で本剤 300mg を 2 週に 1 回投与された 149 例（日本人を含む）又は 24 週以降本剤 300mg を 4 週に 1 回投与された 148 例（日本人含む）において、副作用は 36 例（24.2%）及び 41 例（27.7%）に発現し、主な副作用は注射部位紅斑 11 例（7.4%）及び 10 例（6.8%）、及び注射部位反応 5 例（3.4%）及び 8 例（5.4%）であった。
</td></tr>
<tr><td>会社</td><td>サノフィ株式会社</td></tr>
</table>

別紙

アミノ酸配列及びジスルフィド結合：

L鎖

DIVMTQSPLS LPVTPGEPAS ISCRSSQSLL YSIGYNYLDW YLQKSGQSPQ
LLIYLGSNRA SGVPDRFSGS GSGTDFTLKI SRVEAEDVGF YYCMQALQTP
YTFGQGTKLE IKRTVAAPSV FIFPPSDEQL KSGTASVVCL LNNFYPREAK
VQWKVDNALQ SGNSQESVTE QDSKDSTYSL SSTLTLSKAD YEKHKVYACE
VTHQGLSSPV TKSFNRGEC

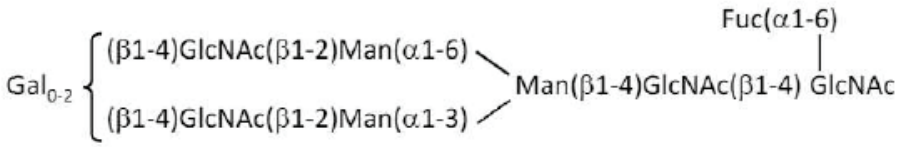
H鎖

EVQLVESGGG LEQPGGSLRL SCAGSGFTFR DYAMTWVRQA PGKGLEWVSS
ISGSGGNTYY ADSVKGRFTI SRDNSKNTLY LQMNSLRAED TAVYYCAKDR
LSITIRPRYY GLDVWGQGTT VTVSSASTKG PSVFPLAPCS RSTSESTAAL
GCLVKDYFPE PVTVSWNSGA LTSGVHTFPA VLQSSGLYSL SSVVTVPSSS
LGTKTYTCNV DHKPSNTKVD KRVESKYGPP CPPCPAPEFL GGPSVFLFPP
KPKDTLMISR TPEVTCVVVD VSQEDPEVQF NWYVDGVEVH NAKTKPREEQ
FNSTYRVVSV LTVLHQDWLN GKEYKCKVSN KGLPSSIEKT ISKAKGQPRE
PQVYTLPPSQ EEMTKNQVSL TCLVKGFYPS DIAVEWESNG QPENNYKTTP
PVLDSDGSFF LYSRLTVDKS RWQEGNVFSC SVMHEALHNH YTQKSLSLSL
GK

H鎖 N302：糖鎖結合；H鎖 K452：部分的プロセシング

L鎖 C219 – H鎖 C139、H鎖 C231 – H鎖 C231、H鎖 C234 – H鎖 C234：ジスルフィド結合

主な糖鎖の推定構造：



追加（下線部）

化学名・別名	
構造式	
効能・効果	
用法・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。 通常、生後 6 カ月以上の小児にはデュピルマブ（遺伝子組換え）として体重に応じて以下を皮下投与する。 5kg 以上 15kg 未満：1 回 200mg を 4 週間隔 15kg 以上 30kg 未満：1 回 300mg を 4 週間隔 30kg 以上 60kg 未満：初回に 400mg、その後は 1 回 200mg を 2 週間隔 60kg 以上：初回に 600mg、その後は 1 回 300mg を 2 週間隔 〈結節性痒疹〉 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。 〈特発性の慢性蕁麻疹〉 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。 通常、12 歳以上の小児にはデュピルマブ（遺伝子組換え）として体重に応じて以下を皮下投与する。 30kg 以上 60kg 未満：初回に 400mg、その後は 1 回 200mg を 2 週間隔 60kg 以上：初回に 600mg、その後は 1 回 300mg を 2 週間隔 〈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。 通常、6 歳以上 12 歳未満の小児にはデュピルマブ（遺伝子組換え）として体重に応じて以下を皮下投与する。 15kg 以上 30kg 未満：1 回 300mg を 4 週間隔 30kg 以上：1 回 200mg を 2 週間隔 〈慢性閉塞性肺疾患〉 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。 〈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。
劇薬等の指定	
市販名及び有効成分・分量	
毒性	
副作用	アトピー性皮膚炎患者を対象とした国際共同試験 3 試験で本剤 300mg を 2 週に 1 回投与された 403 例（日本人を含む）において、副作用は 123 例（30.5%）に発現し、主な副作用は、注射部位反応 29 例（7.2%）、頭痛 12 例（3.0%）、アレルギー性結膜炎 7 例（1.7%）であった。 小児のアトピー性皮膚炎患者を対象とした国内試験で体重に応じて本剤 200mg 又は 300mg を 2 週に 1 回あるいは 4 週に 1 回投与された 30 例において、副作用は 5 例（16.7%）に発現し、主な副作用はアレルギー性結膜炎 2 例（6.7%）であった。 結節性痒疹患者を対象とした国際共同試験で本剤 300mg を 2 週に 1 回投与された 75 例（日本人を含む）において、副作用は 11 例（14.7%）に発現し、主な副作用は注射部位反応 3 例（4.0%）であった。特発性の慢性蕁麻疹患者を対象とした国際共同試験で本剤 300mg 又は 200mg を 2 週に 1 回投与された 70 例（日本人を含む）において、副作用は 10 例（14.3%）に発現し、主な副作用は注射部位反応 3 例（4.3%）であった。 気管支喘息患者を対象とした国際共同試験 2 試験で本剤 300mg を 2 週に 1 回投与された 788 例（日本人を含む）において、副作用は 192 例（24.4%）に発現し、主な副作用は、注射部位紅斑 127 例（16.1%）、注射部位浮腫 44 例（5.6%）、注射部位そう痒感 42 例（5.3%）であった。 小児の気管支喘息患者を対象とした国際共同試験で体重に応じて本剤 100mg 又は 200mg を 2 週に 1 回あるいは 300mg を 4 週に 1 回投与された 13 例において、副作用は 4 例（30.8%）に発現し、発熱 2 例、注射部位紅斑 1 例、注射部位硬結 1 例であった。 慢性閉塞性肺疾患を対象とした国際共同試験で本剤 300mg を 2 週に 1 回投与された 464 例（日本人を含む）において、副作用は 35 例（7.5%）に発現し、最も多く見られた副作用は注射部位反応 7 例（1.5%）であった。 鼻茸を伴う難治性慢性副鼻腔炎患者を対象とした国際共同試験で本剤 300mg を 2 週に 1 回投与された 149 例（日本人を含む）又は 24 週以降本剤 300mg を 4 週に 1 回投与された 148 例（日本人含む）において、副作用は 36 例（24.2%）及び 41 例（27.7%）に発現し、主な副作用は注射部位紅斑 11 例（7.4%）及び 10 例（6.8%）、及び注射部位反応 5 例（3.4%）及び 8 例（5.4%）であった。
会社	

サノフィ株式会社

デュピルマブ（遺伝子組換え）

1.12　添付資料一覧（小児気管支喘息）

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	Screening, Confirmation and Titer Cut Point Determination for REGN668 Anti-Drug Antibody (ADA) Assay Using Baseline Serum Samples from Asthma Patients of Study DRI12544 (REGN668-AV-15153-CP01-SR-0I V2)	20[redacted]	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
5.3.3.5-1	Population Pharmacokinetic Analysis of Dupilumab Using Pooled Data from Two Phase 3 studies in Children 6 to <12 Years of Age with Asthma (POH0766)	20[redacted]	有	参考資料
5.3.3.5-2	Empirical Exposure/Response Modeling of Severe Exacerbation Event and FEV1 for Dupilumab in Pediatric Patients 6 to <12 Years of Age with Asthma (CTS0077)	20[redacted]	有	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	A randomized, double-blind, placebo-controlled, parallel group study to evaluate the efficacy and safety of dupilumab in children 6 to <12 years of age with uncontrolled persistent asthma (EFC14153)	2017/4/21 - 2020/8/26	有	評価資料

5.3.5.2 非対照試験報告書

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
5.3.5.2-1	One year study to evaluate the long-term safety and tolerability of dupilumab in pediatric patients with asthma who participated in a previous dupilumab asthma clinical study (LTS14424 main study Final CSR)	2018/6/21 - 20[redacted]	有	評価資料
5.3.5.2-2	One year study to evaluate the long-term safety and tolerability of dupilumab in pediatric patients with asthma who participated in a previous dupilumab asthma clinical study (LTS14424 Japan substudy Early analysis CSR)	20[redacted] - 20[redacted]	有	評価資料
5.3.5.2-2a	One year study to evaluate the long-term safety and tolerability of dupilumab in pediatric patients with asthma who participated in a previous dupilumab asthma clinical study (LTS14424 Japan substudy Final CSR)	20[redacted] - 20[redacted]	有	評価資料

5.3.5.3 複数の試験成績を併せて解析した報告書

該当資料なし

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	A randomized, double-blind, placebo-controlled, multi-center, parallel-group study to evaluate the efficacy, safety and pharmacokinetics of dupilumab compared to placebo in Japanese patients with atopic dermatitis aged 6 months to <18 years whose disease is not adequately controlled with existing therapies (EFC16823 Final analysis CSR)	2021/1/15 - 2023/10/28	無	参考資料
5.3.5.4-2	Clinical Outcomes Assessment Dossier - Peadiatric Asthma (6 to <12 years)	―	無	参考資料
5.3.5.4-3	SAR231893 AE Listing	―	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 - DUPILUMAB	20[redacted] - 20[redacted]	有	参考資料
5.3.6-2	製造販売後調査報告書 デュピクセント®皮下注 特定使用成績調査（長期使用に関する調査）＜気管支喘息＞ （調査番号：OBS16170）	2019/6/7 - 2022/11/17	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
5.3.7-4	臨床検査値異常変動発現症例一覧表

5.4 参考文献

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