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（水疱性類天疱瘡）

Total number of pages: 5

VV-REG-1632021 3.0

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1.1　　開発の経緯 4

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図 1　デュピルマブの水疱性類天疱瘡に係る開発の経緯図 5

1　起原又は発見の経緯及び開発の経緯

デュピルマブ（遺伝子組換え）（以下、デュピルマブ）は、インターロイキン（IL）-4 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（IL-4Rα）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免疫グロブリン（Ig）G4 モノクローナル抗体である。デュピルマブは 1 型受容体を介して IL-4 シグナル伝達を阻害し、2 型受容体を介して IL-4 及び IL-13 の両方のシグナル伝達を阻害する。デュピルマブが IL-4Rα を阻害すると、炎症誘発性サイトカイン、ケモカイン及び IgE の放出を含む IL-4 及び IL-13 のサイトカイン誘発性炎症反応が阻害され、2 型炎症が広範に抑制される。デュピルマブは、米国 Regeneron Pharmaceuticals 社と Sanofi 社が共同で開発中である。

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、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。

水疱性類天疱瘡（BP）はまれで深刻な自己免疫性の表皮下水疱を生じる疾患であり、主に高齢者で好発し、慢性かつ再燃性の臨床経過をたどり、高い罹患率及び死亡率と関連している。水疱性、びらん性又は膿疱性の病変に関連する難治性のそう痒及び疼痛／不快感のため、BP は患者の睡眠、気分及び生活の質に深刻な悪影響を及ぼすことが多い。2 型炎症過程は、BP の発症において重要な役割を果たす。BP に対する現行のステロイド薬や全身性免疫抑制薬を中心とした標準治療は重大な副作用を伴うため、BP 及び関連する併存疾患を有する脆弱な高齢者集団への使用が制限される。BP の根底にある 2 型炎症過程を標的として病勢をコントロールし、ステロイド薬及び全身性免疫抑制薬の必要性を最小限に抑え、脆弱な高齢者集団における長期使用に対して良好な安全性プロファイルを有するより安全な治療選択肢に対する大きなアンメットメディカルニーズが存在する。

今般、Regeneron Pharmaceuticals 社が実施した日本人患者を含む国際共同第 2/3 相試験（R668-BP-1902 試験）において、成人 BP 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、300 mg シリンジ製剤及び 300 mg ペン製剤の医薬品製造販売承認事項一部変更承認申請を行うこととした。

1.1　開発の経緯

デュピルマブの BP に係る開発の経緯図を図 1、臨床開発プログラムの概要を Module 2.5 の 1.8 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　デュピルマブの水疱性類天疱瘡に係る開発の経緯図

資料区分	試験項目			2020 年	2021 年	2022 年	2023 年	2024 年	2025 年
第五部	臨床試験	国際共同試験	第Ⅱ/Ⅲ相試験	10		R668-BP-1902 試験			1

：国際共同試験
数字は開始及び終了月を示す。

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（水疱性類天疱瘡）

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 2017 年 3 月に米国、2017 年 9 月に欧州（EU）にて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、特発性の慢性蕁麻疹及び慢性閉塞性肺疾患を含む 2 型炎症性疾患の治療薬として複数の国・地域で承認されている。

今回の申請効能である「水疱性類天疱瘡」については、2025 年 6 月に米国にて承認されている。また、20[redacted]年[redacted]月に[redacted]にて適応追加申請を行い、現在承認審査中である。

本剤の企業中核データシート（CCDS）及び米国添付文書（USPI）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、2～190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, Chronic Obstructive Pulmonary Disease (1.6)	09/2024
Indications and Usage, Chronic Spontaneous Urticaria (1.7)	04/2025
Indications and Usage, Bullous Pemphigoid (1.8)	06/2025
Dosage and Administration, Chronic Rhinosinusitis with Nasal Polyps (2.5)	09/2024
Dosage and Administration, Chronic Obstructive Pulmonary Disease (2.8)	09/2024
Dosage and Administration, Chronic Spontaneous Urticaria (2.9)	04/2025
Dosage and Administration, Bullous Pemphigoid (2.10)	06/2025
Dosage and Administration, Missed Doses (2.11)	06/2025
Warnings and Precautions, Hypersensitivity (5.1)	06/2025
Warnings and Precautions, Conjunctivitis and Keratitis (5.2)	06/2025
Warnings and Precautions (5.2, 5.3, 5.7, 5.8)	04/2025
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)

Chronic Spontaneous Urticaria
for the treatment of adult and pediatric patients aged 12 years and older with chronic spontaneous urticaria (CSU) who remain symptomatic despite H1 antihistamine treatment. (1.7)
Limitations of Use: Not indicated for other forms of urticaria. (1.7)

Bullous Pemphigoid
for the treatment of adult patients with bullous pemphigoid (BP). (1.8)

DOSAGE AND ADMINISTRATION

DUPIXENT is administered by subcutaneous injection. (2.1)

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 2 weeks (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 of Age and Older (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 2 weeks; 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 4 weeks (Q4W)
≥30 kg	200 mg every 2 weeks (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 2 weeks (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 2 weeks (Q2W)
30 to less than 40 kg	300 mg every 2 weeks (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 2 weeks (Q2W).

Chronic Obstructive Pulmonary Disease (2.8):
Recommended dosage for adult patients is 300 mg given every 2 weeks (Q2W).

Chronic Spontaneous Urticaria

Dosage in Adults (2.9):
Recommended dosage is an initial dose of 600 mg (two 300 mg injections), followed by 300 mg given every 2 weeks (Q2W).

Dosage in Pediatric Patients 12 to 17 Years of Age (2.9):

Body Weight	Initial Loading Dose	Subsequent Dosage
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

Bullous Pemphigoid (2.10):
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). Use DUPIXENT in combination with a tapering course of oral corticosteroids.

DOSAGE FORMS AND STRENGTHS

Single-Dose Pre-Filled Syringe with Needle Shield (3):
- Injection: 300 mg/2 mL (150 mg/mL)
- Injection: 200 mg/1.14 mL (175 mg/mL)

Single-Dose Pre-Filled Pen (3):
- Injection: 300 mg/2 mL (150 mg/mL)
- Injection: 200 mg/1.14 mL (175 mg/mL)

CONTRAINDICATIONS

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

WARNINGS AND PRECAUTIONS

- Hypersensitivity: Hypersensitivity reactions including anaphylaxis, acute generalized exanthematous pustulosis (AGEP), 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, cardiac complications, kidney injury 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)
- Psoriasis: Advise patients to report new-onset psoriasis symptoms to their healthcare provider. If symptoms persist or worsen, consider dermatologic evaluation and/or discontinuation of DUPIXENT. (5.7)
- Arthralgia and Psoriatic Arthritis: Advise patients to report new onset joint symptoms to their healthcare provider. If symptoms persist or worsen, consider rheumatological evaluation and/or discontinuation of DUPIXENT. (5.8)
- 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. (5.9)
- Vaccinations: Avoid use of live vaccines. (5.10)

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)
- **Chronic Spontaneous Urticaria (incidence ≥2%):** injection site reactions. (6.1)
- **Bullous Pemphigoid (incidence ≥2%):** arthralgia, conjunctivitis, vision blurred, herpes viral infections, keratitis. (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: 6/2025

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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.

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.

1.7 Chronic Spontaneous Urticaria

DUPIXENT is indicated for the treatment of adult and pediatric patients aged 12 years and older with chronic spontaneous urticaria (CSU) who remain symptomatic despite H1 antihistamine treatment.

Limitations of Use:

DUPIXENT is not indicated for treatment of other forms of urticaria.

1.8 Bullous Pemphigoid

DUPIXENT is indicated for the treatment of adult patients with bullous pemphigoid (BP).

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 years of age and older, 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 patients with AD, asthma, PN, CSU, and BP taking an initial 600 mg dose, administer each of the two DUPIXENT 300 mg injections at different injection sites.

For patients with AD, asthma, and CSU 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 (5.10)]*.

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 2 weeks (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 of Age and Older

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

Table 2: Dosage of DUPIXENT in Pediatric Patients 6 Years of Age and Older 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 2 weeks (Q2W)
60 kg or more	600 mg (two 300 mg injections)	300 mg every 2 weeks (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 4 weeks (Q4W)
≥30 kg	200 mg every 2 weeks (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 2 weeks (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 2 weeks (Q2W)
30 to less than 40 kg	300 mg every 2 weeks (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 2 weeks (Q2W).

2.8 Recommended Dosage for Chronic Obstructive Pulmonary Disease

The recommended dosage of DUPIXENT for adult patients is 300 mg given every 2 weeks (Q2W).

2.9 Recommended Dosage for Chronic Spontaneous Urticaria

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 2 weeks (Q2W).

Dosage in Pediatric Patients 12 to 17 Years of Age

The recommended dosage of DUPIXENT for pediatric patients 12 to 17 years of age is specified in Table 6.

Table 6: Dosage of DUPIXENT in Pediatric Patients 12 to 17 Years of Age with CSU

Body Weight	Initial Loading Dose	Subsequent Dosage
30 to less than 60 kg	400 mg (two 200 mg injections)	200 mg every 2 weeks (Q2W)
60 kg or more	600 mg (two 300 mg injections)	300 mg every 2 weeks (Q2W)

2.10 Recommended Dosage for Bullous Pemphigoid

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).

Concomitant Oral Corticosteroids:

Use DUPIXENT in combination with a tapering course of oral corticosteroids. Once disease control has occurred, gradually taper corticosteroids after which continue DUPIXENT as monotherapy. In case of relapse, corticosteroids may be added if medically advisable.

2.11 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 2 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.

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.

2.12 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 (150 mg/mL)

- Injection: 200 mg/1.14 mL (175 mg/mL)

Single-dose pre-filled pen as:

- Injection: 300 mg/2 mL (150 mg/mL)
- Injection: 200 mg/1.14 mL (175 mg/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, acute generalized exanthematous pustulosis (AGEP), serum sickness or serum sickness-like reactions, angioedema, generalized urticaria, rash, erythema nodosum and erythema multiforme have been reported. A case of AGEP was reported in an adult subject who participated in the bullous pemphigoid development program. 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 *[see Adverse Reactions (6.1)]*.

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.

Among subjects with asthma, the frequencies of conjunctivitis and keratitis were 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. There were no cases of keratitis reported in the CRSwNP development program.

Among subjects with EoE, there were no reports of conjunctivitis and keratitis in the DUPIXENT group in placebo-controlled trials.

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.

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.

In subjects with CSU, the frequency of conjunctivitis was similar between DUPIXENT and placebo. There were no cases of keratitis reported in the CSU development program.

Among subjects with BP, the frequency of conjunctivitis and keratitis was 7.5% and 3.8% in the DUPIXENT group and 0% and 0% in the placebo group, respectively.

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.

5.3 Eosinophilic Conditions

Patients being treated for asthma may present with clinical features of eosinophilic pneumonia or eosinophilic granulomatosis with polyangiitis (EGPA). 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, kidney injury, and/or neuropathy presenting in their patients with eosinophilia. Cases of eosinophilic pneumonia were reported in adults who participated in the asthma development program. Cases of EGPA have been reported with DUPIXENT in adults who participated in the asthma development program as well as in adults with co-morbid asthma in the CRSwNP development program. Advise patients to report signs of eosinophilic pneumonia and EGPA to their healthcare provider. Consider withholding DUPIXENT if eosinophilic pneumonia or EGPA are suspected.

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 Psoriasis

Cases of new-onset psoriasis have been reported with the use of DUPIXENT for the treatment of atopic dermatitis and asthma, including in patients without a family history of psoriasis. In

postmarketing reports, onset of psoriasis varied from weeks to months after the first dose of DUPIXENT and resulted in partial or complete resolution of psoriasis with discontinuation of dupilumab, with or without use of supplemental treatment for psoriasis (topical or systemic). Those who continued on dupilumab received supplemental treatment for psoriasis to improve associated symptoms. Advise patients to report new-onset psoriasis symptoms to their healthcare provider. If symptoms persist or worsen, consider dermatologic evaluation and/or discontinuation of DUPIXENT.

5.8 Arthralgia and Psoriatic Arthritis

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.

Cases of new-onset psoriatic arthritis requiring systemic treatment have been reported with the use 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.

5.9 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)]*.

5.10 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)]*
- Psoriasis *[see Warnings and Precautions (5.7)]*
- Arthralgia and Psoriatic Arthritis *[see Warnings and Precautions (5.8)]*
- Parasitic (Helminth) Infections *[see Warnings and Precautions (5.9)]*

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.

Atopic Dermatitis

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 *[see Clinical Studies (14)]*. 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 7 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 7: 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 2 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 Years of Age and Older with Atopic Dermatitis

The safety of DUPIXENT was assessed in a trial of 250 pediatric subjects 12 years of age and older 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 years of age and older 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 years of age and older 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 years of age and older 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 years of age and older with AD.

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 years of age and older 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 years of age and older 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.

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 8 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 8: 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 9 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 9: 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 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 Parts A and B.

Table 10: 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) *[see Clinical Studies (14.5)]*. 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.

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 11 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 11: 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 12 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 12: 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.

Chronic Spontaneous Urticaria

The pooled safety data below reflects the safety of DUPIXENT in adult and pediatric subjects 12 years of age and older with chronic spontaneous urticaria (CSU) who remain symptomatic despite H1 antihistamine treatment. A total of 392 adult and pediatric subjects 12 years of age and older with CSU were evaluated for safety in three randomized, double-blind, parallel-group, multicenter, placebo-controlled, studies, Study A, B, and C, conducted under a master protocol (CUPID) for 36 weeks *[see Clinical Studies (14.7)]*. The pooled safety population received an initial dose of DUPIXENT 600 mg or 400 mg, followed by DUPIXENT 300 mg or 200 mg, respectively, or matching placebo, administered subcutaneously every 2 weeks (Q2W) *[see Dosage and Administration (2.9)]*.

Table 13 summarizes the adverse reactions that occurred in at least 2% in subjects treated with DUPIXENT and at a higher rate than placebo in CUPID Study A, B and C (pooled safety population).

Table 13: Adverse Reactions That Occurred in ≥2% of Adult and Pediatric Subjects 12 Years of Age and Older with CSU Treated with DUPIXENT in CUPID Study A, B, and C (Pooled Safety Population) and Greater than Placebo

Adverse Reaction	CUPID Study A, B, and C	
	DUPIXENT 200 mg Q2W or 300 mg Q2W N=195 n (%)	Placebo N=197 n (%)
Injection site reactions[a]	20 (10.3)	16 (8.1)

[a] Injection site reactions cluster includes injection site dermatitis, injection site erythema, injection site hematoma, injection site induration, injection site pain, injection site pruritus, injection site reaction, injection site swelling

Bullous Pemphigoid

The safety of DUPIXENT was evaluated in a 52-week, randomized, double-blind, parallel-group, multicenter, placebo-controlled trial (ADEPT) in a total of 106 adult subjects with moderate-to-severe bullous pemphigoid (BP) *[see Clinical Studies (14.8)]*. Of the 106 randomized subjects, all received at least one dose of DUPIXENT or placebo with a course of oral corticosteroids (OCS) with a prespecified taper. At the time of analysis, 87 subjects had completed Week 36 and 65 subjects had completed Week 52.

Table 14 summarizes the adverse reactions that occurred in at least 2% of subjects treated with DUPIXENT and at a higher rate than placebo in the ADEPT trial.

Table 14: Adverse Reactions Occurring in ≥2% of Adult Subjects with BP Treated with DUPIXENT in ADEPT and Greater than Placebo[a]

Adverse Reaction	ADEPT	
	DUPIXENT[a] 300 mg Q2W + OCS N=53 n (%)	Placebo[a] + OCS N=53 n (%)
Arthralgia	5 (9%)	3 (6%)
Conjunctivitis	4 (8%)	0%
Vision blurred	4 (8%)	0%
Herpes viral infections[b]	3 (6%)	0%
Keratitis	2 (4%)	0%

[a] In combination with a tapering course of oral corticosteroids
[b] Herpes viral infections include herpes simplex and herpes zoster

A case of AGEP was reported in 1 subject with BP treated with DUPIXENT compared with 0 subjects in the placebo group.

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

Conjunctivitis and Keratitis

In adult subjects with AD, conjunctivitis was reported in 10% (34 per 100 patient-years) in the 300 mg Q2W dose group and in 2% of the placebo group (8 per 100 patient-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 patient-years) and in

9% of the placebo + TCS group (10 per 100 patient-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 patient-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 patient-years) and in 0% of the placebo group (0 per 100 patient-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 patient-years) and in 2% of the placebo + TCS group (2 per 100 patient-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 patient-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.

Among subjects with EoE, there were no reports of conjunctivitis and keratitis in the DUPIXENT group in placebo-controlled trials. 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.

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.

Among subjects with CSU in the pooled safety population, the frequency of conjunctivitis was similar between DUPIXENT and placebo. There were no cases of keratitis reported in the CSU development program.

Among subjects with BP, the frequency of conjunctivitis and keratitis was 8% and 4% in the DUPIXENT group and 0% and 0% in the placebo group, respectively.

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 patient-years) and in <1% of the placebo group (1 per 100 patient-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 patient-years) and 2% of the placebo + TCS group (2 per 100 patient-

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 patient-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 patient-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.

Among subjects with CSU in the pooled safety population, herpes zoster was reported in <1% of the DUPIXENT and placebo groups (1 per 100 patient-years). There were no cases of eczema herpeticum reported in the CSU development program.

Among subjects with BP, herpes zoster was reported in 4% of the DUPIXENT group and 0% of the placebo group.

Hypersensitivity Reactions

Hypersensitivity reactions were reported in <1% of DUPIXENT-treated subjects. These included anaphylaxis, AGEP, serum sickness or serum sickness-like reactions, generalized urticaria, rash, erythema nodosum, and erythema multiforme *[see Contraindications (4), 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 receiving 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 less than 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 adult and pediatric subjects with CSU (CUPID Study A, Study B, and Study C) treated with DUPIXENT, an increase from baseline in blood eosinophil count was not observed compared to placebo at Week 12.

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 DUPIXENT-treated subjects with BP in ADEPT, all of whom received background oral corticosteroid (OCS) treatment, the mean and median decrease in blood eosinophils from baseline to Week 4 were 1022 and 485 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, CRSwNP, and CSU 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.

In the trial for the BP indication, the incidence of treatment-emergent eosinophilia (≥500 cells/mcL) was higher in DUPIXENT (21%) than in the placebo group (11%).

Treatment-emergent eosinophilia (≥5,000 cells/mcL) was observed in <3% of DUPIXENT-treated subjects and <0.5% in subjects receiving placebo (SOLO 1, SOLO 2, and AD-1021; DRI12544, QUEST, and VOYAGE; SINUS-24 and SINUS-52; PRIME and PRIME2; BOREAS and NOTUS; CUPID Study A, B, and C). Blood eosinophil counts declined to near baseline or remained below baseline levels (PRIME and PRIME2; BOREAS and NOTUS; ADEPT) during treatment. In trial AD-1539, treatment-emergent eosinophilia (≥5,000 cells/mcL) was reported in 8% of DUPIXENT-treated subjects and 0% in subjects receiving placebo *[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.

In the 24-week placebo-controlled trial in subjects with CSU (CUPID Study A, B, and C), 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
- *Musculoskeletal system disorders:* psoriatic arthritis
- *Skin and subcutaneous tissue disorders:* Facial skin reactions, including erythema, rash, scaling, edema, papules, pruritus, burning, and pain; new-onset psoriasis, vasculitis

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.

Fetal/Neonatal Adverse Reactions

Transport of endogenous IgG antibodies across the placenta increases as pregnancy progresses, and peaks during the third trimester. Therefore, DUPIXENT may be present in infants exposed *in utero*. The potential clinical impact of dupilumab exposure in infants exposed *in utero* should be considered.

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.

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

- AD-1526 which included 251 pediatric subjects 12 years of age and older 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 years of age and older 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 years of age and older 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. 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) and Clinical Studies (14.1)]*.

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

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

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

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

Prurigo Nodularis

Safety and effectiveness of DUPIXENT have not been established in pediatric patients with PN.

Chronic Obstructive Pulmonary Disease

The safety and effectiveness of DUPIXENT have not been established in pediatric patients with COPD. COPD is largely a disease of adult patients.

Chronic Spontaneous Urticaria

The safety and effectiveness of DUPIXENT for the treatment of CSU in patients who remain symptomatic despite H1 antihistamine treatment have been established in pediatric patients 12 years of age and older. The use of DUPIXENT in this indication is supported by evidence from two adequate and well-controlled studies in adults with additional pharmacokinetic data in 6 pediatric patients 12 years of age and older, and safety data in pediatric patients in other indications *[*see *Dosage and Administration (2.9)*, *Clinical Pharmacology (12.3)*, and *Clinical Studies (14.7)]*.

Safety and effectiveness of DUPIXENT have not been established in pediatric patients younger than 12 years of age, and/or weighing less than 30 kg, with CSU.

Bullous Pemphigoid

The safety and effectiveness of DUPIXENT have not been established in pediatric patients with BP. BP 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 older to determine whether they respond differently from younger subjects.

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 older 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.

Of the 198 subjects with CSU exposed to DUPIXENT, a total of 30 subjects were 65 years or older, including 7 subjects 75 years or older. Efficacy and safety in subjects 65 years or older were similar to the overall study population.

Of the 53 subjects with BP exposed to DUPIXENT, a total of 40 were 65 years or older, including 22 subjects 75 years or older. Ten percent of subjects aged 65 years and older treated with DUPIXENT had an adverse reaction of vision blurred compared to zero in 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, COPD, CSU, and BP. Multiple cell types that express IL-4Rα (e.g., mast cells, basophils, 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.

A continuous decline in total IgE in serum was observed in CSU trials.

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, COPD, CSU, and BP.

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, COPD, CSU, and BP subjects, ranging between 61% and 66%.

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 years of age and older. 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 years of age and older with AD receiving every 2 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 2 week dosing (Q2W) with 200 mg (≥30 kg) or every 4 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 4 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.

Chronic Spontaneous Urticaria

A total of 12 pediatric subjects 12 to 17 years of age with CSU were enrolled in CUPID. The observed steady-state trough concentrations of 6 pediatric subjects 12 to 17 years of age with CSU who received DUPIXENT 300 mg Q2W or 200 mg Q2W were within the range of steady-state trough concentrations in adult subjects with CSU who received DUPIXENT 300 mg Q2W.

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 trials described below with the incidence of anti-drug antibodies in other trials, including those of DUPIXENT or of other dupilumab products.

The anti-drug antibody (ADA) and neutralizing antibody (NAb) incidence rates in subjects treated with DUPIXENT are presented in Table 15.

Table 15: Anti-drug Antibody and Neutralizing Antibody Incidence in Subjects Treated with DUPIXENT

Indication and Population	Dose and Duration of Treatment	Anti-drug Antibody (ADA)		Neutralizing Antibody NAb [c]
		Treatment-Emergent ADA[a]	Persistent ADA[b]	

Atopic Dermatitis				
Adult	300 mg Q2W for 52 weeks	6/105 (6%)	2/105 (2%)	1/6 (17%)
12 to 17 years of age	300 mg or 200 mg Q2W for 16 weeks	13/81 (16%)	2/81 (3%)	4/13 (31%)
6 to 11 years of age	200 mg Q2W or 300 mg Q4W for 16 weeks	3/171 (2%)	0/171 (0%)	1/3 (33%)
6 months to 5 years of age	200 mg Q4W, or 300 mg Q4W for 16 weeks	1/74 (1%)	0/74 (0%)	0/1 (0%)
Asthma				
Adult and 12 years of age or older	300 mg Q2W for 52 weeks	32/626 (5%)	13/626 (2%)	14/32 (44%)
	200 mg Q2W for 52 weeks	58/625 (9%)	26/625 (4%)	27/58 (47%)
6 to 11 years of age	100 mg Q2W or 200 mg Q2W up to 52 weeks	17/269 (6%)	9/269 (3%)	6/17 (35%)
Chronic Rhinosinusitis with Nasal Polyps				
Adult	300 mg Q2W for 52 weeks	8/148 (5%)	3/148 (2%)	5/8 (63%)
Eosinophilic Esophagitis				
Adult and 12 years of age or older	300 mg QW for 52 weeks	1/108 (1%)	0/108 (0%)	0/1 (0%)
1 to 11 years of age	200 mg Q2W or 300 mg Q2W for 52 weeks [e]	1/37 (3%)	0/37 (0%)	0/1 (0%) [d]
Prurigo Nodularis				
Adult	300 mg Q2W for 24 weeks	11/143 (8%)	2/143 (1%)	4/11 (36%)
Chronic Obstructive Pulmonary Disease				
Adult	300 mg Q2W for 52 weeks	77/922 (8%)	24/922 (3%)	28/77 (36%)
Chronic Spontaneous Urticaria				
Adult and 12 years of age or older	200 mg Q2W or 300 mg Q2W through 24 weeks	9/193 (5%)	1/193 (1%)	2/9 (22%)
Bullous Pemphigoid				
Adult	300 mg Q2W up to 52 weeks	2/52 (4%)	0/52 (0%)	2/2 (100%)

[a] Treatment-emergent ADA: A negative result or missing result at baseline with at least 1 positive post-baseline result in the ADA assay.
[b] Persistent ADA: A treatment-emergent ADA positive response with 2 or more consecutive ADA positive samples separated by a greater than 12-week period (>84 days), with no ADA negative result in between.
[c] Neutralizing potential is assessed only for ADA-positive samples. The NAb incidence is reported as a percentage of subjects with treatment emergent ADA.
[d] One subject 1 to 11 years of age with EoE with pre-existing immunoreactivity that was positive for neutralizing antibodies was excluded from the NAb positive subjects.
[e] Immunogenicity was reported on pooled data for pediatric subjects 1 to 11 years of age with EoE receiving SC dupilumab 100 mg Q2W (in subjects weighing ≥5 kg to <15kg), 200 mg Q2W (in subjects weighing ≥15 kg to <30 kg), 300 mg Q2W (in subjects weighing ≥30 kg to <60 kg), and 300 mg QW (in subjects weighing ≥60 kg).

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)]*.

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)]*.

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 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, the mean age of subjects was 38 years; 59% of subjects were male, 67% were White, 24% were Asian, and 6% were Black; 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 2 weeks (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)

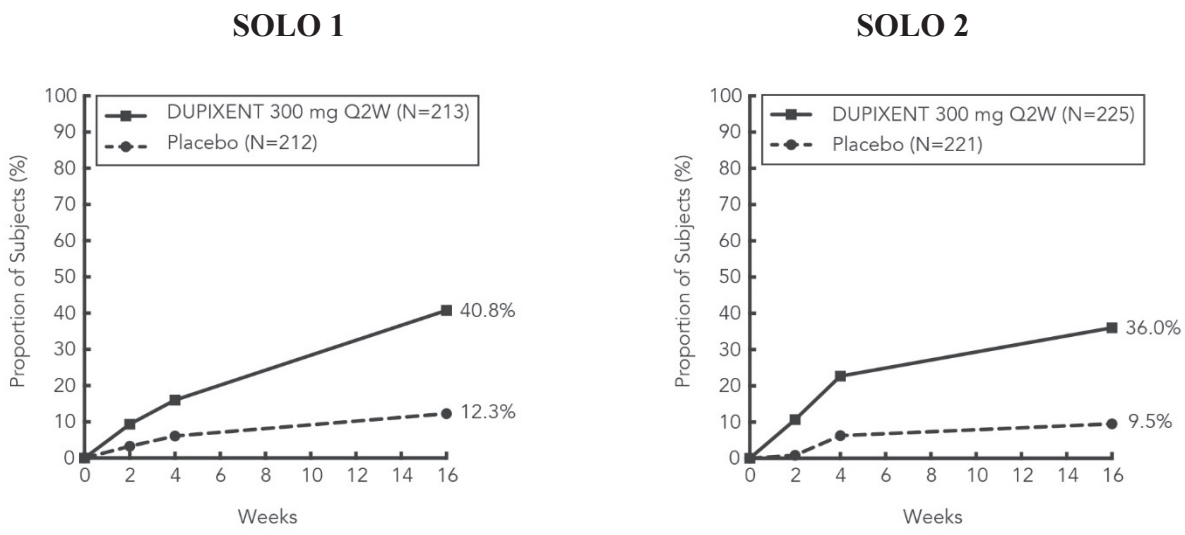
The results of the DUPIXENT monotherapy trials (SOLO 1 and SOLO 2) and the DUPIXENT with concomitant TCS trial (CHRONOS) are presented in Table 16.

Table 16: Efficacy Results of DUPIXENT with or without Concomitant TCS at Week 16 (FAS) in Adult Subjects 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 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 17.

Table 17: Efficacy Results (IGA 0 or 1) of DUPIXENT with Concomitant TCS at Week 16 and 52 in Adult Subjects 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 Years of Age and Older with Atopic Dermatitis

The efficacy of DUPIXENT monotherapy in pediatric subjects 12 years of age and older 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 18.

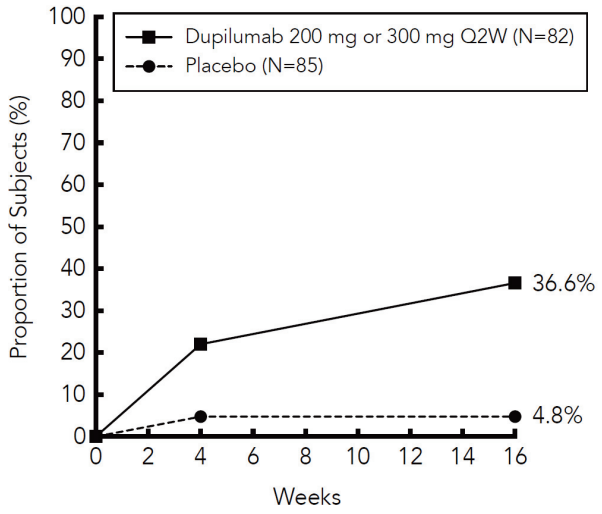
Table 18: Efficacy Results of DUPIXENT in AD-1526 at Week 16 (FAS)[a] in Pediatric Subjects 12 Years of Age and Older with Moderate-to-Severe AD

	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 Years of Age and Older 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 19 presents the results by baseline weight strata for the approved dose regimens.

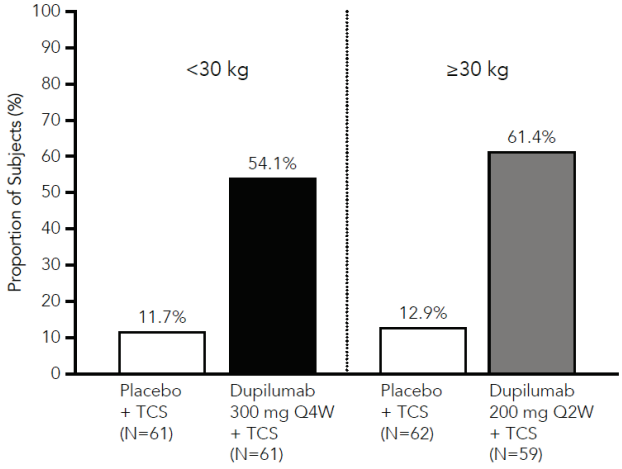
Table 19: Efficacy Results of DUPIXENT with Concomitant TCS in AD-1652 at Week 16 (FAS)[a] in Pediatric Subjects 6 to 11 Years of Age with AD

	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 20.

Table 20: 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 21.

Table 21: Efficacy Results of DUPIXENT in Liberty-AD-HAFT at Week 16 (FAS)[a] in Adult and Pediatric Subjects 12 Years of Age and Older 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 2 weeks (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 22 below.

Table 22: 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 23.

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 23: 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)

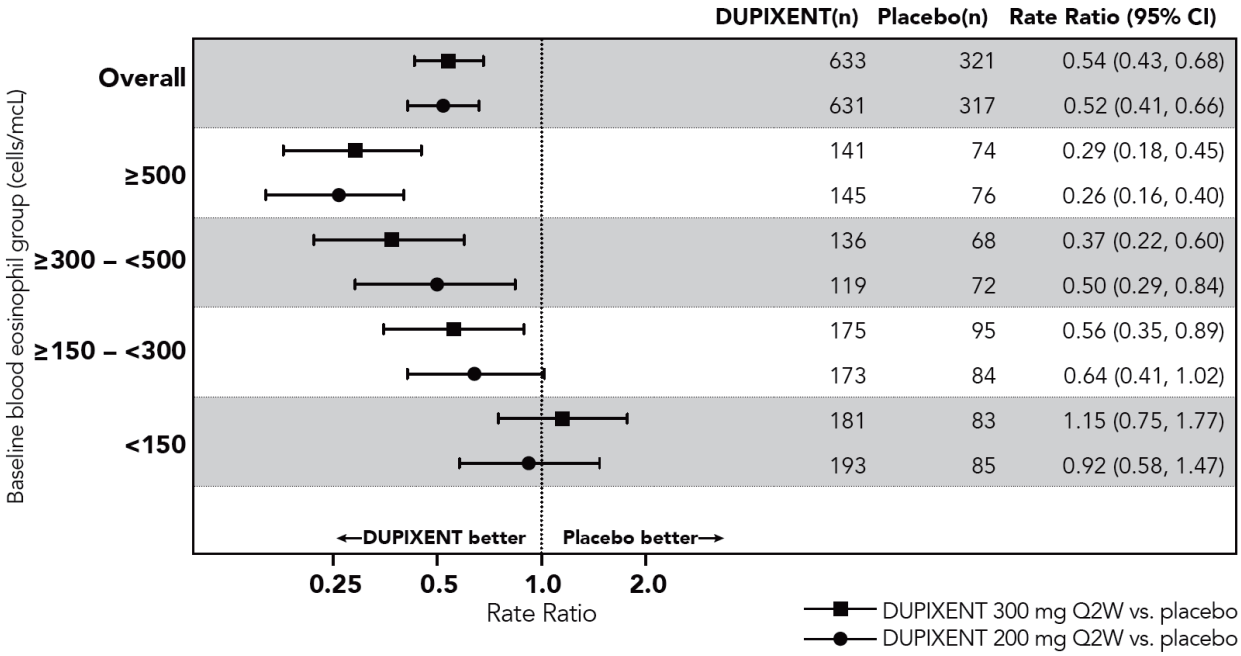
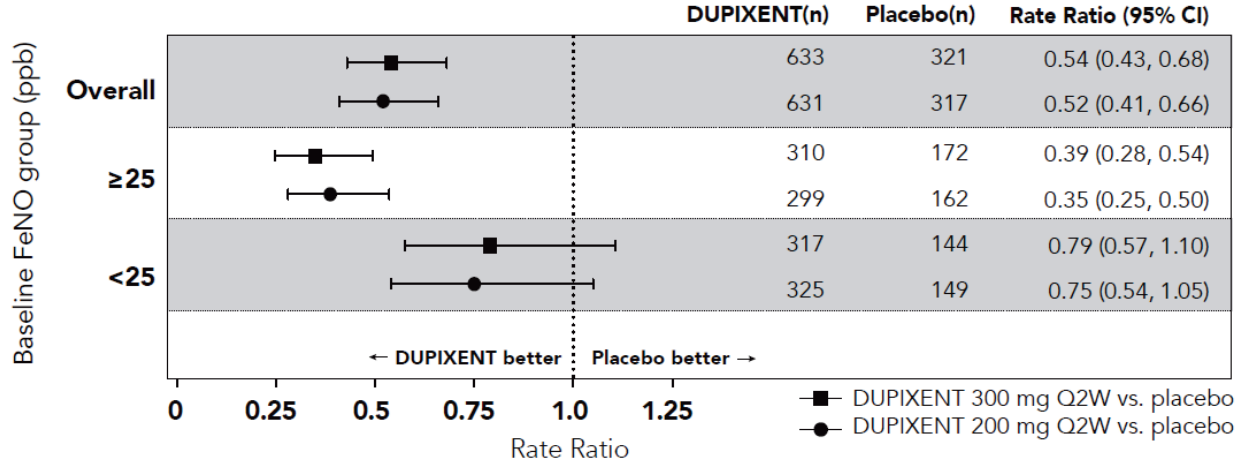
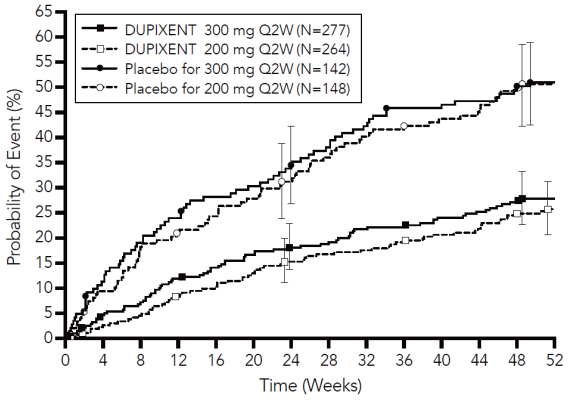


Figure 5: Relative Risk in Annualized Event Rate of Severe Exacerbations across Baseline FeNO Group (ppb) in Subjects with Moderate-to-Severe Asthma (QUEST)



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 24.

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 24: 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)

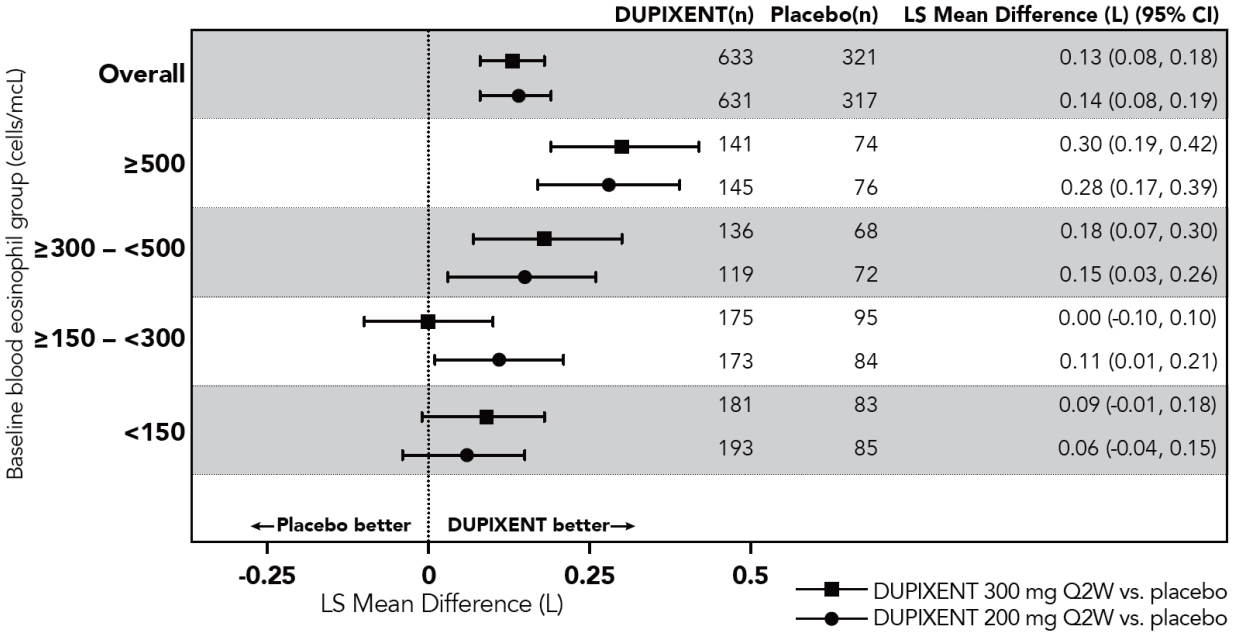


Figure 8: LS Mean Difference in Change from Baseline vs Placebo to Week 12 in Pre-bronchodilator FEV_1 across Baseline FeNO (ppb) in Subjects with Moderate-to-Severe Asthma (QUEST)

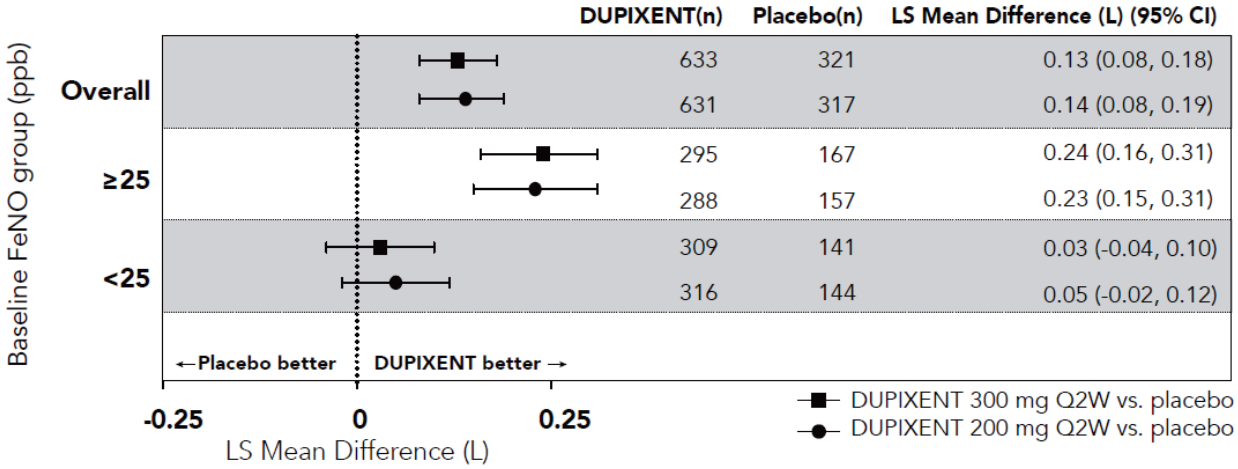
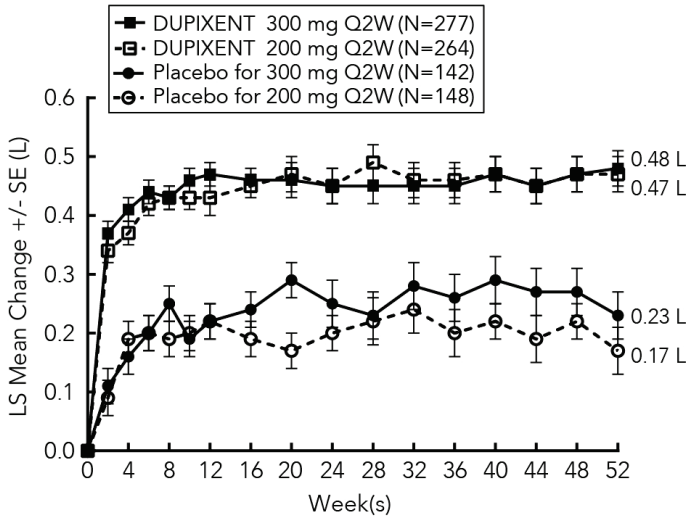


Figure 9: Mean Change from Baseline in Pre-Bronchodilator FEV_1 (L) Over Time in Subjects with Moderate-to-Severe Asthma with Baseline Blood Eosinophils ≥300 cells/mcL (QUEST)



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 2 weeks 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 25 below.

Table 25: 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).

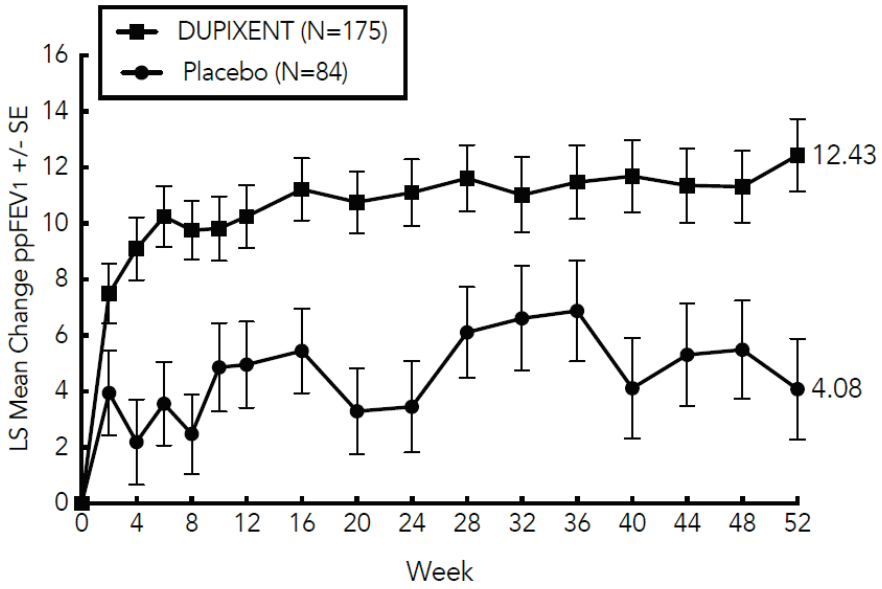
The efficacy results for VOYAGE are presented in Table 26.

Table 26: 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 2 weeks for 24 weeks. In SINUS-52, 448 subjects were randomized to receive either 300 mg DUPIXENT (N=150) every 2 weeks for 52 weeks, 300 mg DUPIXENT (N=145) every 2 weeks 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 27 below.

Table 27: 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 28.

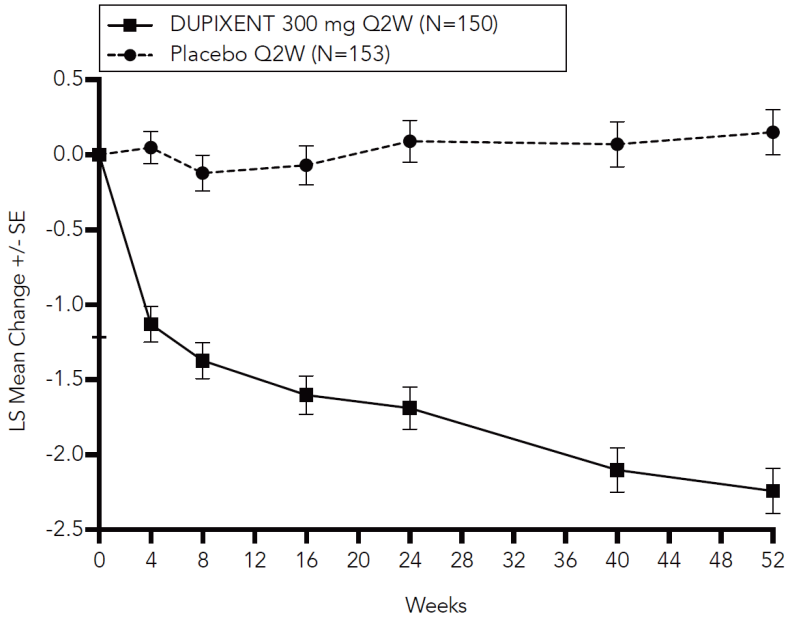
Table 28: Results of the Primary Endpoints in CRSwNP Trials

	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

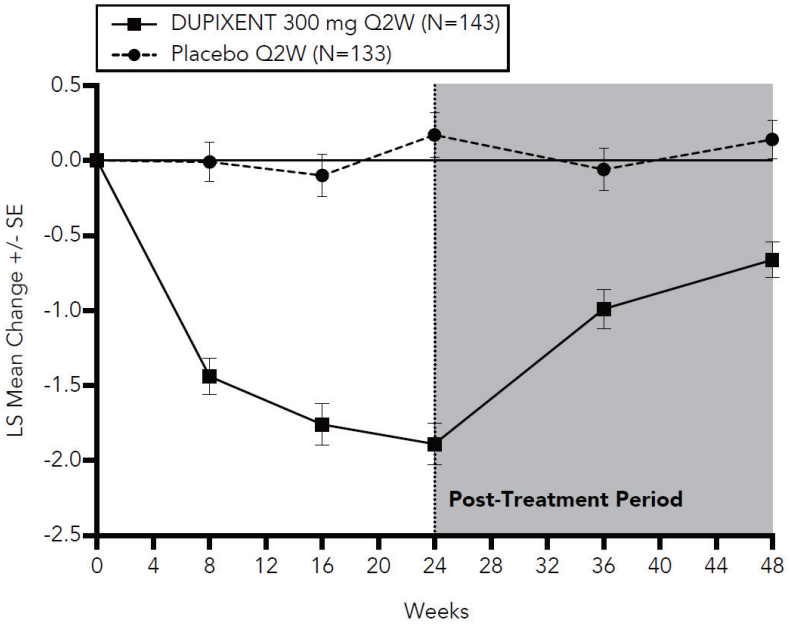
Statistically significant efficacy was observed in SINUS-52 with regard to improvement in bilateral endoscopic NPS score at week 24 and week 52 (see Figure 11).

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.

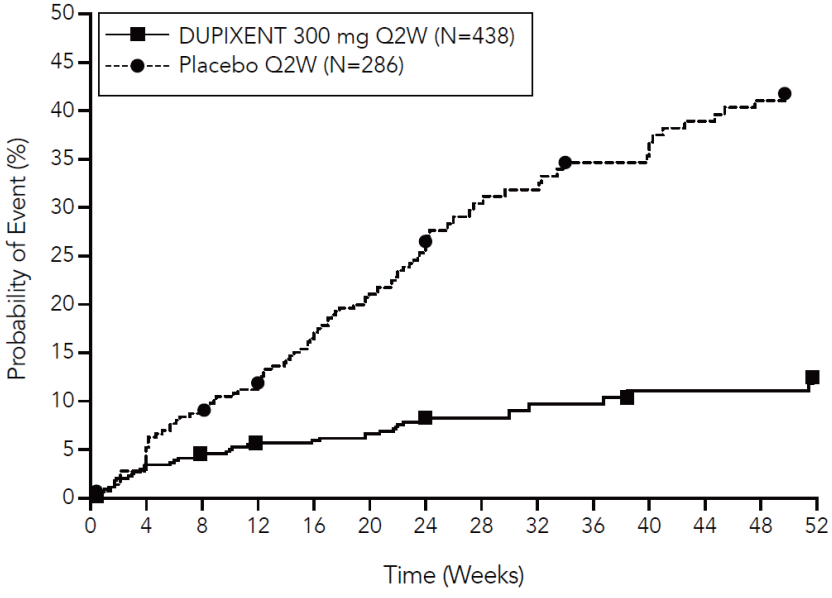
A significant decrease in the LMK sinus CT scan score was observed. The LS mean difference for LMK sinus CT scan score at Week 24 in the DUPIXENT group versus placebo was -7.44 (95% CI: -8.35, -6.53) in SINUS-24 and -5.13 (95% CI: -5.80, -4.46) in SINUS-52. At Week 52, in SINUS-52 the LS mean difference 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 29.

Table 29: 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 30.

Table 30: 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 efficacy of DUPIXENT in adults with prurigo nodularis (PN) was evaluated in two 24-week randomized, double-blind, placebo-controlled, multicenter, parallel-group trials (PRIME (NCT04183335) and PRIME 2 (NCT04202679)). These trials enrolled 311 adult subjects 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 2 weeks (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 31 and Figures 14, 15, and 16.

Table 31: 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

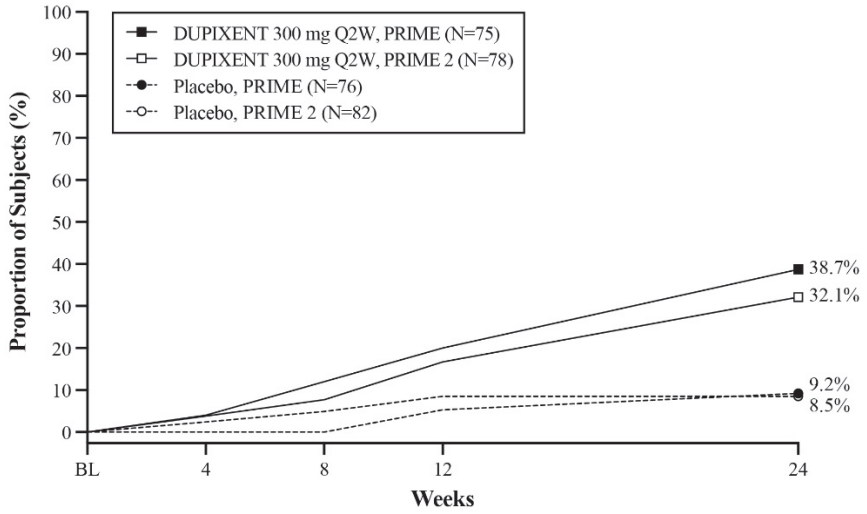


Figure 15: Proportion of Adult Subjects with PN with WI-NRS ≥4-point Improvement Over Time in PRIME and PRIME2

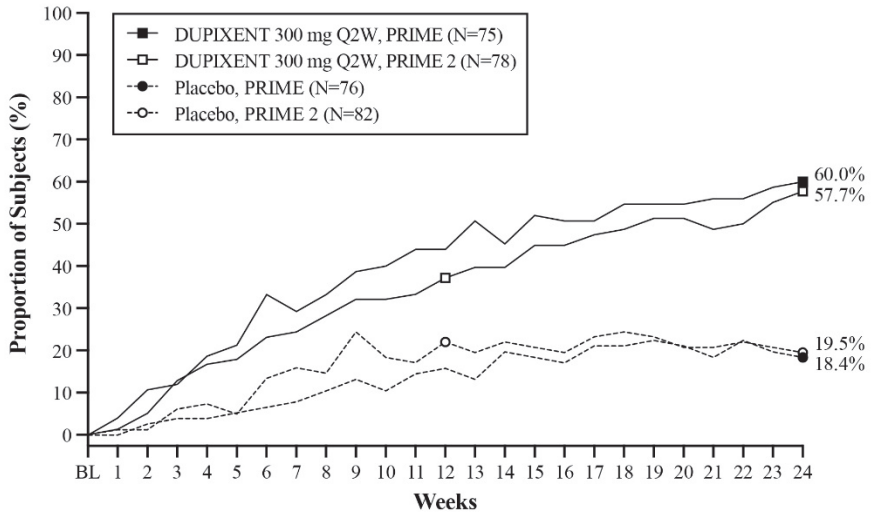
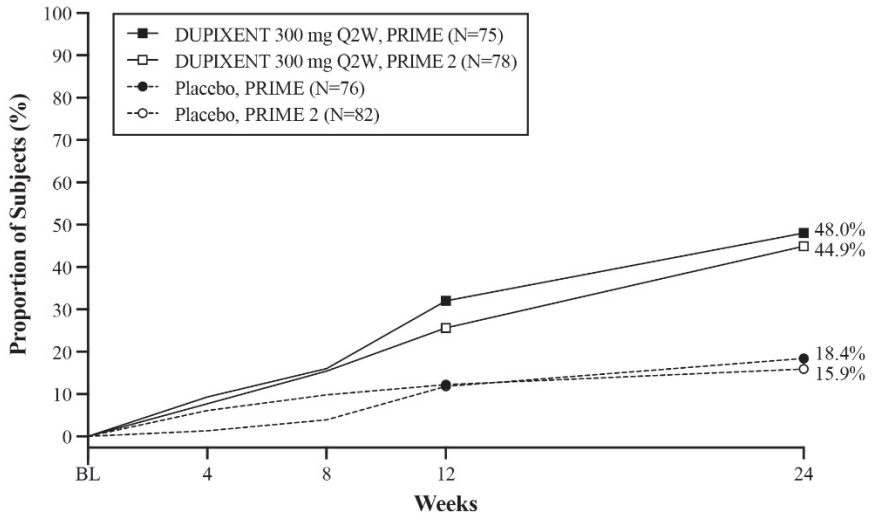


Figure 16: Proportion of Adult Subjects with IGA PN-S 0 or 1 Over Time in PRIME and PRIME 2



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 2 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 32 below.

Table 32: 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 33).

Table 33: 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

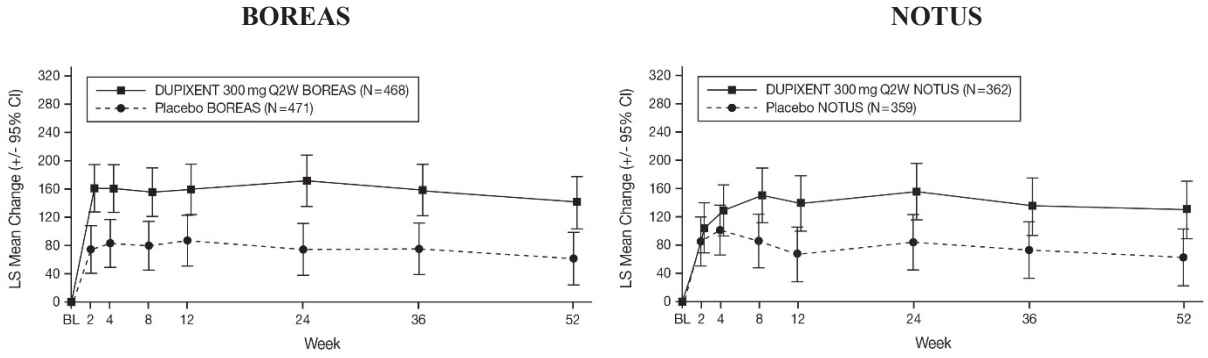
In both trials (BOREAS and NOTUS), DUPIXENT demonstrated numerical improvement in post-bronchodilator FEV_1 at Weeks 12 and 52 compared to placebo when added to background maintenance therapy (see Table 34 and Figure 17). Significant improvements of similar magnitude were observed in change from baseline in pre-bronchodilator FEV_1 at Weeks 12 and 52 in subjects treated with DUPIXENT compared to placebo across both trials.

Table 34: 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).

14.7 Chronic Spontaneous Urticaria

The efficacy of DUPIXENT for the treatment of adult and pediatric patients aged 12 years and older with chronic spontaneous urticaria who remain symptomatic despite H1 antihistamine treatment was evaluated in a master protocol clinical trial (CUPID [NCT04180488]) that included three 24-week, randomized, double-blind, parallel-group, multicenter, placebo-controlled trials (CUPID Study A, Study B, and Study C), followed by 12-week blinded safety follow-up periods. CUPID Study A and Study C included subjects who remained symptomatic despite H1 antihistamine treatment and were anti-IgE treatment naïve, while CUPID Study B included patients who remained symptomatic despite H1 antihistamine and anti-IgE treatments. The efficacy of DUPIXENT was based only on CUPID Study A and Study C; Study B did not meet the primary endpoint.

CUPID Study A and Study C

A total of 284 adult and pediatric patients 12 years of age and older with CSU (Itch Severity Score over 7 days (ISS7) ≥8 on a scale of 0 to 21 and Urticaria Activity Score over 7 days (UAS7) ≥16 on a scale of 0 to 42) who were symptomatic despite the use of H1 antihistamines, but who were anti-IgE treatment naïve, were enrolled in CUPID Study A and Study C. In the DUPIXENT group, adults and pediatric subjects (12 years of age and older) weighing ≥60 kg received a subcutaneous dose of DUPIXENT 600 mg on Day 1, followed by 300 mg every 2 weeks (Q2W), while pediatric subjects (12 years of age and older) weighing 30 kg to less than 60 kg received a subcutaneous dose of DUPIXENT 400 mg on Day 1, followed by 200 mg Q2W. The demographics and baseline characteristics of the efficacy population in CUPID Study A and Study C are provided in Table 35.

Table 35: Demographics and Baseline Characteristics of Subjects with CSU in CUPID Study A and Study C

	CUPID Study A (N=136)	CUPID Study C (N=148)
Mean age (years) (SD)	42 (15.1)	46 (16.3)
% Female	66	70
% White	68	45
% Asian	26	42
% Black	2	1
% Hispanic or Latino	18	16
Mean body weight (kg)	77	74
Mean ISS7	16	15.1
Mean UAS7	31.4	28.2
Mean HSS7	15.4	13.1
% subjects with UAS7 ≥28	70.6	58.8

	CUPID Study A (N=136)	CUPID Study C (N=148)
Median total IgE IU/ml (Q1,Q3)	101 (40.3, 252)	108 (37, 309)

ISS7 = Itch Severity Score over 7 days; UAS7 = Urticaria Activity Score over 7 days; HSS7 = Hives Severity Score over 7 days; H1AH = H1 antihistamine; Q1 = 1st quartile; Q3 = 3rd quartile

The primary endpoint was change from baseline in itch severity score over 7 days (ISS7) at Week 24. The ISS7 score was defined as the sum of the daily itch severity scores (ISS), from 0 to 3, recorded at the same time of the day for a 7-day period, ranging from 0 to 21.

The key secondary endpoint was change from baseline in urticaria activity score over 7 days (UAS7) at Week 24. The UAS7 (range 0 to 42) was a composite of the weekly itch severity score (ISS7, range 0 to 21) and the weekly hive count score (HSS7, range 0 to 21).

The results for primary and secondary endpoints in CUPID Study A and Study C are presented in Table 36.

Table 36: Efficacy Results in Subjects with CSU in CUPID Study A and Study C

	CUPID Study A			CUPID Study C		
	DUPIXENT (N=68)	Placebo (N=68)	DUPIXENT vs. Placebo (95% CI)	DUPIXENT (N=73)	Placebo (N=75)	DUPIXENT vs. Placebo (95% CI)
Primary Endpoint						
Change from baseline in ISS7 at Week 24[a]	-10.44 (0.92)	-6.02 (0.94)	-4.42 (-6.84, -2.01)[b]	-8.50 (1.39)	-6.13 (1.38)	-2.37 (-4.48, -0.27)[b]
Secondary Endpoints						
Change from baseline in UAS7 at Week 24[a]	-20.99 (1.77)	-11.95 (1.81)	-9.04 (-13.68, -4.40)[b]	-15.61 (2.62)	-11.27 (2.61)	-4.34 (-8.31, -0.36)[b]
Change from baseline in HSS7 at Week 24[a]	-10.54 (0.91)	-5.85 (0.93)	-4.69 (-7.08, -2.30)[b]	-7.16 (1.30)	-5.15 (1.29)	-2.01 (-3.98, -0.04)[b]
Proportion of patients with UAS7 ≤6 at Week 24[a]	32 (47.1)	16 (23.5)	3.23 (1.43, 7.27)[c]	29 (39.7)	17 (22.7)	3.05 (1.32, 7.02)[c]
Proportion of patients with UAS7 = 0 at Week 24[a]	22 (32.4)	9 (13.2)	3.09 (1.24, 7.69)[c]	22 (30.1)	13 (17.3)	2.73 (1.15, 6.50)[c]

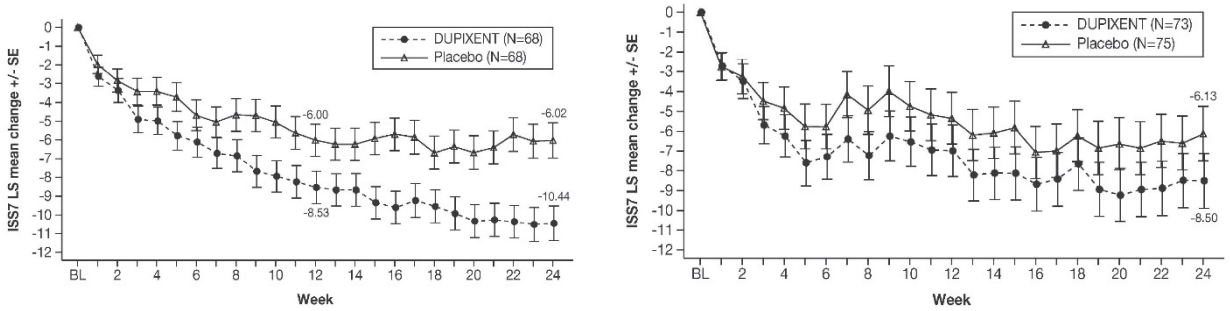
[a] Values presented are LS mean change from baseline (SE) for continuous variables and number and percent of responders for binary variables.
[b] Values presented are LS mean differences.
[c] Values presented are odds ratios.

CUPID Study A showed significant improvement in ISS7 and UAS7 from baseline at Week 12 in the DUPIXENT group (LS mean difference DUPIXENT versus placebo of -2.53 [95% CI: (-4.79, -0.27)] for ISS7 and -5.44 [95% CI: (-9.77, -1.11)] for UAS7). The proportion of patients with UAS7 ≤6 at Week 12 in CUPID Study A was 35.3% in the DUPIXENT group and 17.6% in the placebo group (Odds Ratio: 2.79 [95% CI: (1.22, 6.40)]).

Mean changes in ISS7 over time in CUPID Study A and Study C are shown in Figure 18.

Figure 18: LS Mean Change from Baseline in ISS7 Over 24 Weeks in CUPID Study A and Study C

Study A **Study C**



Similar changes in UAS7 and HSS7 were observed over 24 weeks.

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

CUPID Study B

CUPID Study B enrolled 108 adult and pediatric patients 12 years of age and older with CSU who were inadequate responders (N=104) to H1 antihistamines and anti-IgE treatments or intolerant (N=4) to anti-IgE therapy. At baseline, the mean ISS7 was 16, mean UAS7 score was 31.5 and the mean HSS7 was 15.4. The majority of participants (69.4%) had a UAS7 score of ≥28 at baseline. The median (Q1, Q3) total IgE (IU/mL) at baseline was 77 (20, 204.5). CUPID Study B evaluated efficacy using the same primary and secondary endpoints as CUPID Study A and Study C. The DUPIXENT group in CUPID Study B did not meet statistical significance for reduction in the primary endpoint ISS7 at Week 24.

14.8 Bullous Pemphigoid

The efficacy of DUPIXENT in adults with bullous pemphigoid (BP) was evaluated in a 52-week randomized, double-blind, parallel-group, multicenter, placebo-controlled trial (ADEPT; NCT04206553). This trial enrolled 106 adult subjects with a Bullous Pemphigoid Disease Area Index (BPDAI) activity score ≥24 on a scale of 0-360 and a weekly average Peak Pruritus NRS score ≥4 on a scale of 0-10.

In this trial, subjects were randomized to receive either subcutaneous DUPIXENT 600 mg (two 300 mg injections) on Day 1, followed by 300 mg every other week (Q2W), or matching placebo for 52 weeks. All subjects were also initiated on a standard regimen of oral corticosteroids (prednisone or prednisolone; 0.5 or 0.75 mg/kg/day) on Day 1. After achieving control of disease activity for 2 weeks, oral corticosteroids (OCS) were tapered with the objective to taper them off no later than Week 16 as long as the control of disease activity was maintained. Subjects who experienced a loss of control of disease activity (new lesions form and existing lesions cease to heal) during OCS taper, or who relapsed post-taper, or who used rescue medications were considered treatment failures. During the OCS taper, subjects were permitted to increase their OCS once, with any subsequent increases being considered rescue therapy. Subjects could be

rescued during the trial with topical or oral corticosteroids, non-steroidal immunosuppressive medications, or immunomodulating biologics. Subjects were allowed to continue trial treatment if rescued with topical or oral corticosteroids.

Demographics and baseline characteristics were similar between the treatment arms. Of the 106 subjects enrolled, the mean age was 71.3 years; 53% were female; 68% were White, 2% were Black or African American, and 15% were Asian; 3% of subjects identified as Hispanic or Latino. At baseline, 63% of subjects had prior systemic corticosteroid use for BP. The mean Peak Pruritus NRS score was 7.5 at baseline.

The primary endpoint was the proportion of subjects achieving sustained remission at Week 36. Sustained remission was defined as the achievement of complete remission and off OCS no later than Week 16, absence of disease relapse from the time of completion of the corticosteroid taper to Week 36, and absence of rescue therapy during the 36-week double-blind treatment period. Secondary endpoints included total cumulative dose of OCS and proportion of subjects with a reduction in itch defined as at least a 4-point improvement (reduction) in the Peak Pruritus NRS.

The efficacy results for ADEPT are presented in Table 37. The proportion of subjects that received rescue therapy during the 36-week treatment period was 53% in the DUPIXENT group and 79% in the placebo group.

Table 37: Efficacy Results of DUPIXENT at Week 36 in Adults with BP in ADEPT

	DUPIXENT 300 mg Q2W + OCS (N=53)	Placebo + OCS (N=53)	Difference (95% CI) for DUPIXENT vs. Placebo
Proportion of subjects achieving sustained remission[a]	18.3%	6.1%	12.2% (-0.8, 26.1)
Proportion of subjects with improvement (reduction) of ≥4 points in Peak Pruritus NRS from baseline	38.3%	10.5%	27.8% (11.6, 43.4)

[a] Sustained remission was defined as the achievement of complete remission and off OCS no later than Week 16, absence of disease relapse from the time of completion of the corticosteroid taper to Week 36, and absence of rescue therapy during the 36-week double-blind treatment period.

The median (min, max) cumulative dose of OCS at Week 36 was 2.8 g (1.2, 22.7) in the DUPIXENT group compared to 4.1 g (1.5, 23.3) in the placebo group.

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 (150 mg/mL) Pre-filled Syringe with Needle Shield**	**200 mg/1.14 mL (175 mg/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 (150 mg/mL) Pre-filled Pen**	**200 mg/1.14 mL (175 mg/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)]*.

Advise patients to report signs and symptoms of AGEP to their healthcare provider *[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 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)]*.

Psoriasis

Advise patients that cases of new-onset psoriasis have been reported with the use of DUPIXENT. Advise patients to report new-onset psoriasis symptoms to their healthcare provider *[see Warnings and Precautions (5.7)]*.

Arthralgia and Psoriatic Arthritis

Advise patients that cases of new-onset psoriatic arthritis have been reported with the use of DUPIXENT. Advise patients to report new onset or worsening joint symptoms to their healthcare provider *[see Warnings and Precautions (5.8)]*.

Parasitic (Helminth) Infections

Advise patients to notify their healthcare provider if they present with clinical features consistent with helminthic infection *[see Warnings and Precautions (5.9)]*.

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 (5.10)]*.

Manufactured by:

Regeneron Pharmaceuticals, Inc.

Tarrytown, NY 10591

U.S. License No. 1760

Marketed by:

sanofi-aventis U.S. LLC (Morristown, NJ 07960) and

Regeneron Pharmaceuticals, Inc. (Tarrytown, NY 10591)

For patent information: www.dupixent-patents.com

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REGENERON sanofi

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（水疱性類天疱瘡）

Total number of pages: 2

「水疱性類天疱瘡」に係る本一部変更承認申請時点において、効能・効果、用法・用量、化学構造、薬理作用からみて、本剤に類似していると考えられる同種同効品は存在しない。

※　最新の添付文書を参照すること。

添付文書（案）

20xx 年 X 月改訂（第 X 版）

日本標準商品分類番号
87449

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

	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
- ○ 中等症から重症の水疱性類天疱瘡
- ○ 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］

〈水疱性類天疱瘡〉
5.7 最新の国内診療ガイドラインを参考に、全身性ステロイド薬の投与が必要な中等症から重症の水疱性類天疱瘡患者に対して本剤を投与すること。
5.8 本剤の適用に先立ち、全身性ステロイド薬単独による治療の実施も考慮すること。患者の症状や状態に応じて、全身性ステロイド薬単独による治療を行わず、本剤と全身性ステロイド薬の併用による治療を開始する場合は、最新の国内診療ガイドライン等を参照の上で、本剤の投与の必要性を慎重に判断すること。
〈気管支喘息〉
5.9 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。
5.10 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。［17.1.7-17.1.9 参照］
5.11 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〉
5.12 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。
5.13 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。［17.1.10 参照］
5.14 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〉
5.15 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
〈水疱性類天疱瘡〉
通常、成人にはデュピルマブ（遺伝子組換え）として初回に 600mg を皮下投与し、その後は 1 回 300mg を 2 週間隔で皮下投与する。
〈気管支喘息〉
通常、成人及び 12 歳以上の小児にはデュピルマブ（遺伝子組換え）として初回に 600mg を皮下投与し、その後は 1 回 300mg を 2 週間隔で皮下投与する。
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］
〈水疱性類天疱瘡〉
7.4 本剤は全身性ステロイド薬と併用で投与を開始すること。病勢のコントロールが得られた後には全身性ステロイド薬の漸減を考慮すること。

8. 重要な基本的注意

〈効能共通〉

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

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

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

8.4 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。[11.1.3 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、水疱性類天疱瘡、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〉

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 急性汎発性発疹性膿疱症（0.1%未満）

11.1.3 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、	眼そう痒症、~~角膜~~

		眼瞼炎、眼乾燥、角膜炎	~~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反応発現割合は、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

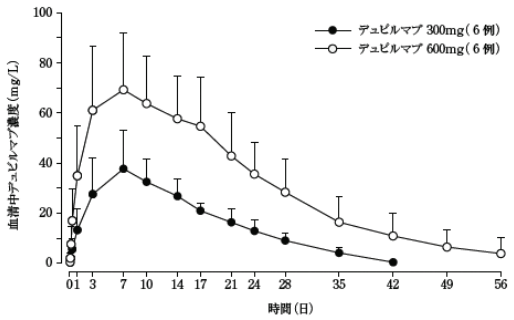
効能		ADA 陽性反応発現割合	持続する ADA 陽性反応発現割合	中和抗体陽性反応発現割合
アトピー性皮膚炎	成人	約 6%	約 2%	約 1%
	12～17 歳	約 16%	約 3%	約 5%
	生後 6 カ月～11 歳	約 2%	0%	約 1%
結節性痒疹		約 8%	約 1%	約 3%
特発性の慢性蕁麻疹		約 7%	約 1%	約 2%
水疱性類天疱瘡		約 4%	0%	約 4%
気管支喘息	12 歳以上	約 5%	約 2%	約 2%
	6～11 歳	約 6%	約 3%	約 2%
慢性閉塞性肺疾患		約 8%	約 3%	約 3%
鼻茸を伴う慢性副鼻腔炎		約 5%	約 2%	約 3%

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、水疱性類天疱瘡、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)-9),12),13)]（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
水疱性類天疱瘡	48	66.7±47.4	16
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),11)]（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 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、水疱性類天疱瘡、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、61～66 ~~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
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]

〈水疱性類天疱瘡〉

17.1.6 国際共同第Ⅱ/Ⅲ相試験

ベースラインでの疾患重症度が中等症から重症[注1)]に該当する18歳以上の水疱性類天疱瘡患者106例（日本人患者10例を含む）を対象に、本剤300mgを2週に1回、又はプラセボを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。全ての患者が経口ステロイド薬の基本治療を併用し、病勢コントロールが2週間維持された時点で経口ステロイド薬の漸減を開始することとした。主要評価項目である投与後36週時点の持続的な寛解[注2)]を達成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に高かった（P値：0.0250）[8)]。

注1）中等症はBPDAI総スコアが24以上60未満、重症は60以上

注2）以下の全てをみたすことと定義：

- 投与後16週までに完全寛解かつ経口ステロイド薬非使用が達成される。完全寛解は、新たな病変が認められることなく、既存の病変の上皮化が認められることと定義される。
- 経口ステロイド薬の漸減を完了した時点（投与後16週まで）から投与後36週まで疾患の再燃がない。再燃は、1か月に3か所以上の新たな病変（水疱、湿疹性病変又は蕁麻疹様紅斑）、又は1週間以内に治癒しない1か所以上の大きな（直径10cmを超える）湿疹性病変若しくは蕁麻疹様紅斑が出現することと定義される。
- 36週間の二重盲検治験薬投与期間中に救済治療の必要がない。救済治療には、経口ステロイド薬漸減中の経口ステロイド薬の増量、経口ステロイド薬漸減完了後の経口ステロイド

薬の再開、又は疾患に対する治療の開始が含まれる。

投与後 36 週時点の有効性の成績

評価項目	本剤群 (53 例)	プラセボ群 (53 例)	プラセボ群との差 [95%信頼区間] p 値
持続的寛解達成率 (%) 注 3)	18.2	4.0	14.2 [1.97, 27.74] 注 4) 0.0250 注 5)

注 3) 救済治療を受けた患者は、救済治療後はノンレスポンダーとした。投与後 36 週以前に、有効性の欠如、副作用又は死亡により試験を中止し、投与後 36 週時の持続的寛解の評価が欠測となった患者はノンレスポンダーとされ、その他の理由で投与後 36 週時の持続的寛解の評価が欠測となった患者は多重補完法により補完した。

注 4) Miettinen and Nurminen の方法により信頼区間を算出

注 5) 有意水準両側 5%、Barnard の正確検定

本剤群での副作用は 26.4% (14/53 例)、プラセボ群では 15.1% (8/53 例) に認められ、本剤群の主な副作用は結膜炎 3.8%であった。

〈気管支喘息〉

17.1.7 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[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) 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 300mg 群	 プラセボ群	プラセボ群との比[注 7)] [95%信頼区間]
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。［5.10 参照］

17.1.8 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[10)]。

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、ベースライン時の体重区分、地域、民族、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、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。

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)]		プラセボ群との比[注10)] ［95%信頼区間］
		本剤群	プラセボ群	
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。[5.10 参照]

17.1.9 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[11)]。

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 30 kg 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%信頼区間]	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
年間増悪発生率（回/人･年）[注4)]		0.462	0	1.001	0.430

注 4）喘息増悪発生件数を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。[5.10 参照]

〈慢性閉塞性肺疾患〉

17.1.10 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）[12)]。

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）

	本剤群 (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。［5.13 参照］

〈鼻茸を伴う慢性副鼻腔炎〉

17.1.11 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 $p<0.0001$）[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 [95%信頼区間][注5)]	10.30 [8.50, 12.10]	10.76 [8.95, 12.57]	

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。

17.1.12 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[14)]。

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、水疱性類天疱瘡、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[15)]。

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[15)]。

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[15)]。

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、CTD2.7.6.2.16）
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、CTD2.7.6.2.1, CTD 2.7.6.2.2）
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、CTD2.7.6.2.1）
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、CTD2.7.6.2.1）
8）社内資料：水疱性類天疱瘡患者を対象とした国際共同第Ⅱ/Ⅲ相試験（20xx 年 x 月 x 日承認、CTD2.7.6.2.1, CTD 2.7.6.2.2）
9）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、CTD2.7.6.2.4）
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海外第Ⅲ相試験（2025 年 12 月 22 日承認、CTD2.7.6.2.1）

11)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（2025 年 12 月 22 日承認、CTD2.7.6.2.3）
12)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、CTD2.7.6.2.1）
13)Bachert,C.,et al.: Lancet. 2019; 394（10209）：1638-50
14)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相単独療法試験
15)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

4 「効能又は効果」（案）

中等症から重症の水疱性類天疱瘡

[設定根拠]

本申請におけるデュピルマブの「効能又は効果」（案）は、中等症から重症の水疱性類天疱瘡（BP）を対象とした第 2/3 相国際共同ピボタル試験（日本を含む）である R668-BP-1902 試験の成績に基づき設定した。

以下に、効能又は効果（案）の設定根拠を示す。

BP はまれで深刻な自己免疫性の表皮下水疱を生じる疾患であり、主に高齢者で好発し、慢性かつ再燃性の臨床経過をたどり、高い罹患率及び死亡率と関連している。水疱性、びらん性又は膿疱性の病変に関連する難治性のそう痒及び疼痛／不快感のため、BP は患者の睡眠、気分及び生活の質（QoL）に深刻な悪影響を及ぼすことが多い。2 型炎症過程は、BP の発症において重要な役割を果たす。日本での BP の定義及び診断は、米国及び欧州で用いられているものと同様である。

BP の治療の主な目的は、皮膚の発疹やかゆみをコントロールし、QoL を向上させ、疾患の再燃のリスクを予防又は低減し、治療に関連する副作用を最小限に抑えることである。高齢の BP 患者集団に対する治療方針は、併存疾患に対する負荷の増大、加齢に伴う薬物代謝の変化、多剤併用に関連するリスク、通院に関する配慮、及び治療の副作用が QoL に及ぼす影響のため、特別な考慮が必要である。

BP の治療は、日本、米国及び欧州で同様であり、外用ステロイド薬又は経口ステロイド薬（OCS）が通常の治療選択肢として用いられている。OCS は中等症から重症の BP に対する治療の中心と考えられるが、高用量 OCS の慢性的な使用は、特に高齢者では有害でときに重篤な副作用を引き起こし、BP に関連する死亡率が高くなる一因となる。また、特に OCS の漸減下で疾患の再燃が頻繁に起こる。Very potent（Group IV）の外用ステロイド薬は有効性があること及び OCS よりも死亡率が低いことが示されている一方で、BP の再燃率は OCS よりも高く、皮膚への副作用、全身吸収及び長期持続使用の実現が難しいことから、単独での使用は制限される。ステロイド薬に対する反応性が低い再燃若しくは難治の BP の場合、又はステロイド薬が禁忌の場合は、免疫抑制薬又は免疫調節薬を使用することができる。これらの全身性免疫抑制療法は、特に高齢の BP 患者集団に用いる際には死亡率の上昇を含む、重篤な副作用を伴うため、短期間の使用や断続的な治療に限定される。このこ

とにより、治療の中止や疾患の再燃につながることが多く、罹患率及び死亡率に悪影響を及ぼすことになる。以上より、BP に対する現行の標準治療は重大な副作用を伴うため、BP 及び関連する併存疾患を有する脆弱な高齢者集団への使用が制限される。BP の根底にある 2 型炎症過程を標的として病勢をコントロールし、ステロイド薬及び全身性免疫抑制薬の必要性を最小限に抑え、脆弱な高齢者集団における長期使用に対して良好な安全性プロファイルを有するより安全な治療選択肢に対する大きなアンメットメディカルニーズが存在する。

デュピルマブは、インターロイキン（IL）-4 受容体 α サブユニット（IL-4Rα）に結合し、リガンドである IL-4 及び IL-13 を介したシグナル伝達を阻害する遺伝子組換えヒト免疫グロブリン G4 モノクローナル抗体であり、これにより BP の発症に関与する 2 型炎症経路を選択的に阻害する。BP の新しい治療薬としてのデュピルマブの目標は、特に高齢者集団におけるステロイド薬非使用下での疾患の持続的な寛解の達成、BP に関連する徴候及び症状の軽減、疾患の再燃の防止であり、特に重要な点は、OCS の使用及びステロイド薬に関連する重大な副作用、並びに罹患率を最小限に抑えることである。

R668-BP-1902 試験は、中等症から重症の成人 BP 患者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国際共同（日本を含む）、多施設共同、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る。被験者のベースラインの重症度は Bullous Pemphigoid Disease Area Index［BPDAI］総スコアに従って評価し、総スコア 24 以上 60 未満を中等症、60 以上を重症と定義した。合計 106 名（日本人被験者 10 名を含む）がデュピルマブ 300 mg q2w 群（以下、デュピルマブ群）又はプラセボ群のいずれかに 1：1 の比でランダム化された（デュピルマブ群：53 名、プラセボ群：53 名）。

主要評価項目は、Week 36 で持続的寛解を達成した被験者の割合という厳格な複合評価項目であり、各被験者は以下に示す BP の臨床的に意義のある 3 つの側面の全てを満たす必要があった。

1. Week 16 までに完全寛解かつ OCS 非使用を達成すること
2. OCS の漸減を完了した時点から Week 36 まで疾患の再燃がないこと
3. 36 週間の二重盲検治験薬投与期間中に救済治療の必要がないこと

本治験では主要評価項目を達成し、プラセボ群と比較して、デュピルマブ群では Week 36 に持続的寛解を達成した被験者の割合が約 5 倍高かった。また、主要評価項目を構成する各項目の結果から、プラセボ群と比較して、デュピルマブ群ではより多くの被験者が Week 36 まで OCS 非使用下で疾患の再燃がない持続的な寛解及び Week 36 まで救済治療の必要ない持続的な寛解を達成したことが明らかになった。

主要なベネフィットである持続的な寛解の達成及び顕著な OCS 節約効果に加えて、デュピルマブは、Week 36 でのそう痒（かゆみ：最大のそう痒数値評価スケール［NRS］スコアで評価）、並びに皮膚の水疱／びらん、皮膚の膨疹／紅斑、及び粘膜の水疱／びらん（BPDAI スコアで評価）におい

て、プラセボと比較して統計学的に有意かつ臨床的に意味のある改善をもたらした。プラセボ群ではOCS 使用量が多かったにもかかわらず、デュピルマブ群でプラセボ群を上回るこれらのベネフィットが示されたことは注目すべきである。プラセボ群と比較して、デュピルマブ群では 36 週間の治験薬投与期間を通して OCS の総累積投与量が少なかった。また、プラセボ群と比較して、デュピルマブ群では救済治療薬を使用した被験者が少なく、救済治療薬の初回使用までの時間で評価した場合、36 週間の治験薬投与期間における救済治療薬使用のリスクはプラセボ群と比較してデュピルマブ群で統計学的に有意に低減した。OCS 非使用へと漸減した場合、プラセボ群と比較して、デュピルマブ群では 36 週間の治験薬投与期間を通して再燃が認められることなく、救済治療を使用せずに病勢コントロールが持続した被験者が多かった。プラセボ群では、かゆみ及び BPDAI スコアの悪化に伴って病勢コントロールが喪失し、OCS 非使用を達成できなかった又は病勢コントロールを得るための救済治療薬の使用を必要とした被験者が多かった。プラセボ群と比較して、デュピルマブ群では Week 36 における体表面積（BSA）に占める BP 病変の割合も低下した。デュピルマブ投与のベネフィットは、QoL の指標（自己免疫性水疱性疾患の QoL）、BPDAI そう痒スコア、並びに毎日の睡眠の質 NRS スコア及び毎日の皮膚疼痛 NRS スコアの週平均の数値的な改善で示された患者報告アウトカムの改善にも反映された。

デュピルマブは成人 BP 患者において忍容性が良好で、許容可能な安全性プロファイルを有していた。BP 患者において、安全性に関する新たな懸念又は BP に特有の懸念は特定されなかった。

R668-BP-1902 試験には、日本人 BP 患者が 10 名組み入れられた（デュピルマブ群：4 名、プラセボ群：6 名）。主要有効性評価項目において日本人部分集団と日本人以外の部分集団での一貫性が確認され、安全性の結果において日本人部分集団と全体集団で大きな差は認められなかった。これらの結果は、BP 患者でのデュピルマブに対する臨床反応において、民族的要因に基づく大きな違いはないことを示している。したがって、申請者は、R668-BP-1902 試験の良好な結果に基づくデュピルマブのベネフィット及びリスクが日本人集団に適用可能であると結論付けた。

R668-BP-1902 試験で認められたデュピルマブのベネフィット・リスクプロファイルは、BP に対する他の全身療法及び局所療法とは一線を画していた。現行の治療法に対する選択肢が限られていることを踏まえると、デュピルマブは、BP の病因に関与する根底にある 2 型炎症経路を標的とすることで、ステロイド及び他の全身性免疫抑制薬の使用に通常伴う重大な副作用を伴わずに、BP の治療に対して効果的かつ新しい治療選択肢を提供することが期待される。

以上のことから、本申請でのデュピルマブの効能又は効果（案）を設定した。

6　「用法及び用量」（案）

通常、成人にはデュピルマブ（遺伝子組換え）として初回に 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。

[設定根拠]

成人の BP 患者に推奨されるデュピルマブの用法及び用量は、初回に 600 mg の皮下投与、その後は 300 mg q2w の皮下投与である。この用法及び用量は、これまでのデュピルマブの全ての適応症の臨床開発プログラム全体に含まれる試験データから選択され、上述の BP 患者を対象とした第 2/3 相国際共同ピボタル試験（R668-BP-1902 試験）で評価された。

以下に臨床試験の結果に基づく用法及び用量（案）の設定根拠を示す。

R668-BP-1902 試験では、デュピルマブの用法・用量として、Day 1 に初回用量 600 mg を皮下投与後、300 mg q2w の皮下投与が選択された。この用法・用量は、他の 2 型炎症性皮膚疾患の適応症（アトピー性皮膚炎［AD］及び結節性痒疹［PN］）において、有効かつ良好な安全性プロファイルを示した。また、AD では、有効な薬物濃度により迅速に到達するために初回用量を投与したことによって、AD の特徴であるそう痒の改善によって示される迅速な薬力学的反応が得られた。BP でもそう痒は中心的な症状であることから、有効な薬物濃度により迅速に到達するために、R668-BP-1902 試験で初回用量が選択された。さらに、デュピルマブ 300 mg q2w（初回用量 600 mg）を皮下投与した BP 患者の症例報告においても、BP におけるデュピルマブの有効性に関する予備的な臨床的エビデンスが得られた。選択された用法・用量は、被験者の大多数において標的を飽和させる血清中濃度に到達することが予想され、それによって治療が困難な BP 患者集団において、最大のベネフィットが得られ、最適なベネフィット・リスク比が達成されることが期待された。

R668-BP-1902 試験において、デュピルマブ 300 mg q2w を投与された成人 BP 患者におけるデュピルマブの血清中トラフ濃度（C_{trough}）の実測値は、AD、喘息、鼻茸を伴う慢性副鼻腔炎、好酸球性食道炎、PN 及び慢性閉塞性肺疾患を含むこれまでに検討された患者集団における同一用法・用量での実測値と同程度であった。また、これまでに開発した母集団薬物動態モデルで予測されたデュピルマブ濃度は、成人 BP 患者の実測デュピルマブ濃度と同程度であった。

R668-BP-1902 試験の結果、デュピルマブ 300 mg q2w（初回用量 600 mg）は、プラセボと比較して、Week 36 で持続的な寛解を達成した被験者の割合及び BPDAI スコアのベースラインから Week 36 までの変化率において顕著な改善を示した。有効性に関する濃度－反応解析では、デュピルマブ濃度の上昇と被験者が Week 36 で持続的な寛解を達成する確率の上昇に明らかな関連性は示されなかった。同様に、BPDAI スコアのベースラインからの変化率の平均値の経時的な推移では、デュピルマ

ブの C_{trough} の四分位群による順位付けと関連が見られなかった。このことから、より高い用量の投与がより有効な反応と関連するものではないことが示唆された。

デュピルマブ 300 mg q2w（初回用量 600 mg）は、成人 BP 患者において忍容性が良好で、許容可能な安全性プロファイルを有していた。BP 患者において、安全性に関する新たな懸念又は BP に特有の懸念は特定されなかった。

以上のことから、本申請でのデュピルマブの用法及び用量（案）を設定した。

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]

現行の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]

現行の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

〈アトピー性皮膚炎〉

省略

〈結節性痒疹〉

省略

〈特発性の慢性蕁麻疹〉

省略

〈水疱性類天疱瘡〉

5.7　最新の国内診療ガイドラインを参考に、全身性ステロイド薬の投与が必要な中等症から重症の水疱性類天疱瘡患者に対して本剤を投与すること。

5.8　本剤の適用に先立ち、全身性ステロイド薬単独による治療の実施も考慮すること。患者の症状や状態に応じて、全身性ステロイド薬単独による治療を行わず、本剤と全身性ステロイド薬の併用による治療を開始する場合は、最新の国内診療ガイドライン等を参照の上で、本剤の投与の必要性を慎重に判断すること。

〈気管支喘息〉

省略

〈慢性閉塞性肺疾患〉

省略

〈鼻茸を伴う慢性副鼻腔炎〉

省略

[設定根拠]

水疱性類天疱瘡患者を対象とした臨床試験結果や国内診療ガイドラインを踏まえ、投与対象となる患者を設定した。

7　用法及び用量に関連する注意

〈アトピー性皮膚炎〉

省略

〈アトピー性皮膚炎、特発性の慢性蕁麻疹、気管支喘息〉

省略

〈特発性の慢性蕁麻疹〉

省略

〈水疱性類天疱瘡〉

7.4　本剤は全身性ステロイド薬と併用で投与を開始すること。病勢のコントロールが得られた後には全身性ステロイド薬の漸減を考慮すること。

[設定根拠]

水疱性類天疱瘡患者を対象とした臨床試験結果を踏まえ、併用薬について設定した。

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。［11.1.3 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〉

省略

[設定根拠]

現行の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

〈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、水疱性類天疱瘡、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〉

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　水疱性類天疱瘡では小児を対象とした臨床試験は実施されていないことを追記した。（下線部追加）

その他は現行の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　急性汎発性発疹性膿疱症（0.1%未満）

11.1.3 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、角膜炎	眼そう痒症、潰瘍性角膜炎、~~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　水疱性類天疱瘡患者を対象とした臨床試験及びこれまでに得られた製造販売後の安全性情報に基づき、急性汎発性発疹性膿疱症を追加した。（下線部追加）

11.2　本剤の CCDS 及び水疱性類天疱瘡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。（下線部追加、取消線部削除）

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]

14.2.2　記載整備を行った。（取消線部削除）

その他は、現行の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反応発現割合は、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%
水疱性類天疱瘡		約 4%	0%	約 4%
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]

水疱性類天疱瘡患者における結果を追記した。（下線部追加）

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（水疱性類天疱瘡）

Total number of pages: 8

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	別紙のとおり
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〉 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。

<table>
<tr><td></td><td>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。</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
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>サル</td><td>静脈内（5 週間反復投与試験）</td><td>> 100</td></tr>
<tr><td></td><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>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></td><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>25</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及び注射部位紅斑各 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 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（日本人を含む）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
```

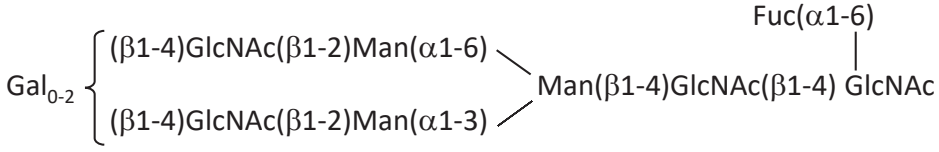
H 鎖

```
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	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 <u>中等症から重症の水疱性類天疱瘡</u> 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〉 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 <u>〈水疱性類天疱瘡〉</u> <u>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。</u>

	〈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及び注射部位紅斑各 3 例（4.3%）であった。 水疱性類天疱瘡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 53 例（日本人を含む）において、副作用は 14 例（26.4%）に発現し、主な副作用は結膜炎 2 例（3.8%）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 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（日本人を含む）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（水疱性類天疱瘡）

VV-REG-1669232 6.0

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
該当資料なし

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 in Adult and Pediatric Patients (>=1 Year of Age) with Eosinophilic Esophagitis (R668-PK-23108-SR-01V1)	20[redacted]	有	参考資料
5.3.3.5-2	Population Pharmacokinetic Analysis of Dupilumab in Adult Patients with Bullous Pemphigoid (R668-PM-24222-SR-01V1)	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 Multicenter, Randomized, Double-Blind, Placebo-Controlled, Parallel Group Study to Evaluate the Efficacy and Safety of Dupilumab in Adult Patients with Bullous Pemphigoid (R668-BP-1902 Primary Analysis CSR)	2020/10/28 - 2024/07/12	有	評価資料
5.3.5.1-1a	A Multicenter, Randomized, Double-Blind, Placebo-Controlled, Parallel Group Study to Evaluate the Efficacy and Safety of Dupilumab in Adult Patients with Bullous Pemphigoid (R668-BP-1902 Primary Analysis CSR Amendment 1)	2020/10/28 - 2024/07/12	有	評価資料
5.3.5.1-1b	A Multicenter, Randomized, Double-Blind, Placebo-Controlled, Parallel Group Study to Evaluate the Efficacy and Safety of Dupilumab in Adult Patients with Bullous Pemphigoid (R668-BP-1902 Addendum to Primary Analysis CSR Amendment 1)	2020/10/28 - 2025/01/05	有	評価資料

5.3.5.2 非対照試験報告書
該当資料なし

5.3.5.3 複数の試験成績を併せて解析した報告書

資料番号	標題	試験実施期間	電子データの有無	評価資料／参考資料
5.3.5.3-1	ISS: SUSARs and deaths from ongoing studies	20[redacted] - 20[redacted]	無	参考資料
5.3.5.3-2	R668-BP-1902 Primary Analysis CSR Post Hoc Analysis: Post-text Tables	–	無	参考資料
5.3.5.3-3	CTD 2.7.2 Post-text Tables, Figures, and Listings: R668-SCP-BP_20[redacted]	–	無	参考資料

5.3.5.4 その他の臨床試験報告書

資料番号	標題	試験実施期間	電子データの有無	評価資料／参考資料
5.3.5.4-1	Clinical Outcome Assessment Evidence Dossier for the BPDAI Activity Score, Peak Pruritus NRS, and ABQOL in Moderate to Severe Bullous Pemphigoid	–	無	参考資料
5.3.5.4-2	R668-BP-1902 Japanese subgroup	–	無	参考資料
5.3.5.4-3	CTD 2.7.6 Listing	–	無	参考資料
5.3.5.4-4	R668-BP-1902 Japanese subgroup - Final analysis	–	無	参考資料
5.3.5.4-5	CTD 2.7.6 Listing - Final analysis	–	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 - [redacted]	20[redacted] - 20[redacted]	無	参考資料
5.3.6-2	PERIODIC BENEFIT RISK EVALUATION REPORT - Dupilumab - [redacted]	20[redacted] - 20[redacted]	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	副作用発現症例一覧表
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

資料番号	第五部参考文献
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