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MINI REVIEW

Dupilumab: Mechanism of action, clinical, and translational science

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Abstract

Allergic disease prevalence has increased globally with the subset of type 2 inflammatory diseases playing a substantial role. Type 2 inflammatory diseases may differ in clinical presentation, but they exhibit shared pathophysiology that is targeted by the unique pharmacology of dupilumab. Dupilumab binds to the interleukin (IL)-4 receptor alpha subunit (IL-4Rα) that blocks IL-4 and IL-13 signaling, two key drivers of type 2 inflammation. Herein, we review the mechanism of action and pharmacology of dupilumab, and the clinical evidence that led to the regulatory approvals of dupilumab for the treatment of numerous type 2 inflammatory diseases: atopic dermatitis, asthma, chronic rhinosinusitis with nasal polyposis, eosinophilic esophagitis, and prurigo nodularis.

INTRODUCTION

An estimated 30% of the global population is impacted by an allergic disease during their lifespan, often first presenting as atopic dermatitis in early childhood and progressing to a variety of type 2 inflammatory diseases with increasing age—the atopic march or trajectories.[1–4] Allergic disease involves a systemic type 2 immune response, but a type 2 inflammatory disease phenotype occurs when type 2 inflammatory mediators persist chronically and in excess.[1,2]

Excessive type 2 inflammation is a hallmark of allergic diseases and occurs when the complex interaction between environmental triggers and the immune system weakens protective barriers of the skin, gastrointestinal tract, and respiratory system. The damaged epithelial barrier cells and tissue-resident innate cells produce alarmins—short-lived proteins and peptides including IL-33, thymic stromal lymphopoietin, and IL-25—that initiate type 2 inflammatory responses.[2] Eosinophils, type 2 innate lymphoid cells, mast cells, basophils, and dendritic cells amplify the response by releasing inflammatory mediators such as histamine, prostaglandins, IL-4, IL-5, and IL-13.[1,2] IL-4 stimulates T cell differentiation and proliferation of the T helper 2 (T_H2) cell subtype, the namesake for type 2 inflammation. T_H2 cells drive the type 2 response by producing key effector cytokines (IL-4, IL-5, IL-13) that can influence the pathophysiology of type 2 diseases by increasing systemic levels of immunoglobulin E (IgE), eosinophils, and thymus and activation-regulated chemokine (TARC).[1] IL-4 and IL-13 activate B cell isotype class switching toward IgE production, smooth muscle cell proliferation, goblet cell hyperplasia, mucus production, and fibrosis.[2] The IgE pathway protects the epithelial barrier from parasitic infections, but excessive production of IgE in response to innocuous antigens leads to the allergic symptoms observed in many chronic type 2 diseases.[1] IL-5 causes eosinophil differentiation, while IL-4, IL-5, and IL-13 promote eosinophil trafficking to tissues.[1] Eosinophils can

exacerbate the epithelial damage and contribute to the development of fibrosis across type 2 inflammatory diseases.

Dupilumab, a human IgG4 monoclonal antibody, inhibits the signaling of IL-4 and IL-13 by binding to the shared IL-4 receptor subunit alpha (IL-4Rα) of IL-4 and IL-13 receptor complexes (Figure 1a).[2] Dupilumab is approved for use in numerous type 2 inflammatory diseases—atopic dermatitis (AD), asthma, chronic rhinosinusitis with nasal polyposis (CRSwNP), eosinophilic esophagitis (EoE), and prurigo nodularis (PN).[5]

MECHANISM OF ACTION

Dupilumab targets IL-4Rα imposing a dual blockade on IL-4 and IL-13 signaling through type 1 and 2 receptors (Figure 1a). The type 1 receptor— which is present in B cells, T cells, monocytes, eosinophils, and fibroblasts— is a heterodimeric receptor complex consisting of IL-4Rα and common γ chain subunits.[1] The type 2 receptor—which is present in monocytes, fibroblasts, eosinophils, activated B cells, epithelial cells, goblet cells, and smooth muscle cells — is a heterodimeric receptor complex consisting of IL-4Rα and IL-13Rα1 subunits.[1] IL-4 binds to type 1 and type 2 receptors, while IL-13 binds to the type 2 receptor. Dupilumab binds to the shared subunit of both receptors, halting the downstream signaling cascade of IL-4 and IL-13.

Both cytokines significantly contribute to type 2 inflammation, but IL-4 drives T_2H cell differentiation and expansion, B cell growth, isotype class switching to IgE, and eosinophil trafficking (Figure 1b).[1] IL-13 not only promotes several of those functions as well but also stimulates goblet cell hyperplasia, mucus production, and increased smooth muscle contractility and hypertrophy.[1] IL-4 and IL-13 stimulate epithelial and endothelial cells to produce chemokines, like eotaxin-3, that recruit eosinophils to the afflicted tissues.[6] IL-4 activates adhesion molecules that facilitate eosinophil attachment to vascular endothelial cells; then eosinophils infiltrate the tissue where TARC and other chemokines guide the cells to the site of inflammation.[7] Due to the redundant functions of IL-4 and IL-13, only targeting IL-4 or IL-13 leads to incomplete blockade of type 2 inflammatory pathways.[6] Dual blockade of IL-4 and IL-13 signaling via IL-4Rα binding is required to inhibit critical type 2 inflammatory pathways such as T_H2 cell-induced antigen-presentation cell activation, eosinophil infiltration of the lungs, and expression of inflammatory cytokines and chemokines in the lungs.[6]

The IL-4/IL-13 axis drives many of the foundational pathways common among type 2 inflammatory diseases, which emphasizes the therapeutic power of simultaneously blocking IL-4 and IL-13 signaling with dupilumab.

Clinical and Translational Card for Dupilumab

Mechanism of action: Inhibition of interleukin (IL)-4 and IL-13 signaling via IL-4 receptor alpha subunit binding.

Indication (s): Atopic dermatitis, asthma, chronic rhinosinusitis with nasal polyposis, eosinophilic esophagitis, prurigo nodularis.

Dosage and administration: Most adult patients receive dupilumab 300 mg subcutaneous (SC) every other week (Q2W) but for indication and population-specific dosing, please see Table 1.

Major metabolic pathway: Like other IgG monoclonal antibodies, proteolytic catabolism and target-mediated clearance via drug–receptor complex endocytosis.

Key PK characteristics:

For specific population and dose pharmacokinetic parameters, see Table 2.

AUC—For dupilumab 300 mg SC Q2W, the range of means (±SD) for AUC over a 4-week interval at steady state is 2070 (896) to 2404 (912) mg*day/L.

Maximum concentration—For dupilumab 300 mg SC Q2W, the range of means (±SD) at steady state is 83.6 (34.5) to 95.1 (39.4) mg/L.

Time to maximum concentration—For dupilumab 300 mg SC Q2W, the range of medians is 2–7 days.

Elimination—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 (<0.078 mg/L) ranged from 9 to 13 weeks in adults and pediatric subjects 12–17 years of age.

Type 2 inflammation induces common biological effects—epithelial hyperplasia, basal membrane thickening, barrier disruption, and inflammatory infiltrate—that cause symptoms in the affected tissues across the spectrum of type 2 inflammatory diseases (Figure 1c).[1]

DRUG REGULATORY APPROVAL

The Food and Drug Administration (FDA) initially approved dupilumab in 2017 for adult patients with moderate-to-severe AD whose disease is not adequately controlled by topical prescription therapies or when those agents are not advisable.[5] Subsequent approvals

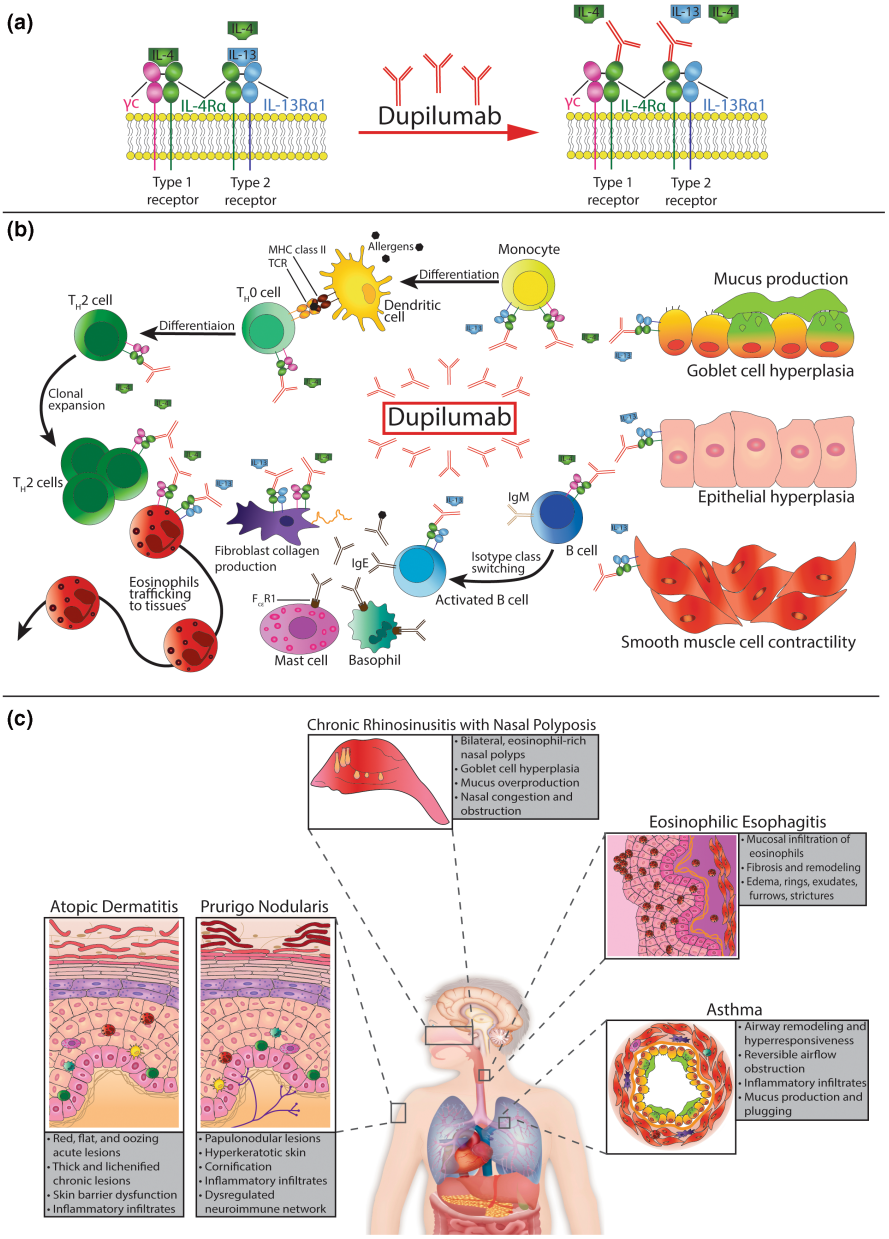

FIGURE 1 Dupilumab mechanism of action within the type 2 inflammatory cascade. (a) Dupilumab binds to the shared IL-4 receptor subunit alpha (IL-4Rα) of type 1 and type 2 receptors, which are the targets of IL-4 and IL-13. (b) The type 1 receptor is found on monocytes, T_H0 cells, T_H2 cells, fibroblasts, eosinophils, and B cells. The type 2 receptor is found on monocytes, fibroblasts, eosinophils, activated B cells, epithelial cells, goblet cells, and smooth muscle cells. Dupilumab mitigates type 2 inflammation by inhibiting the IL-4/IL-13 axis, which is a primary driver of type 2 inflammation. IL-4 stimulates the differentiation and clonal expansion of T_H2 cells, further driving production of IL-4 and IL-13. IL-4 and IL-13 promote several type 2 inflammation processes such as eosinophil trafficking to tissues, B cell isotype class switching to IgE, and fibroblast production of collagen. IL-13 is primarily responsible for mucus production, goblet cell hyperplasia, and smooth muscle cell contractility. (c) Type 2 inflammatory disease possesses many overlapping features but still presents with tissue-specific pathologies and differing clinical symptoms. Dupilumab is effective at treating these diseases due to their shared underlying type 2 inflammation pathways. MHC class II = major histocompatibility complex used for antigen presentation; TCR, T cell receptor; $F_{cε}$R1 = a high-affinity IgE receptor. This is based on a series of figures from a publication by Gandhi et al.[1]

for dupilumab included patients 12 years and older with moderate-to-severe asthma, patients 12–17 years old with AD, adults with chronic rhinosinusitis with nasal polyposis (CRSwNP), patients 6–11 years old with AD, patients 6–11 years old with asthma, patients 12 years and older weighing at least 40 kg with eosinophilic esophagitis (EoE), children aged 6 months to 5 years old with AD, and adults with prurigo nodularis (PN). Table 1 shows the indication and population-specific doses from the US label.[5]

TABLE 1 Dupilumab posology by indication and population.

Indication	Age	Weight group	Dose
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	6 months to 5 years	5 to <15 kg	200 mg Q4W
		15 to <30 kg	300 mg Q4W
	6–17 years	15 to <30 kg	300 mg Q4W[a]
		30 to <60 kg	200 mg Q2W[b]
		≥60 kg	300 mg Q2W[a]
	≥18 years	Any	300 mg Q2W[a]
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	6–11 years	15 to <30 kg	300 mg Q4W
		≥30	200 mg Q2W
	≥12 years	Any	200 mg Q2W[b] or 300 mg Q2W[a,c]
Chronic rhinosinusitis with nasal polyposis as an add-on maintenance treatment in adult patients with inadequately controlled chronic rhinosinusitis with nasal polyposis	≥18 years	Any	300 mg Q2W
Eosinophilic esophagitis	≥1 years	15 to <30 kg	200 mg Q2W
		30 to <30 kg	300 mg Q2W
		≥40 kg	300 mg QW
Prurigo nodularis	≥18 years	Any	300 mg Q2W[a]

Note: All doses are given subcutaneously. Dosing information from US label.

[a]Initial loading dose of 600 mg followed by 300 mg Q2W or Q4W.

[b]Initial loading dose of 400 mg followed by 200 mg Q2W.

[c]Either dose may be used, except 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 polyposis that should receive 300 mg Q2W.

Dupilumab is available in various strengths as a pre-filled syringe (300 and 200 mg) or as a pre-filled pen (300 and 200 mg) for subcutaneous injection. The pre-filled syringe is approved for use in patients 6 months and older, while the pre-filled pen is for patients 2 years and older in the US.

European Medicines Agency (EMA) approved dupilumab for the following indications: moderate-to-severe AD in adults and adolescents 12 years and older who are candidates for systemic therapy; severe AD in children 6 months to 11 years old who are candidates for systemic therapy; adults and adolescents 12 years and older as add-on maintenance treatment for severe asthma with type 2 inflammation characterized by raised blood eosinophils and/or raised fraction of exhaled nitric oxide (FeNO) who are inadequately controlled with high-dose inhaled corticosteroids (ICS) plus another medicinal product for maintenance treatment; children 6–11 years old as add-on maintenance treatment for severe asthma with type 2 inflammation characterized by raised blood eosinophils and/or raised FeNO, who are inadequately controlled with medium- to high-dose ICS plus another medicinal product for maintenance treatment; add-on therapy with intranasal corticosteroids for the treatment of adults with severe CRSwNP for whom therapy with systemic corticosteroids and/or surgery do not provide adequate disease control; adults with moderate-to-severe PN who are candidates for systemic therapy; adults and adolescents 12 years and older with EoE, weighing at least 40 kg, who are inadequately controlled by, are intolerant to, or who are not candidates for conventional medicinal therapy.[8]

This review covers the regulatory approvals in the US and Europe, but dupilumab is also approved for various type 2 inflammatory diseases in different populations in other countries, including chronic spontaneous urticaria in Japan.[9]

PHARMACOKINETICS/ PHARMACODYNAMICS CHARACTERISTICS

Pharmacokinetics

Early clinical trials evaluated intravenous and subcutaneous (SC) administration of dupilumab in healthy subjects with SC receiving the subsequent approval.[10] Single-dose clinical studies revealed that the pharmacokinetics of dupilumab are highly dependent on concentration (Figure 2), which were confirmed in subsequent multiple-dose studies. Absorption of dupilumab following SC administration occurs through the

TABLE 2 Dupilumab pharmacokinetic parameters by dose and population.

Dose	Age	$AUC_{4wk,ss}$[a,c] (mg*day/L)	$C_{max,ss}$[a,c] (mg/L)	$C_{trough,ss}$[a,c] (mg/L)	T_{max}[b,e] (day)
300 mg QW	Adults and adolescents[d]	5360 (2180)	211 (85)	198 (83)	2–7
300 mg Q2W		2070 (896)–2404 (912)	83.6 (34.5)–95.1 (39.4)	60.4 (29.5)–72.5 (30.3)	
200 mg Q2W		1192 (672)–2031 (691)	50.1 (25.3)–83.5 (27.2)	38.9 (23.1)–57.7 (22.3)	
200 mg Q2W	6–11 years[d]	2902 (1030)–3306 (1062)	114 (38.4)–135 (41.6)	86.6 (34.0)–95.3 (34.6)	
300 mg Q4W		2143 (884)–3845 (1286)	102 (35.5)–189 (49.7)	48.0 (26.5)–98.7 (41.0)	
300 mg Q4W	6 months to 5 years[d]	4495 (1402)	230 (57.1)	111 (46.5)	
200 mg Q4W		4506 (1465)	224 (56.0)	123 (52.3)	

Note: Multiple population pharmacokinetic analyses were developed to support regulatory applications for each indication and/or age group. The range of mean (SD) or median parameters from those models is listed for approved regimens.

Abbreviations: $AUC_{4wk,ss}$, area under the concentration–time curve over 4-week interval at steady state; $C_{max,ss}$, maximum concentration at steady state; $C_{trough,ss}$: trough concentration at steady state; T_{max}, time to maximum concentration.

[a]Range of means (SD).

[b]Range of medians.

[c]Estimated by population PK analysis.

[d]Adults and adolescents with atopic dermatitis, asthma, or EoE, and adults with CRSwNP and PN, children 6–11 years with atopic dermatitis or asthma, and children 6 months to 5 years with atopic dermatitis.

[e]The T_{max} value corresponds to all doses.

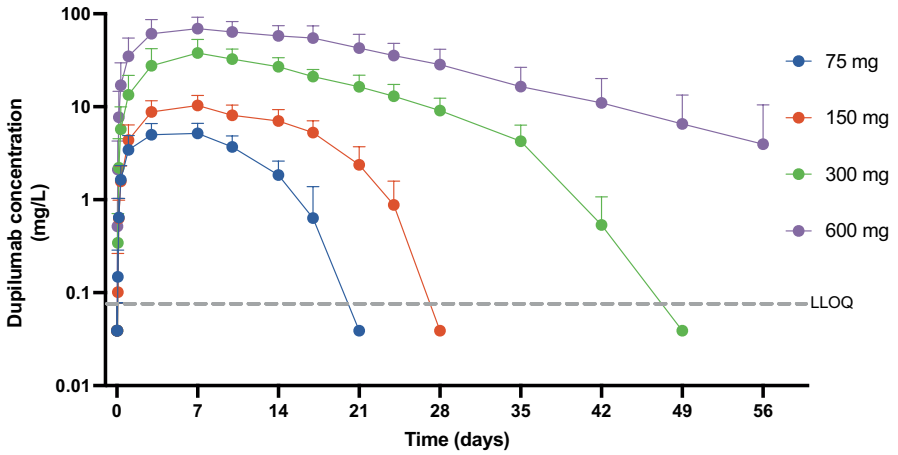

FIGURE 2 Concentration–time profile of dupilumab given subcutaneously in healthy adult males. The figure shows a semi-log scale plot of mean (+SD) concentrations of functional dupilumab in serum from a single ascending dose study (TDU1226; NCT01537653) of dupilumab given subcutaneously in healthy adult males from Japan.[10] Elimination of dupilumab is nonlinear at low concentrations, but approach linear pharmacokinetics at higher concentrations as the receptor-mediated elimination pathway is saturated. Mean values reported as LLOQ were included as zero, and the sum of the values was divided by all subjects, which was $N = 6$ for each dose group. The values reported as LLOQ were plotted as half the LLOQ of 0.078 mg/L for illustrative purposes. LLOQ, lower limit of quantification.

interstitial space followed by uptake in the lymphatic system, leading to peak serum concentrations around 7 days post-injection.[5,11] SC bioavailability of dupilumab is approximately 61%–64%.[5] Due to the large molecular size (147 kDa), dupilumab is mostly confined to the systemic circulation with an estimated total volume of distribution of 4.8 L.[5] Dupilumab concentrations reached steady state by week 16 across the various approved dosages, with or without a loading dose.[5]

The metabolism/elimination pathway for dupilumab is uncharacterized. However, since dupilumab is a fully human monoclonal IgG4 antibody, it is likely catabolized into peptides and amino acids similar to endogenous IgG.[5] The concentration–time profile (Figure 2) suggests that dupilumab also exhibits target-mediated drug disposition (TMDD) via receptor-mediated endocytosis, when a high-affinity, highly specific compound binds to cellular receptors leading to internalization and degradation

of the drug–receptor complex.[12,13] The combination of linear and target-mediated pathways leads to concentration–time profiles that demonstrate rapid clearance at low concentrations but approach linear elimination at concentrations sufficient to saturate receptor-mediated clearance (Figure 2).

Body weight is the most influential covariate affecting exposure to dupilumab.[5] Consistent with this, subjects with higher body weight tend to have lower trough concentrations of dupilumab.[5,10] Pediatric patients receive weight-tiered regimens of dupilumab with longer dosing intervals and/or lower doses to normalize the exposures across patients of varying body sizes. The pharmacokinetics of dupilumab are consistent between disease states (AD, asthma, CRSwNP, EoE, PN).[5]

Like most monoclonal antibodies, patients can develop anti-drug antibodies (ADA) to dupilumab. Most ADA responses were low titer with rates of treatment-emergent ADA varying between indications and age groups (1%–16%).[5] High titer responses were associated with lower concentrations of dupilumab in serum and two dupilumab-treated adult patients with AD who experienced high titer antibody responses developed serum sickness or serum sickness-like reactions.[5]

Pharmacodynamics

Dupilumab broadly suppresses an array of type 2 inflammatory biomarkers across multiple diseases. The responses to dupilumab on TARC, eotaxin-3, total IgE, periostin, and blood eosinophils in patients with AD, asthma, CRSwNP, or EoE are extensively compared elsewhere.[14] Briefly, rapid decreases in TARC, eotaxin-3, and periostin are observed within weeks of initiating dupilumab. Decreases in total IgE, a secondary result of dupilumab inhibiting class switching of B cells to IgE-producing plasma cells, occur with a more gradual onset.[14,15] Dupilumab-mediated reductions in eosinophil tissue infiltration may lead to transient increases in serum eosinophil levels, followed by decreases to less than baseline.[7,10] Dupilumab is also capable of normalizing disease-specific biomarkers, including decreasing FeNO in patients with asthma and modulating gene expression profiles in lesion of AD patients to more closely resemble non-lesioned control areas by downregulating genes associated with epidermal proliferation and upregulating genes associated with cellular structure, lipid metabolism, and barrier-related functions.[5,16,17] Although type 2 biomarker levels may be correlated with disease severity (e.g., TARC and AD), baseline TARC was not significantly predictive of clinical response to dupilumab in patients with AD.[1,18]

KEY CLINICAL TRIALS

Table 3 summarizes the pivotal Phase 3 clinical trials conducted in AD, asthma, CRSwNP, EoE, and PN. More study details can be found using the listed NCT# in Table 3.

CLINICAL EFFICACY AND SAFETY

Dupilumab demonstrated clinically meaningful improvements in efficacy with an acceptable safety profile across different type 2 inflammatory diseases in adults and pediatric patients.

In AD, type 2 inflammation drives many of the symptoms—itch, erythema, barrier disruption, and induration—that lead to the decline in mental health and quality of life.[19] Compared to placebo, dupilumab treatment significantly reduced disease severity using different metrics that evaluate physical signs and symptoms (IGA, EASI, NRS), mental health (HADS), and quality of life (POEM, DLQI).[5,19,20] In the pivotal phase 3 trials, more patients treated with dupilumab 300 mg Q2W had clear or almost clear skin (IGA 0/1) and ≥2 points reduction in IGA score compared to placebo, respectively (SOLO 1%–38% vs 10%; SOLO 2%–36% vs 9%; CHRONOS- 39% vs 12%).[5] In the same trials, dupilumab treatment also led to a higher proportion of patients achieving 75% and 90% reductions from baseline in the EASI score and reductions in pruritis (NRS).[5] The studies of younger patients—6 months to 5 years, 6–11 years, and 12–17 years—also showed these robust patterns in reduction of signs, symptoms, and quality of life.[5] The alleviation of symptom burden ultimately led to improvements in anxiety, depression, and quality of life.[19,20] Pooled data from three monotherapy trials showed dupilumab 300 mg Q2W resulted in higher rates of injection site reactions (10% vs 5%) and conjunctivitis (10% vs 2%) compared to placebo.[5] Studies including topical corticosteroids with dupilumab or placebo showed a similar difference between dupilumab and placebo (injection site reaction—10% vs 6%; conjunctivitis—9% vs 5%; keratitis—4% vs 0%). The safety profiles are similar among younger populations as well.

Dupilumab is effective for the treatment of moderate-to-severe asthma with an eosinophilic/type 2 phenotype, and the efficacy is higher when patients have baseline characteristics of type 2 inflammation (blood eosinophils ≥150 cells/μL and/or FeNO ≥20 ppb), regardless of an allergic asthma IgE-derived phenotype—emphasizing the relationship between the mechanism of action and disease pathophysiology.[21] The IL-4/IL-13 axis drives numerous pathways—airway hyperresponsiveness, inflammatory infiltration, smooth muscle cell contractility, fibrosis, and

TABLE 3 Pivotal Phase 3 clinical trials with dupilumab.

Indication	Study name (NCT#)	Population (*n*; randomization)	Dose	Treatment duration	Primary end point
Atopic dermatitis	SOLO-1 (NCT02277743)	Moderate-to-severe; ≥18 years (*N* = 671; 1:1:1)	300 mg QW[a] 300 mg Q2W[a] Placebo	16 weeks	IGA score 0/1 and ≥2 point reduction from baseline[e]
	SOLO-2 (NCT02277769)	Moderate-to-severe; ≥18 years (*N* = 708; 1:1:1)	300 mg QW[a] 300 mg Q2W[a] Placebo	16 weeks	IGA score 0/1 and ≥2 point reduction from baseline[e]
	LIBERTY AD CHRONOS[f] (NCT02260986)	Moderate-to-severe; ≥18 years (*N* = 740; 3:1:3)	300 mg QW[a] 300 mg Q2W[a] Placebo	52 weeks	IGA score 0/1 and ≥2 point reduction from baseline[e]
	LIBERTY AD ADOL (NCT03054428)	Moderate-to-severe; ≥12 to ≤17 years (*N* = 251; 1:1:1)	<60 kg: 200 mg Q2W[b]; ≥60 kg: 300 mg Q2W[a] No weight tier: 300 mg Q4W[a] Placebo	16 weeks	IGA score 0/1 and ≥2 point reduction from baseline[e]
	LIBERTY AD PEDS[f] (NCT03345914)	Severe; ≥6 to ≤11 years (*N* = 367; 1:1:1)	15 to <30 kg: 100 mg Q2W[c]; ≥30 kg: 200 mg Q2W[b] 300 mg Q4W[a] Placebo	16 weeks	IGA score 0/1[e]
	LIBERTY AD PRESCHOOL, Part B[f] (NCT03346434)	Moderate-to-severe; ≥6 months to ≤5 years (*N* = 162; 1:1)	5 to <15 kg: 200 mg Q4W; 15 kg to <30 kg: 300 mg Q4W Placebo	16 weeks	IGA score 0/1[e]
Asthma	LIBERTY ASTHMA QUEST[g] (NCT02414854)	Moderate-to-severe; ≥12 years (*N* = 1902; 2:2:1:1)	200 mg Q2W[b] 300 mg Q2W[a] Placebo Placebo	52 weeks	Exacerbation rate; FEV_1 change from baseline
	LIBERTY ASTHMA VOYAGE[g] (NCT02948959)	Moderate-to-severe; ≥6 to ≤11 years (*N* = 408; 2:1)	≤30 kg: 100 mg Q2W; ≥30 kg 200 mg Q2W Placebo	52 weeks	Exacerbation rate
Chronic rhinosinusitis with nasal polyposis	LIBERTY NP SINUS-24[h] (NCT02912468)	Severe; ≥18 years (*N* = 276; 1:1)	300 mg Q2W Placebo	24 weeks	Change from baseline at week 24 NPS, nasal congestion or obstruction, and sinus Lund MacKay CT score
	LIBERTY NP SINUS-52[h] (NCT02898454)	Severe; ≥18 years (*N* = 448; 1:1:1)	300 mg Q2W 300 mg Q2W for 24 weeks then Q4W for 28 weeks Placebo	52 weeks	Change from baseline at week 24 NPS, nasal congestion or obstruction, and sinus Lund MacKay CT score
Eosinophilic esophagitis	Parts A, B, and C (NCT03633617)	Part A: ≥12 years (*N* = 81; 1:1)	300 mg QW Placebo	24 weeks	Histologic remission (peak esophageal intraepithelial eosinophil count of ≤6 eos/hpf); DSQ change from baseline
		Part B: ≥12 years (*N* = 240; 1:1:1)	300 mg QW 300 mg Q2W Placebo	24 weeks	
		Part C: ≥12 years (*N* = 304[d])	300 mg QW 300 mg Q2W	28 weeks	
	EoE KIDS[j] (NCT04394351)	Part A: 1 to ≤11 years (*N* = 61; 1:1)	15 to <30 kg: 200 mg Q2W; 30 to <60 kg: 300 mg Q2W Placebo	16 weeks	Histologic remission (peak esophageal intraepithelial eosinophil count of ≤6 eos/hpf)
		Part B: 1 to ≤11 years (*N* = 47[i])	15 to <30 kg: 200 mg Q2W; 30 kg to <60 kg: 300 mg Q2W	52 weeks	

(Continues)

TABLE 3 (Continued)

Indication	Study name (NCT#)	Population (*n*; randomization)	Dose	Treatment duration	Primary end point
Prurigo nodularis	LIBERTY-PN PRIME (NCT04183335)	≥18 years ($N=151$; 1:1)	300 mg Q2W[a] Placebo	24 weeks	≥4-point reduction in WI-NRS
	LIBERTY-PN PRIME2 (NCT04202679)	≥18 years ($N=160$; 1:1)	300 mg Q2W[a] Placebo	24 weeks	≥4-point reduction in WI-NRS

Note: All doses were given subcutaneously.

Abbreviations: EASI, eczema area and severity index; FEV_1, forced expiratory volume in 1 s; hpf, high-power field; IGA, Investigator's Global Assessment; LD, loading dose; NPS, nasal poly score; WI-NRS, worst itch numeric rating scale.

[a]Patients received initial loading dose of 600 mg.

[b]Patients received initial loading dose of 400 mg.

[c]Subjects received initial loading dose of 200 mg.

[d]Part C was an extension of Part A and Part B that randomized subjects (1:1) from the placebo arm of Part B into dupilumab 300 mg QW or Q2W, but Part C did not include a placebo treatment arm, see reference for more study details.[22]

[e]EASI-75 was a co-primary end point in European Union countries and Japan.

[f]All subjects received concomitant topical corticosteroids.

[g]All subjects received concomitant inhaled corticosteroids and/or second controller medication, more study details available at clinicaltrials.gov.

[h]All subjects received concomitant intranasal corticosteroids.

[i]Placebo patients from Part A transitioned to the dupilumab weight-based dosing in Part B so no randomization.

[j]The trial studied low/high dosing arms that included 200 mg Q2W and 300 mg Q2W, which received approval.

mucus secretion—that contribute to exacerbations and reduced lung function.[1] In LIBERTY ASTHMA QUEST, dupilumab lowered severe exacerbation rates compared to matched placebo in the overall study population (200 mg Q2W—0.46 vs 0.87; 300 mg Q2W—0.52 vs 0.97).[5] When patients were stratified by baseline blood eosinophils and FeNO levels, the relative risk of exacerbations decreased with increasing levels of both biomarkers. Patients with elevated eosinophils and/or FeNO also show better response in lung function (pre-bronchodilator FEV_1) when treated with dupilumab compared to placebo. Compared to placebo, patients treated with dupilumab experienced higher rates of injection site reactions (14%–18% vs 6%), oropharyngeal pain (2% vs 1%), and eosinophilia ≥3000 cells/μL (2% vs <1%).[5] The efficacy and safety findings were similar across age groups from 6 to 11 years, 12–17 years, and 18 years or older. Dupilumab was generally well tolerated and effectively treated patients with asthma—better responses were observed with increasing evidence of type 2 inflammation.

Eosinophils play a prominent role in the disease pathophysiology of CRSwNP and EoE—nasal polyps are "bags of eosinophils" and EoE is diagnosed based on eosinophil infiltration in the esophagus.[1] Dupilumab blocks eosinophil trafficking to tissues by inhibiting the signaling of the IL-4/IL-13 axis.[1] In the clinical trials for CRSwNP and EoE, dupilumab mitigated tissue infiltration of eosinophils as evidenced by achieving the primary end points, respectively, Nasal Polyp Score (NPS) reduction and histologic remission (peak esophageal intraepithelial eosinophil count ≤6 eosinophils per high-power field).[5] By reducing the type 2 inflammation associated with eosinophil infiltration, dupilumab improved clinical symptoms while being generally well tolerated. In CRSwNP, dupilumab 300 mg Q2W resulted in a greater least square mean change from baseline for NPS (SINUS-24: −1.89 vs 0.17; SINUS-52: −1.71 vs 0.10) and nasal congestion/obstruction (SINUS-24: −1.34 vs −0.45; SINUS-52: −1.25 vs −0.38) compared to placebo.[5] In the CRSwNP studies, patients treated with dupilumab had higher rates of injection site reactions (6% vs 4%), conjunctivitis (2% vs 1%.), arthralgia (3% vs 2%), and gastritis (2% vs 1%) compared to placebo. In EoE, dupilumab 300 mg QW led to a higher proportion of patients with histologic remission (58.8%–59.5% vs 5.1%–6.3%) and absolute change from baseline in dysphagia questionnaire score (−23.8 to −21.9 vs −13.9 to −9.6) compared to placebo.[5] The EoE study showed higher adverse event rates in the dupilumab arm versus placebo for injection site reactions (38% vs 33%), upper respiratory tract infections (18% vs 10%), arthralgia (2% vs 1%), and herpes viral infections (2% vs 1%). Dupilumab provided robust clinical benefits with acceptable safety margins in both the CRSwNP and EoE patient populations through its effect on eosinophils and other pathways of the IL-4/IL-13 axis.

IL-4 and IL-13 promote skin fibrosis via fibroblast proliferation and dysregulate the skin neuroimmune network that drives the intense scratch-itch cycle observed in patients with PN.[2] By targeting the IL-4/IL-13 axis, dupilumab alleviates the intense itch and reduces the development of papulonodular lesions.[5] More patients treated with dupilumab 300 mg Q2W had ≥4 point reductions in

WI-NRS and achieved IGA for Prurigo Nodularis Stage 0 or 1 compared to placebo (32.1%–38.7% vs 8.5%–9.2%). In patients with PN, dupilumab treatment resulted in higher rates of nasopharyngitis (5% vs 2%), conjunctivitis (4% vs 1%), herpes infection (3% vs 0%), dizziness (3% vs 1%), myalgia (3% vs 1%), and diarrhea (3% vs 1%) compared to placebo. Mitigation of IL-4 and IL-13 signaling with dupilumab led to clinical improvement with low adverse event rates in the PN patient population.

The safety and efficacy profile of dupilumab has remained consistent for type 2 inflammatory diseases irrespective of where the inflammation occurs. As the indications expand, the doses and exposures necessary to provide therapeutic benefit have evolved over time. Most adult patients with airway and skin indications receive dupilumab 300 mg Q2W; however, patients with EoE—a gastrointestinal (GI) tract disease—require 300 mg QW to derive a symptomatic benefit. The patients who received dupilumab 300 mg QW had more than twice the systemic exposures as the patients who received dupilumab 300 mg Q2W.[22] The higher exposures necessary in EoE may in part be related to reduced penetration of antibodies to GI tissue compared with the lungs and skin.[23]

FUTURE PROSPECTS

Chronic obstructive pulmonary disease

A subset of non-asthmatic patients with chronic obstructive pulmonary disease (COPD) present with evidence of type 2 inflammation.[24] Two placebo-controlled, phase 3 trials tested dupilumab in COPD patients with evidence of type 2 inflammation (blood eosinophils ≥300 cells/μL at screening) that are uncontrolled with the standard inhaled triple therapy.[24,25] In both trials, BOREAS and NOTUS, dupilumab given 300 mg Q2W SC significantly reduced COPD exacerbations (BOREAS 30%; NOTUS 34%) and improved lung function (BOREAS 160 mL vs 77 mL; NOTUS 139 mL vs 57 mL) compared to placebo at week 12.[24,25]

The FDA designated Breakthrough Therapy status for dupilumab as an adjunct therapy in adult patients with uncontrolled COPD that present with an eosinophilic phenotype. Dupilumab can change the treatment paradigm for type 2 inflammatory COPD patients by targeting a previously untreated pathway, the IL-4/IL-13 axis.

CONCLUSION

Dupilumab is approved for uses in major type 2 inflammatory diseases—atopic dermatitis, asthma, chronic rhinosinusitis with nasal polyposis, eosinophilic esophagitis, and prurigo nodularis. The two phase 3 clinical trials in patients with COPD and evidence of type 2 inflammation showed that dupilumab has therapeutic potential outside of the classical type 2 diseases. As researchers increasingly employ precision medicine approaches to identify subsets of patient populations, more patients with type 2 inflammatory phenotypes are likely to be identified— extending the potential reach of dupilumab into new inflammatory diseases.

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M.R.M., M.P.K., J.D.D., and M.A.K. are employees of Regeneron Pharmaceuticals, Inc. and may hold stock and/or stock options in the company. C.X. is an employee of Sanofi and may hold stock and/or stock options in the company.

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