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May 13, 2024

Maryland Prescription Drug Affordability Board
16900 Science Drive, Suite 112-114
Bowie, MD 20715

Re: Therapeutic Alternatives for Drugs Referred to the Stakeholder Council

Dear Members of the Maryland Prescription Drug Affordability Board,

Sanofi appreciates the opportunity to submit comments to the Maryland Prescription Drug Affordability Board ("Board") on the posted List of Proposed Therapeutic Alternatives to Dupixent ("Proposed List"). These comments were prepared by Sanofi's team of internal medical and scientific experts, which includes specialists in each of Dupixent's approved indications.

Please feel free to contact me at deanne.calvert@sanofi.com with any questions.

Sincerely,

Deanne Calvert
Head, State Government Relations, Sanofi

Executive Summary

Dupixent® (dupilumab) is a novel biologic agent, specifically designed to target the interleukin (IL)-4 and IL-13 pathways that are implicated in the direct causation of multiple type 2 inflammatory disease states (Dupixent United States Prescribing Information [USPI] 2024). It was first approved by the US Food and Drug Administration (FDA) on March 28, 2017, for atopic dermatitis (AD) and has been approved for four additional type 2 inflammatory disease states to date including: asthma, chronic rhinosinusitis with nasal polyposis (CRSwNP), prurigo nodularis (PN), and eosinophilic esophagitis (EoE) (Dupixent USPI 2024). Further, dupilumab has also received FDA approval for multiple age ranges: as young as 6 months in AD, as young as 6 years in asthma, and as young as 1 year in EoE. Approval in these indications and age ranges was based on thorough demonstration of efficacy and tolerability in a large clinical development program (Dupixent USPI 2024).

There are three additional potential indications under review by the FDA, with regulatory decisions anticipated by mid-2025: chronic obstructive pulmonary disease (COPD) with type 2 inflammation (FDA regulatory action date 06/27/24 [Sanofi Press Release 2024]), chronic spontaneous urticaria (CSU), and bullous pemphigoid (BP). The breadth of these indications, encompassing a range of diseases and therapeutic areas, highlights the unique mechanism of action of dupilumab and Sanofi's commitment to addressing unmet needs for patients impacted by diseases driven in part by type 2 inflammation.

Determination of therapeutic alternatives to a medicine is complex and involves multiple factors, including efficacy, safety, pharmacology, cost-effectiveness, and shared decision-making between a patient and their healthcare provider. Dupilumab is not an immunosuppressant (Cuellar-Barboza 2020), does not require laboratory monitoring as per the FDA prescribing information (Dupixent USPI 2024, Wollenberg 2020, Beck 2022), and has more than 7 years of real-world evidence demonstrating efficacy and safety in clinical practice. Compared with the therapeutic alternatives proposed by the Maryland Prescription Drug Affordability Board (MD PDAB), dupilumab is the only agent with a dual mechanism (blocks the signaling of both IL-4 and IL-13), making it pharmacologically separate from the other agents and not therapeutically interchangeable. These characteristics set it apart from the proposed alternatives identified by the MD PDAB, which have significant limitations including the following:

- Dupilumab is the only therapy with FDA-approved indications for five type 2 inflammatory diseases that frequently coexist
- Dupilumab is the only proposed alternative FDA approved and indicated for use in patients as young as 6 months with moderate-to-severe AD
- Dupilumab is the only AD biologic that is also FDA approved for use in asthma; up to 50% of patients with AD have coexisting asthma (Silverberg 2018)
  - The tralokinumab clinical development program failed and was discontinued in asthma (Panettieri 2018)
- Dupilumab is the only FDA-approved asthma biologic also approved in AD; up to 38% of patients with asthma have coexisting AD (Lee 2018)
  - All other FDA-approved asthma biologics have failed in AD (Guttman-Yassky 2023, Kang 2020, Heil 2010)
- Dupilumab is the only FDA-approved asthma biologic that is approved for oral corticosteroid (OCS)-dependent asthma
- Dupilumab is the only FDA-approved biologic for PN
- Dupilumab is the only FDA-approved biologic for EoE
- Dupilumab is the only FDA-approved AD biologic also approved in CRSwNP
- The Janus kinase (JAK) inhibitor listed alternatives (eg, upadacitinib and abrocitinib) are broad immunosuppressants. These agents are FDA approved in a limited manner (ie, to patients who have failed or are intolerant to other systemic therapies, including biologics). These agents are indicated in

a restrictive patient population, and require laboratory monitoring, tuberculosis testing, effective contraception, and herpes zoster vaccine before initiation of therapy
  - Further, the JAK inhibitor class of medicines has a Boxed Warning, which is the most serious warning issued by the FDA for an approved medicine in the US, due to this class having significant or potential life-threatening risks of adverse events such as serious infections, mortality, malignancy, major adverse cardiovascular events (MACE), and thrombosis (Cibinqo USPI 2023, Rinvoq USPI 2024, FDA Guidance Document 2011)
- Topical therapies like tacrolimus ointment (Protopic®) are considered the mainstay of initial treatment for AD. Dupilumab is recommended as the first-line systemic therapy after failure of topical therapies; hence, tacrolimus is not interchangeable for dupilumab

Table 1 includes key characteristics of dupilumab and the proposed MD PDAB alternatives. In addition to these data, we have also provided background information related to the overlap of diseases with a type 2 inflammation component as well as considerations for the treatment of the five indications for dupilumab, including guidelines and practice parameters from the literature in **Appendix 1**. A summary of the clinical and economic value of dupilumab can be found in **Appendix 2**. We believe these comprehensive data, in addition to the above bulleted points, underscore the unique value proposition dupilumab provides to patients with a range of diseases driven in part by type 2 inflammation and ultimately supports our recommendation against including dupilumab in any drug cost review by the Board.

Table 1. Key characteristics of dupilumab and proposed MD PDAB alternatives[a]

Indications	Approvals and guideline recommendations	Dupixent® (dupilumab)[1–4]	Adbry® (tralokinumab)[2,5,6]	Cibinqo™ (abrocitinib)[2,7]	Rinvoq® (upadacitinib)[2,8]	Xolair® (omalizumab)[9–13]	Nucala® (mepolizumab)[14–21]	Fasenra® (benralizumab)[13,22–28]
	FDA approved for five type 2 inflammatory diseases	YES	No	No	No	No	No	No
AD	AAAAI/ACAAI recommended first-line systemic therapy	YES	YES	Second line after biologic failure	Second line after biologic failure	No	No	No
	FDA approved for ages ≥6 months	YES	Approved for ages ≥12 years	Approved for ages ≥12 years	Approved for ages ≥12 years	Failed clinical trial	Failed clinical trial	Failed clinical trial
ASTHMA	FDA approved for moderate-to-severe eosinophilic asthma ages ≥6 years	YES	Failed clinical trial	No	No	Approved for allergic asthma only	Approved for severe eosinophilic asthma only	Approved for severe eosinophilic asthma only
	FDA approved for OCS-dependent asthma	YES	No	No	No	No	No	No
EoE	FDA approved for EoE ages ≥1 years	YES	No	No	No	Failed clinical trial	Failed clinical trial	Failed clinical trial
PN	FDA approved for PN	YES	No	No	No	No	No	No
CRSwNP	FDA approved for CRSwNP	YES	No	No	No	YES	YES	No
COPD	Met primary end points in Phase 3 trials	YES	Not studied	Not studied	Not studied	Not studied	Failed clinical trial	Failed clinical trial

[a]Tacrolimus ointment (Protopic®) is not included, because it is not a systemic treatment for AD.

Table 1 abbreviations and references

AAAAI, American Academy of Allergy, Asthma, and Immunology; ACAAI, American College of Allergy, Asthma, and Immunology; AD, atopic dermatitis; COPD, chronic obstructive pulmonary disease; CRSwNP, chronic rhinosinusitis with nasal polyps; EoE, eosinophilic esophagitis; FDA, US Food and Drug Administration; MD PDAB, Maryland Prescription Drug Affordability Board; OCS, oral corticosteroids; PN, prurigo nodularis.

1. Dupixent (dupilumab). US Prescribing Information. Sanofi-Aventis US, Regeneron Pharmaceuticals; 2024. 2. Chu DK, Schneider L, Asiniwasis RN, et al. Atopic dermatitis (eczema) guidelines: 2023 American Academy of Allergy, Asthma and Immunology/American College of Allergy, Asthma and Immunology Joint Task Force on Practice Parameters GRADE- and Institute of Medicine-based recommendations. *Ann Allergy Asthma Immunol*. 2024;132:274–312. 3. Bhatt SP, Rabe KF, Hanania NA, et al. Dupilumab for COPD with type 2 inflammation indicated by eosinophil counts. *N Engl J Med*. 2023;389:205–214. 4. https://www.sanofi.com/en/media-room/press-releases/2023/2023-11-27-06-30-00-2785836. Accessed May 2024. 5. Adbry (tralokinumab-ldrm). US Prescribing Information. Leo Pharma; 2023. 6. Panettieri RA Jr, Sjöbring U, Péterffy A, et al. Tralokinumab for severe, uncontrolled asthma (STRATOS 1 and STRATOS 2): two randomised, double-blind, placebo-controlled, phase 3 clinical trials. *Lancet Respir Med*. 2018;6(7):511-525. 7. Cibinqo (abrocitinib). US Prescribing Information. Pfizer; 2023. 8. Rinvoq (upadacitinib). US Prescribing Information. AbbVie; 2024. 9. Xolair (omalizumab). US Prescribing Information. Genentech; 2024. 10. Humbert M, Beasley R, Ayres J, et al. Benefits of omalizumab as add-on therapy in patients with severe persistent asthma who are inadequately controlled despite best available therapy (GINA 2002 step 4 treatment): INNOVATE. *Allergy*. 2005;60:309–316. 11. Hanania NA, Alpan O, Hamilos DL, et al. Omalizumab in severe allergic asthma inadequately controlled with standard therapy: a randomized trial. *Ann Intern Med*. 2011;154:573–582. 12. Heil PM, Maurer D, Klein B, et al. Omalizumab therapy in atopic dermatitis: depletion of IgE does not improve the clinical course – a randomized, placebo-controlled and double blind pilot study. *J Dtsch Dermatol Ges*. 2010;8:990–998. 13. Ridolo E, Barone A, Ottoni M, et al. The new therapeutic frontiers in the treatment of eosinophilic esophagitis: biological drugs. *Int J Mol Sci*. 2024;25:1702. 14. Nucala (mepolizumab). US Prescribing Information. GlaxoSmithKline; 2023. 15. https://www.gsk.com/en-gb/media/press-releases/nucala-is-the-first-biologic-approved-in-the-us-for-six-to-11-year-old-children-with-severe-eosinophilic-asthma/. Accessed May 2024. 16. Pavord ID, Korn S, Howarth P, et al. Mepolizumab for severe eosinophilic asthma (DREAM): a multicentre, double-blind, placebo-controlled trial. *Lancet*. 2012;380:651–659. 17. Ortega HG, Liu MC, Pavord ID, et al. Mepolizumab treatment in patients with severe eosinophilic asthma. *N Engl J Med*. 2014;371:1198–1207. 18. Bel EH, Wenzel SE, Thompson PJ, et al. Oral glucocorticoid-sparing effect of mepolizumab in eosinophilic asthma. *N Engl J Med*. 2014;371:1189–1197. 19. Chupp GL, Bradford ES, Albers FC, et al. Efficacy of mepolizumab add-on therapy on health-related quality of life and markers of asthma control in severe eosinophilic asthma (MUSCA): a randomised, double-blind, placebo-controlled, parallel-group, multicentre, phase 3b trial. *Lancet Respir Med*. 2017;5:390–400. 20. Kang EG, Narayana PK, Pouliquen IJ, et al. Efficacy and safety of mepolizumab administered subcutaneously for moderate to severe atopic dermatitis. *Allergy*. 2020;75:950–953. 21. Pavord ID, Chanez P, Criner GJ, et al. Mepolizumab for eosinophilic chronic obstructive pulmonary disease. *N Engl J Med*. 2017;377:1613–1629. 22. Fasenra (benralizumab). US Prescribing Information. AstraZeneca; 2024. 23. FitzGerald JM, Bleecker ER, Nair P, et al. Benralizumab, an anti-interleukin-5 receptor α monoclonal antibody, as add-on treatment for patients with severe, uncontrolled, eosinophilic asthma (CALIMA): a randomised, double-blind, placebo-controlled phase 3 trial. *Lancet*. 2016;388:2128–2141. 24. Bleecker ER, FitzGerald JM, Chanez P, et al. Efficacy and safety of benralizumab for patients with severe asthma uncontrolled with high-dosage inhaled corticosteroids and long-acting β2-agonists (SIROCCO): a randomised, multicentre, placebo-controlled phase 3 trial. *Lancet*. 2016;388:2115–2127. 25. Nair P, Wenzel S, Rabe KF, et al. Oral glucocorticoid-sparing effect of benralizumab in severe asthma. *N Engl J Med*. 2017;376:2448–2458. 26. https://clinicaltrials.gov/study/NCT02869438. Accessed May 2024. 27. Criner GJ, Celli BR, Brightling CE, et al. Benralizumab for the prevention of COPD exacerbations. *N Engl J Med*. 2019;381:1023–1034. 28. Guttman-Yassky E, Bahadori L, Brooks L, et al. Lack of effect of benralizumab on signs and symptoms of moderate-to-severe atopic dermatitis: Results from the phase 2 randomized, double-blind, placebo-controlled HILLIER trial. *J Eur Acad Dermatol Venereol*. 2023;37:e1211–e1214.

References

Beck LA, Thaçi D, Deleuran M, et al. Laboratory safety of dupilumab for up to 3 years in adults with moderate-to-severe atopic dermatitis: results from an open-label extension study. *J Dermatolog Treat*. 2022;33(3):1608–1616.

Cibinqo (abrocitinib). US Prescribing Information. Pfizer; 2023.

Cuellar-Barboza A, Zirwas M, Feldman SR. Is dupilumab an immunosuppressant? *J Drugs Dermatol*. 2020;19(2):209–210.

Dupixent (dupilumab). US Prescribing Information. Sanofi-Aventis US, Regeneron Pharmaceuticals; 2024.

FDA Guidance Document. Warnings and Precautions, Contraindications, and Boxed Warning Sections of Labeling for Human Prescription Drug and Biological Products — Content and Format. October 2011. https://www.fda.gov/media/71866/download. Accessed May 2024.

Guttman-Yassky E, Bahadori L, Brooks L, et al. Lack of effect of benralizumab on signs and symptoms of moderate-to-severe atopic dermatitis: Results from the phase 2 randomized, double-blind, placebo-controlled HILLIER trial. *J Eur Acad Dermatol Venereol*. 2023;37:e1211–e1214.

Heil PM, Maurer D, Klein B, et al. Omalizumab therapy in atopic dermatitis: depletion of IgE does not improve the clinical course – a randomized, placebo-controlled and double blind pilot study. *J Dtsch Dermatol Ges*. 2010;8:990–998.

Kang EG, Narayana PK, Pouliquen IJ, et al. Efficacy and safety of mepolizumab administered subcutaneously for moderate to severe atopic dermatitis. *Allergy*. 2020;75:950–953.

Lee JK, Han D. Atopic dermatitis is an important comorbidity in severe asthma. *Ann Allergy Asthma Immunol*. 2018;120:661–662.

Panettieri RA Jr, Sjöbring U, Péterffy A, et al. Tralokinumab for severe, uncontrolled asthma (STRATOS 1 and STRATOS 2): two randomised, double-blind, placebo-controlled, phase 3 clinical trials. *Lancet Respir Med*. 2018;6(7):511-525.

Rinvoq (upadacitinib). US Prescribing Information. AbbVie; 2024.

Sanofi Press Release. Dupixent® sBLA accepted for FDA Priority Review for treatment of COPD with type 2 inflammation. February 2024. https://www.news.sanofi.us/2024-02-23-Dupixent-R-sBLA-accepted-for-FDA-Priority-Review-for-treatment-of-COPD-with-type-2-inflammation. Accessed May 2024.

Silverberg JI, Gelfand JM, Margolis DJ, et al. Association of atopic dermatitis with allergic, autoimmune, and cardiovascular comorbidities in US adults. *Ann Allergy Asthma Immunol*. 2018;121:604–612e3.

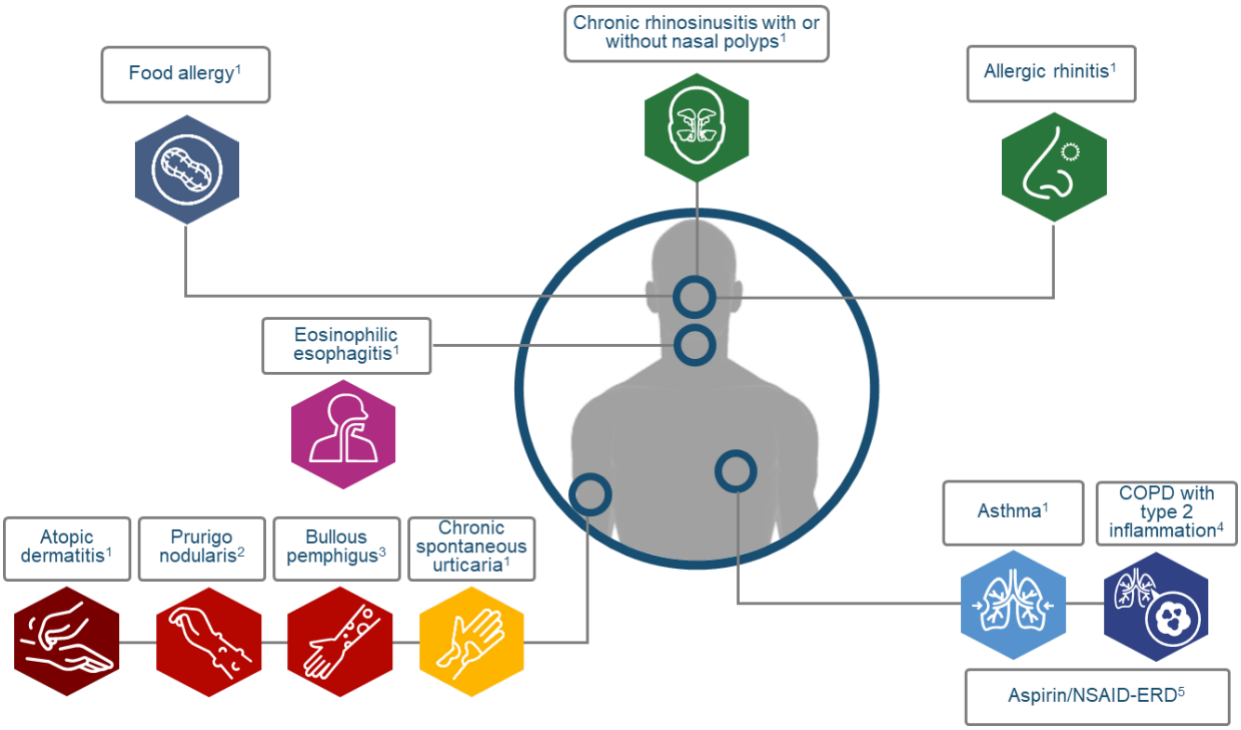
Wollenberg A, Beck LA, Blauvelt A, et al. Laboratory safety of dupilumab in moderate-to-severe atopic dermatitis: results from three phase III trials (LIBERTY AD SOLO 1, LIBERTY AD SOLO 2, LIBERTY AD CHRONOS). *Br J Dermatol*. 2020;182(5):1120–1135.

Appendix 1: Considerations for Treatment Choice in Patients With Atopic Dermatitis (AD), Asthma, Chronic Rhinosinusitis with Nasal Polyps (CRSwNP), Prurigo Nodularis (PN), and Eosinophilic Esophagitis (EoE)

Type 2 Inflammation

Type 2 inflammation plays a role in several chronic inflammatory disease states, including AD, asthma, CRSwNP, PN, EoE, and others. Figure 1 shows the broad range of diseases with a type 2 inflammatory component. Dupilumab is unique in that it is the only human monoclonal antibody that binds specifically to interleukin-4 receptor alpha (IL-4Rα), the shared receptor subunit for IL-4 and IL-13, thus inhibiting the dual signaling pathways of both IL-4 and IL-13 (Gandhi 2016, Le Floc'h 2020).

Figure 1. Diseases with a type 2 inflammation component



Co-existence of diseases driven in part by type 2 inflammation often affects treatment choices and shared decision-making between health care providers, patients, and caregivers. **Table 1** shows the percentage of patients in the dupilumab Phase 3 trials for AD, asthma, CRSwNP, and EoE who reported a history of select diseases with a type 2 component.

Table 1. Coexistence of type 2 inflammatory diseases in select dupilumab Phase 3 trials: Percentage of patients reporting a history of another atopic condition at screening visit for dupilumab clinical trials

	AD			Asthma		CRSwNP	EoE
	Adults aged ≥18 years (CHRONOS)[1]	Adolescents aged 12–17 years (ADOL)[2]	Children aged 6–11 years (AD-1652)[3,a]	Adults and adolescents aged ≥12 years (QUEST & VENTURE)[4–7]	Children aged 6–11 years (VOYAGE)[8]	Adults aged aged ≥18 years (SINUS)[9–11]	Adults and adolescents aged ≥12 years (TREET Part A)[12]
AD	NA	NA	NA	10%	36.3%	6%	19%
Any atopy	NA	NA	91.7%	NA	92.4%	N/A	84%
Asthma	39%	54%	46.7%	NA	NA	59%	31%
CRS[b]	6%	8%	3.0%	23%[b]	NA	100%	10%
CRSwNP	2%	2%	0.6%			NA	1%
Allergic rhinitis	43%	66%	60.2%	67%	81.9%	58%	59%
EoE	0.1%	0.4%	0.6%	0.1%	0.7%	0.6%	NA
Food allergy	33%	61%	64.4%	8%	17.9%	9%	44%
Allergic conjunctivitis	23%	23%	12.2%	13%	18.6%	11%	16%

Atopic Dermatitis

Dupilumab is the only US Food and Drug Administration (FDA)-approved AD systemic therapy that is also approved for asthma. The alternate biologic therapies approved for AD have failed in asthma clinical trials. Dupilumab is also the only AD biologic approved in patients aged 6 months and older.

The American Academy of Dermatology (AAD) 2023 guidelines gave dupilumab a strong recommendation for the treatment of moderate-to-severe AD, based on moderate certainty of evidence (Davis 2024). The guideline stated that dupilumab had an excellent safety track record in clinical trials and few major emergent safety concerns after more than 5 years in clinical practice. Despite having similar levels of recommendation for tralokinumab and Janus kinase (JAK) inhibitors, when surveyed, all participants from the guideline workgroup favored dupilumab as their first-line systemic agent. Dupilumab was also considered first-line by an international expert panel for use in special populations of adults, including older adults and those with renal disease, liver disease, viral hepatitis, HIV, or a history of cancer (Davis 2024). A summary of the AAD systemic therapy guidelines can be found in the supporting documents that follow this appendix.

The American Academy of Allergy, Asthma and Immunology (AAAAI)/American College of Allergy, Asthma and Immunology (ACAAI) Joint Task Force also recently published practice parameters for atopic dermatitis (Chu 2024). A summary of the AAAAI/ACAAI 2023 practice parameters can be found in the supporting documents that follow this appendix.

This panel recommended adding dupilumab in patients aged 6 months of age or older with moderate-to-severe AD refractory, intolerant, or unable to use mid-potency or greater topical treatments (*strong recommendation, high certainty evidence*) (Chu 2024). When considering dupilumab vs other biologics, the panel did not issue a formal recommendation for one agent over another, but stated “The evidence for benefits, however, provides stronger support for dupilumab compared with agents targeting solely anti-IL-13, such as tralokinumab and lebrikizumab” (Chu 2024).

The panel considered oral JAK inhibitors, including abrocitinib and upadacitinib, second-line systemic therapy after biologics, specifically recommending use "in adults and adolescents with moderate-severe AD refractory, intolerant, or unable to use mid- to high-potency topical treatment and systemic treatment inclusive of a recommended biologic (dupilumab or tralokinumab)" *(conditional recommendation, low-certainty evidence)* (Chu 2024). They further stated that the risk-benefit profile of JAK inhibitors should be considered because of safety concerns and the boxed warnings for this class of agents. JAK inhibitors have a boxed warning for serious infections, mortality, malignancy, major adverse cardiovascular events (MACE), and thrombosis (Chen 2023, Cibinqo US Prescribing Information [USPI] 2023, Rinvoq USPI 2024).

Asthma

Dupilumab is the only FDA-approved asthma biologic also approved in AD. This is important because real-world data estimate that up to 50% of patients with AD have coexisting asthma (Silverberg 2018). All the proposed therapeutic alternatives approved for asthma have failed in AD clinical trials.

The Global Initiative for Asthma (GINA), which launched in 1993 in collaboration between the National Heart, Lung, and Blood Institute, National Institutes of Health, and World Health Organization with the mission of improving the lives of people with asthma, releases a highly influential annual report that serves as guidance for clinical asthma treatment. In its 2023 report, GINA stressed the importance of comorbidities in asthma and recognized the additional FDA-approved indications for dupilumab, including for patients with comorbid CRSwNP, AD, and EoE as specific considerations for biologic agent selection. **Dupilumab is the only FDA-approved asthma biologic that is approved for patients with oral corticosteroid (OCS)-dependent asthma (without biomarker requirements)** (Dupixent USPI 2024). Overall, 30%–40% of patients aged ≥12 years with severe asthma require regular use of OCS, and up to 93% of patients aged >12 years with corticosteroid-dependent severe persistent asthma have at least 1 complication potentially due to OCS use (Lefebvre 2017, Sweeney 2016).

Several professional and patient advocacy organizations recognize the need to minimize OCS use in patients with severe asthma given the significant risk of adverse events. In its most recent release, the GINA report identifies multiple strategies to minimize OCS use, noting this as a high priority in severe asthma treatment to minimize common side effects. The report also includes chronic maintenance with OCS for asthma control as a criterion in favor of dupilumab when selecting a biologic in its treatment algorithm (GINA 2023).

The Allergy and Asthma Network, in its OCS Stewardship Statement, recognizes OCS overuse as a treatment plan failure and highlights the need to protect patients from both short-term and long-term health risks related to overexposure to OCS (OCS Stewardship Statement 2018).

The 2023 GINA Report can be found at this link, and the OCS Stewardship Statement can be found at this link.

Chronic Rhinosinusitis With Nasal Polyps

Dupilumab is the only FDA-approved biologic for patients with CRSwNP that is also approved for patients with AD.

The Joint Task Force on Practice Parameters (GRADE) guidelines for the management of CRSwNP, published in 2023 in the *Journal of Allergy and Clinical Immunology,* rendered an opinion in favor of the use of biologics in people with CRSwNP (Rank 2023). Furthermore, when considering patient-important and surrogate outcomes, dupilumab was considered most impactful in improving quality of life, symptoms, and smell improvement, and decreasing need for OCS and surgery when compared with the currently approved treatments, including the proposed therapeutic alternatives mepolizumab and omalizumab (Rank 2023).

Oykhman et al conducted a systematic review and network meta-analysis of 29 randomized controlled trials including data from >3400 patients and evaluating 8 advanced therapies (7 biologics and aspirin desensitization) for CRSwNP (Oykhman 2022).

The authors concluded that dupilumab uniquely ranked among the most beneficial for 7 out of 7 studied patient outcomes, in contrast to the proposed therapeutic alternatives omalizumab and mepolizumab, which were found to be most beneficial in 2 of 7 and 1 of 7 studied patient outcomes, respectively. This meta-analysis provides compelling evidence regarding the best CRSwNP treatments and better informs patients, clinicians, and policy makers on how to select from many CRSwNP treatment options (Oykhman 2022).

Complete results from Oykhman et al can be found in this manuscript.

Table 2. Summary of findings (Oykhman 2022)[1]

	Patient-important outcomes						Surrogate outcomes	
	HRQOL SNOT-22 (0–110)	**Symptoms** VAS (0–10 cm)	**Smell** UPSIT (0–40)[b]	**Rescue OCS**	**Rescue polyp surgery**	**Adverse events**	**Nasal polyp size** (0–8)	**CT score** LMK (0–24)
Standard care[a]	50.11	6.84	14.04	31.96%	21.05%	73.78%	5.94	18.35
Dupilumab	−19.91 (−22.50, −17.32)	−3.25 (−4.31, −2.18)	10.96 (9.75, 12.17)	−21.73 (−24.61, −18.22) RR 0.32 (0.23, 0.43)	−16.35 (−18.13, −13.48) RR 0.22 (0.14, 0.36)	0.13 (−8.12, 9.88) RR 1.00 (0.88, 1.13)	−2.04 (−2.73, −1.35)	−7.51 (−10.13, −4.89)
Omalizumab	−16.09 (−19.88, −12.30)	−2.09 (−3.15, −1.03)	3.75 (2.14, 5.35)	−12.46 (−23.65, 12.78) RR 0.61 (0.26, 1.40)	−7.40 (−11.04, −2.43) RR 0.65 (0.48, 0.88)	−2.60 (−15.58, 13.28) RR 0.96 (0.79, 1.18)	−1.09 (−1.70, −0.49)	−2.66 (−5.70, 0.37)
Mepolizumab	−12.89 (−16.58, −9.19)	−1.82 (−3.13, −0.50)	6.13 (4.07, 8.19)	−10.23 (−15.98, −2.88) RR 0.68 (0.50, 0.91)	−12.33 (−15.56, −7.22) RR 0.41 (0.26, 0.66)	−3.07 (−13.44, 9.07) RR 0.96 (0.82, 1.12)	−1.06 (−1.79, −0.34)	
Benralizumab	−7.68 (−12.09, −3.27)	−1.15 (−2.47, 0.17)	2.95 (1.02, 4.88)	−9.91 (−16.30, −0.96) RR 0.69 (0.49, 0.97)	−2.53 (−9.05, 7.16) RR 0.88 (0.57, 1.34)	−1.48 (−13.28, 12.54) RR 0.98 (0.82, 1.17)	−0.64 (−1.39, 0.12)	−1.00 (−3.83, 1.83)
Reslizumab					−18.82 (−20.93, 20.56) RR 0.11 (0.01, 1.98)	−2.55 (−19.49, 19.18) RR 0.97 (0.74, 1.26)		
AK001						2.54 (−27.11, 51.03) RR 1.03 (0.63, 1.69)	−0.20 (−1.61, 1.21)	
Etokimab	−1.30 (−8.99 to 6.40)					188.14 (−59.76, 4879.1) RR 3.55 (0.19, 67.13)	−0.33 (−1.58, 0.92)	
ASA Desensitization	−10.61 (−14.51, −6.71)	−2.74 (−3.92, −1.57)	2.72 (−1.17, 6.61)		−16.00 (−19.79, 0.21) RR 0.24 (0.06, 1.01)	209.21 (8.30, 901.87) RR 3.84 (1.11, 13.22)	−0.95 (−2.44, 0.55)	−0.31 (−3.50, 2.88)

Classification of intervention (color)[2]				Certainty (shading)[2,3]
Among most beneficial	Among intermediate beneficial	Among beneficial/not clearly different from placebo	No data (blank)	High/moderate (solid)
Among most harmful	Among intermediate harmful			Low/very low (shaded)

Eosinophilic Esophagitis

Dupilumab is the only FDA-approved asthma biologic also approved in EoE. Four different asthma biologics have failed in EoE clinical trials (omalizumab, reslizumab, mepolizumab, benralizumab) (Clayton 2014, Ridolo 2024).

EoE is a food allergen-triggered, immune-mediated, chronic inflammatory disease of the esophagus characterized by symptoms of esophageal dysfunction, such as swallowing difficulties and esophageal food impactions in adults and abdominal pain, food refusal, and vomiting in children, and histological/anatomical changes in the esophagus, such as strictures, due to chronic disease (Dellon

2018a; Muir 2021). EoE has emerged as a major cause of upper gastrointestinal morbidity over the past 3 decades, with current prevalence estimates in the US reaching 1 case per 1000 (Dellon 2018b). Epidemiological burden of EoE is also increasing rapidly, with the most recent nationwide data showing EoE-associated emergency department visits tripled between 2009 and 2019; these are projected to further double by 2030 (Lam 2023). Dupilumab was extensively studied in 52-week clinical trials and approved in May 2022 as the first and only medical therapy for EoE (for adolescents and adults), and later in January 2024, this indication was extended down to children as young as 1 year of age. **Dupilumab is the first and only biologic therapy approved for EoE, without any therapeutic alternatives approved for long-term use.** Real-world data from a study conducted at the Children's Hospital of Philadelphia have also demonstrated that dupilumab allowed safe introduction of EoE trigger foods in patients with EoE while controlling symptoms, preserving histologic integrity, and preventing endoscopic disease progression while also reducing the burden of dietary restrictions in children with this condition (Wolfset 2023).

Prurigo Nodularis

Dupilumab remains the first and only FDA-approved therapy for adult patients with PN, irrespective of disease severity and prior topical prescription treatment. PN is a chronic, inflammatory skin condition with an estimated prevalence of 72 per 100,000 adults in the US (Huang 2020). The diagnosis of PN is based on the following clinical features: firm, itchy lesions that can present as nodules, papules, or plaques, generally with a bilateral distribution on the arms and trunk; chronic pruritus lasting ≥6 weeks; history and/or signs of repeated scratching, picking, or rubbing (Pereira 2018, Kwon 2019, Elmariah 2021). Excoriations, crusts, lichenification, and pigmentary alterations develop due to ongoing scratching; areas less accessible to scratching, such as the middle of the back, are usually spared (Kwon et al 2019). PN mostly affects middle-aged to older patients (aged 50+ years) (Hughes 2020) and appears to be more common in skin of color (Whang 2019). PN signs and symptoms (intense itch, skin lesions, bleeding of excoriated lesions, scars) (Iking 2013, Pereira 2018, Pereira 2020) can have a severe impact on patients' quality of life and are associated with sleep disturbance, absenteeism from work, symptoms of depression and anxiety, and a feeling of shame and helplessness (Jørgensen 2017, Pereira 2018).

Dupilumab Pipeline

Dupilumab is expected to be the first FDA-approved therapy for the chronic treatment of the following diseases: COPD with type 2 inflammation and bullous pemphigoid (BP) (ClinicalTrials.gov NCT05649579). The FDA has accepted for Priority Review the supplemental Biologics License Application for dupilumab, with a target action date of June 27, 2024 for the FDA decision. Dupilumab is anticipated to be the first advanced therapy approved in patients with COPD in over a decade (Bhatt 2023, Sanofi Press Release 2023).

Results from dupilumab Phase 3 trials in patients with COPD with type 2 inflammation can be found in this manuscript (BOREAS) and this Sanofi press release (NOTUS).

Dupilumab is also in development for chronic spontaneous urticaria (CSU), chronic pruritus of unknown origin, eosinophilic gastritis, and ulcerative colitis with an eosinophilic phenotype (Maurer 2024, ClinicalTrials.gov NCT04180488, ClinicalTrials.gov NCT05263206, ClinicalTrials.gov NCT05831176, ClinicalTrials.gov NCT05731128).

Figure 1 abbreviations and references

COPD, chronic obstructive pulmonary disease; NSAID-ERD, nonsteroidal anti-inflammatory drug–exacerbated respiratory disease.

1. Gandhi NA, Bennett BL, Graham NMH, Pirozzi G, Stahl N, Yancopoulos GD. Targeting key proximal drivers of type 2 inflammation in disease. *Nat Rev Drug Discov*. 2016;15(1):35–50. 2. Williams KA, Huang AH, Belzberg M, Kwatra SG. Prurigo nodularis: pathogenesis and management. *J Am Acad Dermatol*. 2020;83(6):1567–1575. 3. Amber KT, Valdebran M, Kridin K, Grando SA. The role of eosinophils in bullous pemphigoid: a developing model of eosinophil pathogenicity in mucocutaneous disease. *Front Med (Lausanne)*. 2018;5:201. 4. Garudadri S, Woodruff PG. Targeting chronic obstructive pulmonary disease phenotypes, endotypes, and biomarkers. *Ann Am Thorac Soc*. 2018;15(Suppl 4):S234–S238. 5. White AA, Doherty TA. Role of group 2 innate lymphocytes in aspirin-exacerbated respiratory disease pathogenesis. *Am J Rhinol Allergy*. 2018;32(1):7–11.

Table 1 footnotes, abbreviations, and references

[a]Percentages were calculated using prevalence in each of the 3 treatment arms (placebo, dupilumab 300 mg q4w + TCS, and dupilumab 100 mg or 200 mg q2w + TCS). [b]Includes nasal polyps and/or CRS in QUEST study.
AD, atopic dermatitis; CRS, chronic rhinosinusitis; CRSwNP, chronic rhinosinusitis with nasal polyps; EoE, eosinophilic esophagitis; NA, not applicable; q2w, every 2 weeks; q4w, every 4 weeks; TCS, topical corticosteroids.

1. Blauvelt A, de Bruin-Weller M, Gooderham M, et al. Long-term management of moderate-to-severe atopic dermatitis with dupilumab and concomitant topical corticosteroids (LIBERTY AD CHRONOS): a 1-year, randomised, double-blinded, placebo-controlled, phase 3 trial. *Lancet*. 2017;389(10086):2287–2303. 2. Simpson EL, Paller AS, Siegfried EC, et al. Efficacy and safety of dupilumab in adolescents with uncontrolled moderate to severe atopic dermatitis: a Phase 3 randomized clinical trial. *JAMA Dermatol*. 2020;156(1):44–56. 3. Paller AS, Siegfried EC, Thaçi D, et al. Efficacy and safety of dupilumab with concomitant topical corticosteroids in children 6 to 11 years old with severe atopic dermatitis: a randomized, double-blinded, placebo-controlled phase 3 trial [published correction appears in *J Am Acad Dermatol*. 2021;84(1):230]. *J Am Acad Dermatol*. 2020;83(5):1282–1293. 4. Sanofi and Regeneron. Data on file. LIBERTY ASTHMA QUEST Clinical Study Report. 2017. 5. Sanofi and Regeneron. Data on file. LIBERTY ASTHMA VENTURE Clinical Study Report. 2017. 6. Castro M, Corren J, Pavord ID, et al. Dupilumab efficacy and safety in moderate-to-severe uncontrolled asthma. *N Engl J Med*. 2018;378(26):2486–2496. 7. Rabe KF, Nair P, Brusselle G, et al. Efficacy and safety of dupilumab in glucocorticoid-dependent severe asthma. *N Engl J Med*. 2018;378(26):2475–2485. 8. Sanofi and Regeneron. Data on file. LIBERTY ASTHMA VOYAGE Clinical Study Report. 2021. 9. Sanofi and Regeneron. Data on file. SINUS-24 Clinical Study Report. 2018. 10. Sanofi and Regeneron. Data on file. SINUS-52 Clinical Study Report. 2018. 11. Bachert C, Han JK, Desrosiers M, et al. Efficacy and safety of dupilumab in patients with severe chronic rhinosinusitis with nasal polyps (LIBERTY NP SINUS-24 and LIBERTY NP SINUS-52): results from two multicentre, randomised, double-blind, placebo-controlled, parallel-group phase 3 trials [published correction appears in *Lancet*. 2019;394(10209):1618]. *Lancet*. 2019;394(10209):1638–1650. 12. Rothenberg ME, et al. Baseline demographics and disease characteristics of patients with eosinophilic esophagitis in part A of the 3-part, randomized, placebo-controlled, phase 3 TREET study. *EAACI-PAAM*. 2021. Abstract.

Table 2 footnotes, abbreviations, and references

Numbers in the colored cells are the estimated mean differences (95% CI) for HRQOL, symptoms, smell, nasal polyp size, and CT score, and absolute risk differences (95% CI) per 100 patients (with accompanying relative risks [95% CI]) for rescue OCS, rescue nasal polyp surgery and adverse events vs standard care. GRADE certainty[2,3]: high certainty—further research is very unlikely to change our confidence in the estimate of effect; moderate certainty—further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate; low certainty—further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate; very low certainty—any estimate of effect is very uncertain.
[a]The expected risk of each outcome with standard care is reported in the gray row. [b]The only scale presented where higher is better. Higher scores indicate worse outcomes for all other scales shown.
ASA, aspirin desensitization; CT, computed tomography; HRQOL, health-related quality of life; LMK, Lund-Mackay; OCS, oral corticosteroids; RR, risk ratio; SNOT-22, 22-item Sinonasal Outcome Test; UPSIT, University of Pennsylvania Smell Identification Test; VAS, visual analog score.

1. Oykhman P, Paramo FA, Bousquet J, Kennedy DW, Brignardello-Petersen R, Chu DK. Comparative efficacy and safety of monoclonal antibodies and aspirin desensitization for chronic rhinosinusitis with nasal polyposis: a systematic review and network meta-analysis. *J Allergy Clin Immunol*. 2022;149(4):1286–1295. 2. Brignardello-Petersen R, Florez ID, Izcovich A, et al. GRADE approach to drawing conclusions from a network meta-analysis using a minimally contextualised framework. *BMJ*. 2020;371:m3900. 3. Schünemann H, Brożek J, Guyatt G, et al. GRADE handbook for grading quality of evidence and strength of recommendations. Updated October 2013. The GRADE Working Group, 2013. Available at: https://gdt.gradepro.org/app/handbook/handbook.html. Accessed May 2024.

References

Bhatt SP, Rabe KF, Hanania NA, et al. Dupilumab for COPD with type 2 inflammation indicated by eosinophil counts. *N Engl J Med*. 2023;389(3):205–214.

Chen Q, Cui L, Hu Y, Chen Z, Gao Y, Shi Y. Short-term efficacy and safety of biologics and Janus kinase inhibitors for patients with atopic dermatitis: a systematic review and meta-analysis. *Heliyon*. 2023;9(11):e22014.

Chu DK, Schneider L, Asiniwasis RN, et al. Atopic dermatitis (eczema) guidelines: 2023 American Academy of Allergy, Asthma and Immunology/American College of Allergy, Asthma and Immunology Joint Task Force on Practice Parameters GRADE- and Institute of Medicine-based recommendations. *Ann Allergy Asthma Immunol*. 2024;132(3):274–312.

Cibinqo (abrocitinib). US Prescribing Information. Pfizer; 2023.

Clayton F, Fang JC, Gleich GJ, et al. Eosinophilic esophagitis in adults is associated with IgG4 and not mediated by IgE. *Gastroenterology*. 2014;147(3):602–609.

ClinicalTrials.gov NCT04180488. https://clinicaltrials.gov/study/NCT04180488. Accessed May 2024.

ClinicalTrials.gov NCT05263206. https://clinicaltrials.gov/study/NCT05263206. Accessed May 2024.

ClinicalTrials.gov NCT05649579. https://clinicaltrials.gov/study/NCT05649579. Accessed May 2024.

ClinicalTrials.gov NCT05731128. https://clinicaltrials.gov/study/NCT05731128. Accessed May 2024.

ClinicalTrials.gov NCT05831176. https://clinicaltrials.gov/study/NCT05831176. Accessed May 2024.

Davis DMR, Drucker AM, Alikhan A, et al. Guidelines of care for the management of atopic dermatitis in adults with phototherapy and systemic therapies. *J Am Acad Dermatol*. 2024;90(2):e43-e56.

Dellon ES, Liacouras CA, Molina-Infante J, et al. Updated international consensus diagnostic criteria for eosinophilic esophagitis: proceedings of the AGREE conference. *Gastroenterology*. 2018a;155(4):1022–1033.e10.

Dellon ES, Hirano I. Epidemiology and natural history of eosinophilic esophagitis. *Gastroenterology*. 2018b;154(2):319–332.e3.

Dupixent (dupilumab). US Prescribing Information. Sanofi-Aventis US, Regeneron Pharmaceuticals; 2024.

Elmariah S, Kim B, Berger T, et al. Practical approaches for diagnosis and management of prurigo nodularis: United States expert panel consensus. *J Am Acad Dermatol*. 2021;84(3):747–760.

Gandhi NA, Bennett BL, Graham NMH, Pirozzi G, Stahl N, Yancopoulos GD. Targeting key proximal drivers of type 2 inflammation in disease. *Nat Rev Drug Discov*. 2016;15(1):35–50.

GINA 2023. Global strategy for asthma management and prevention. Available at: https://ginasthma.org/wp-content/uploads/2023/07/GINA-2023-Full-report-23_07_06-WMS.pdf. Accessed May 2024.

Huang AH, Canner JK, Khanna R, Kan S, Kwatra SG. Real-world prevalence of prurigo nodularis and burden of associated diseases. *J Invest Dermatol*. 2020;140(2):480–483.e4.

Hughes J-DM, Woo TE, Belzberg M, et al. Association between prurigo nodularis and etiologies of peripheral neuropathy: suggesting a role for neural dysregulation in pathogenesis. *Medicines (Basel)*. 2020;7(1):4.

Iking A, Grundmann S, Chatzigeorgakidis E, Phan NQ, Klein D, Ständer. Prurigo as a symptom of atopic and non-atopic diseases: aetiological survey in a consecutive cohort of 108 patients. *J Eur Acad Dermatol Venereol*. 2013;27(5):550–557.

Jørgensen KM, Egeberg A, Gislason GH, Skov L, Thyssen JP. Anxiety, depression and suicide in patients with prurigo nodularis. *J Eur Acad Dermatol Venereol*. 2017;31(2):e106–e107.

Kwon CD, Khanna R, Williams KA, Kwatra MM, Kwatra SG. Diagnostic workup and evaluation of patients with prurigo nodularis. *Medicines (Basel)*. 2019;6(4):97.

Lam AY, Lee JK, Coward S, et al. Epidemiologic burden and projections for eosinophilic esophagitis-associated emergency department visits in the United States: 2009-2030. *Clin Gastroenterol Hepatol*. 2023;21(12):3041–3050.e3.

Le Floc'h A, Allinne J, Nagashima K, et al. Dual blockade of IL-4 and IL-13 with dupilumab, an IL-4Rα antibody, is required to broadly inhibit type 2 inflammation. *Allergy*. 2020;75(5):1188–1204.

Lefebvre P, Duh MS, Lafeuille MH, et al. Burden of systemic glucocorticoid-related complications in severe asthma. *Curr Med Res Opin*. 2017;33(1):57–65.

Maurer M, Casale TB, Saini SS, et al. Dupilumab in patients with chronic spontaneous urticaria (LIBERTY-CSU CUPID): two randomized, double-blind, placebo-controlled, phase 3 trials. *J Allergy Clin Immunol*. 2024:S0091-6749(24)00196-9.

Muir A, Falk GW. Eosinophilic esophagitis: a review. *JAMA*. 2021;326(13):1310–1318.

OCS Stewardship Statement 2018. Available at: https://www.ocsoverexposed.com/partners.html. Accessed May 2024.

Oykhman P, Paramo FA, Bousquet J, Kennedy DW, Brignardello-Petersen R, Chu DK. Comparative efficacy and safety of monoclonal antibodies and aspirin desensitization for chronic rhinosinusitis with nasal polyposis: a systematic review and network meta-analysis. *J Allergy Clin Immunol*. 2022;149(4):1286–1295.

Pereira MP, Hoffmann V, Weisshaar E, et al. Chronic nodular prurigo: clinical profile and burden. A European cross-sectional study. *J Eur Acad Dermatol Venereol*. 2020;34(10):2373–2383.

Pereira MP, Steinke S, Zeidler C, et al. European academy of dermatology and venereology European prurigo project: expert consensus on the definition, classification and terminology of chronic prurigo. *J Eur Acad Dermatol Venereol*. 2018;32(7):1059–1065.

Rank MA, Chu DK, Bognanni A, et al. The Joint Task Force on Practice Parameters GRADE guidelines for the medical management of chronic rhinosinusitis with nasal polyposis. *J Allergy Clin Immunol*. 2023;151(2):386–398.

Ridolo E, Barone A, Ottoni M, Peveri S, Montagni M, Nicoletta F. The new therapeutic frontiers in the treatment of eosinophilic esophagitis: biological drugs. *Int J Mol Sci*. 2024;25(3):1702.

Rinvoq (Upadacitinib). US Prescribing Information. AbbVie; 2024.

Sanofi Press Release. Dupixent® significantly reduced COPD exacerbations in second positive Phase 3 trial, accelerating FDA submission and confirming potential to become first approved biologic for this serious disease. November 27, 2023. https://www.sanofi.com/assets/dotcom/pressreleases/2023/2023-11-27-06-30-00-2785836-en.pdf. Accessed May 2024.

Silverberg JI, Gelfand JM, Margolis DJ, et al. Association of atopic dermatitis with allergic, autoimmune, and cardiovascular comorbidities in US adults. *Ann Allergy Asthma Immunol*. 2018;121(5):604–612.e3.

Sweeney J, Patterson CC, Menzies-Gow A, et al. Comorbidity in severe asthma requiring systemic corticosteroid therapy: cross-sectional data from the Optimum Patient Care Research Database and the British Thoracic Difficult Asthma Registry. *Thorax*. 2016;71(4):339–346.

Whang KA, Kang S, Kwatra SG. Inpatient burden of prurigo nodularis in the United States. *Medicines (Basel)*. 2019;6(3):88.

Wolfset N, Muir A, Williams D, et al. Efficacy of dupilumab on facilitated food introduction: in eosinophilic esophagitis. *Ann Allergy Asthma Immunol*. 2023;131(5):S78.

SUPPORTING DOCUMENTS

AAD Guidelines Update for Atopic Dermatitis (AD)

Please complete a 2-minute survey to share your thoughts about this medical resource

Section I: AAD Guidelines on Topical Therapies and Comorbidities in Patients With AD

Topical Therapies

- The AAD workgroup developed 12 recommendations on the use of topical therapies in adults with AD, including nonprescription agents and prescription TCS, TCI, JAK inhibitors, PDE-4 inhibitors, antimicrobials, and antihistamines[1]
- For nonprescription therapies, moisturizers are strongly recommended with moderate certainty of evidence. However, the working group does not recommend using a particular moisturizer or active ingredient in an emollient based on the limited available evidence[1]
- There is a strong recommendation and high certainty of evidence for the use of prescription therapies, including TCS, TCI, and topical PDE-4 inhibitors[1]

Comorbidities

- In adults, there is clear evidence of an association between AD and atopic and immune-mediated conditions; ample evidence supporting an association between AD and mental health conditions (eg, depression, anxiety); and limited, but consistent evidence, supporting an association between AD and adverse bone health (eg, osteoporosis, fractures)[2]
- Targeted therapies that are effective for both severe AD and asthma, such as dupilumab, have the potential to benefit patients with both conditions[2]
- As biologics and other targeted agents continue to be evaluated, approved, and prescribed across different inflammatory conditions, medications with multiple indications have the potential to treat patients with 2 or more diseases simultaneously[2]

Section II: AAD Guidelines on Systemic Therapies in Patients With AD[3]

Monoclonal antibodies (biologics)

- For the treatment of moderate-to-severe AD (moderate certainty of evidence), **dupilumab** is strongly recommended
  - Dupilumab has an excellent safety track record in clinical trials and few major emergent safety concerns after more than 5 years in clinical practice. When surveyed, all participants from the guideline workgroup particularly favored dupilumab as their first-line systemic agent
  - It was also considered first-line therapy by an international expert panel (conducted before the approval of tralokinumab and JAK inhibitors) for use in special populations of adults, including older adults and those with renal disease, liver disease, viral hepatitis, HIV, or a history of cancer
  - Dupilumab at standard dosing (600 mg subcutaneously at initiation, then 300 mg every 2 weeks) is somewhat less efficacious than higher doses of abrocitinib and upadacitinib, with somewhat better efficacy than abrocitinib 100 mg daily and comparable efficacy to upadacitinib 15 mg daily
- For the treatment of moderate-to-severe AD (moderate certainty of evidence), **tralokinumab** is strongly recommended
- The AAD Guideline committee recommend both dupilumab and tralokinumab. These medications appear safe, and no laboratory monitoring is required before initiation or during treatment. Conjunctivitis is a common adverse event with both dupilumab and tralokinumab. For most patients, conjunctivitis is self-limited and can be managed conservatively with the use of artificial tears. Referral to ophthalmology should be considered, particularly if conjunctivitis is more severe, persistent, or refractory to conservative measures

JAK inhibitors

- **Upadacitinib** and **abrocitinib** are approved in patients with moderate-to-severe AD that did not respond to other systemic therapies. As such, in most circumstances, these medications are not considered to be a first-line systemic therapy. For the treatment of moderate-to-severe AD (moderate certainty of evidence), both **upadacitinib** and **abrocitinib** are strongly recommended
  - Both upadacitinib and abrocitinib demonstrated very high efficacy at reducing the signs and symptoms of AD and improving QOL, with rapid onset of action in their Phase 3 clinical trial programs among adolescents and adults with AD
  - The higher doses of upadacitinib (30 mg daily) and abrocitinib (200 mg daily) demonstrate the highest efficacy at reducing EASI scores for up to 16 weeks of treatment among all currently available treatments in a network meta-analysis and were superior to dupilumab in head-to-head trials
- For the treatment of moderate-to-severe AD (moderate certainty of evidence), **baricitinib** is strongly recommended. It is approved and available in the US for other immune-related conditions, but is not approved by the FDA to treat patients with AD
  - Although no head-to-head trials were done, network meta-analysis suggests baricitinib is less efficacious than upadacitinib and abrocitinib
- Because of potential safety concerns, the FDA recommended these medications be started at their lower doses. Serious adverse events, including death and thromboembolic events, have occurred in trials of patients with AD
- Based on safety data from other JAK inhibitors used in other populations, the FDA applied warnings of increased risk of serious heart-related events, cancer, blood clots, and death for the **JAK inhibitor class**
  - Other potential safety concerns with JAK inhibitors include an increased risk of serious and opportunistic infections, including herpes zoster. Vaccination for shingles is recommended before initiating a JAK inhibitor, particularly for older patients
  - The FDA recommends performing the following laboratory monitoring: complete blood count with differential and liver enzymes at baseline and after initiation or dose-escalation; lipids after initiation; testing for viral hepatitis, tuberculosis, and pregnancy at baseline

Systemic treatments with insufficient evidence to make recommendations

- There are insufficient data to make a recommendation on the use of PUVA phototherapy, systemic antibiotics, oral antihistamines, montelukast, apremilast, ustekinumab, IVIG, interferon-γ, omalizumab, TNF-α inhibitors, systemic calcineurin inhibitors (other than cyclosporine), or mepolizumab in the management of AD

References

1. Sidbury R, Alikhan A, Bercovitch L, et al. Guidelines of care for the management of atopic dermatitis in adults with topical therapies. *J Am Acad Dermatol*. 2023;89(1):e1–e20.
2. Davis DMR, Drucker AM, Alikhan A, et al. American Academy of Dermatology Guidelines: Awareness of comorbidities associated with atopic dermatitis in adults. *J Am Acad Dermatol*. 2022;86(6):1335–1336.e18.
3. Davis DMR, Drucker AM, Alikham A, et al. Guidelines of care for the management of atopic dermatitis in adults with phototherapy and systemic agents. *J Am Acad Dermatol*. 2023. doi: https://doi.org/10.1016/j.jaad.2023.08.102.

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Section III: Recommendations From the AAD Guidelines on Systemic Therapies in Patients With AD[3]

Recommendations for the management of AD in adults with phototherapy and systemic agents

Intervention	US Regulatory Status[a]	Recommendation[b] and Strength	Certainty of Evidence	Remarks
Dupilumab	On-label	For adults with moderate-to-severe AD, we **strongly** recommend dupilumab	Moderate	
Tralokinumab	On-label	For adults with moderate-to-severe AD, we **strongly** recommend tralokinumab	Moderate	
Upadacitinib	On-label	For adults with moderate-to-severe AD, we **strongly** recommend upadacitinib	Moderate	Upadacitinib is approved by the FDA in patients with AD that has not responded to other systemic therapies or when use of those therapies is inadvisable
Abrocitinib	On-label	For adults with moderate-to-severe AD, we **strongly** recommend abrocitinib	Moderate	Abrocitinib is approved by the FDA in patients with AD that has not responded to other systemic therapies or when use of those therapies is inadvisable
Baricitinib	Off-label	For adults with moderate-to-severe AD, we **strongly** recommend baricitinib	Moderate	Baricitinib is not approved by the FDA in AD
Methotrexate	Off-label	For adults with moderate-to-severe AD, we **conditionally** recommend methotrexate with proper monitoring	Low	Comorbidities or drug interactions may exacerbate toxicity, making this intervention inappropriate for select patients. In the US, the FDA has not approved methotrexate in AD
Systemic corticosteroids (eg, prednisone)	On-label	For adults with AD, we **conditionally** recommend against systemic corticosteroids	Low	Their use should be reserved exclusively for acute, severe exacerbations and as a short-term bridge therapy to other systemic, steroid-sparing therapy
Mycophenolate mofetil[c]	Off-label	For adults with refractory moderate-to-severe AD, we **conditionally** recommend mycophenolate mofetil with proper monitoring	Very low	Mycophenolate mofetil is not approved by the FDA in AD. Comorbidities or drug interactions may exacerbate toxicity, making this intervention inappropriate for select patients
Azathioprine	Off-label	For adults with refractory moderate-to-severe AD, we **conditionally** recommend TPMT-dosed azathioprine with proper monitoring	Low	Comorbidities or drug interactions may exacerbate toxicity, making this intervention inappropriate for select patients
Cyclosporine	Off-label	For adults with refractory moderate-to-severe AD, we **conditionally** recommend limited term use of cyclosporine with proper monitoring	Low	The FDA has not approved cyclosporine in AD. Comorbidities or drug interactions may exacerbate toxicity, making this intervention inappropriate for select patients
Phototherapy (all types)	On-label	For adults with AD, we **conditionally** recommend phototherapy	Low	Most current literature reports the efficacy and safety of narrow band UVB. Wherever possible, use a light source that minimizes the potential for harm under the supervision of a qualified clinician

[a]For medications, whether they are used on- or off-label for AD based on FDA approval. [b]The supporting evidence used for this table can be found here. [c]Mycophenolic acid can be used interchangeably depending on availability. Note that dosing differs for mycophenolic acid and mycophenolate mofetil.

Links to relevant documentation

- Dupilumab USPI
- AAD Guidelines for AD Systemic Therapies
- AAD Guidelines for AD Topical Therapies
- AAD Guidelines for AD Comorbidities

Abbreviations

AAD	American Academy of Dermatology
AD	Atopic dermatitis
EASI	Eczema Area and Severity Index
FDA	US Food and Drug Administration
IVIG	Intravenous immunoglobin
JAK	Janus kinase
PDE-4	Phosphodiesterase-4
PUVA	Psoralen plus ultraviolet A
QOL	Quality of life
TCI	Topical calcineurin inhibitors
TCS	Topical corticosteroids
TNF	Tumor necrosis factor
TPMT	Thiopurine methyltransferase
USPI	United States prescribing information
UV	Ultraviolet

AD Executive Summary: AAAAI / ACAAI Joint Task Force Atopic Dermatitis Guidelines

Please complete this 2-minute survey to share your thoughts about this medical resource

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Please see a summary of the evidence-based recommendations for the optimal management of AD in infants, children, and adults. This guidance was developed by a multidisciplinary guideline panel consisting of patients and caregivers, AD experts, PCPs, and allied health professionals using the GRADE approach. Access guidelines HERE.

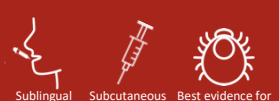
Background

How do the 2023 AAAAI/ACAAI JTF AD guidelines differ from the 2012 guidelines?

- Emphasis on evidence-based medicine and patient values and preferences
- Increased focus on diagnosis, education, trigger avoidance, proper medication use/adherence, and use of moisturizer for symptoms
- Inclusion of new therapies that have emerged in the past 10 years, including biologics

AD AAAAI/ACAAI JTF 2023 Guidelines: Summary of Recommendations

INTERVENTION Treatment or category of treatments considered	SEVERITY Severity of AD	RECOMMENDATION Text summary of recommendation	STRENGTH The strength of the recommendation	CERTAINTY GRADE rating for the certainty of evidence
SYSTEMIC TREATMENTS Consider if refractory, intolerant, or unable to use mid- to high-potency topical treatment	MODERATE, SEVERE	BIOLOGICS / MONOCLONAL ANTIBODIES **DUPILUMAB** (Age 6 mo+) We **recommend** adding dupilumab	**Strong** in favor	**High** certainty evidence
	MODERATE, SEVERE	BIOLOGICS / MONOCLONAL ANTIBODIES **TRALOKINUMAB** (Age 12 yo+) We **recommend** adding tralokinumab	**Strong** in favor	**High** certainty evidence
Consider if refractory, intolerant, or unable to use mid- to high-potency topical treatment and systemic treatment inclusive of a biologic recommended above See conditions to consider, eg, comorbidities, risk factors, values and preferences, and exceptional circumstances	MODERATE, SEVERE	**UVB TREATMENT** We **suggest** adding clinic-based narrow band UVB treatment	**Conditional** in favor	**Low** certainty evidence
	MODERATE, SEVERE	SMALL MOLECULE IMMUNOSUPPRESSANTS **ABROCITINIB, BARICITINIB, OR UPADACITINIB** (Age varies: 12 or 18 yo+) We **suggest** adding one of these three JAK inhibitors Suggested daily doses: Abrocitinib 100–200 mg; Baricitinib 2–4 mg; Upadacitinib 15–30 mg	**Conditional** in favor	**Low** certainty evidence
	MODERATE, SEVERE	SMALL MOLECULE IMMUNOSUPPRESSANTS **BARICITINIB 1 mg DAILY** We **recommend against** adding baricitinib 1 mg daily	**Strong** against	**Low** certainty evidence
	MODERATE, SEVERE	SMALL MOLECULE IMMUNOSUPPRESSANTS **AZATHIOPRINE** We **suggest against** adding azathioprine	**Conditional** against	**Low** certainty evidence
	MODERATE, SEVERE	SMALL MOLECULE IMMUNOSUPPRESSANTS **CYCLOSPORINE** We **suggest** adding cyclosporine Shared decision-making should determine whether to start therapy at high dose (5 mg/kg) or low dose (3 mg/kg)	**Conditional** in favor	**Low** certainty evidence
	MODERATE, SEVERE	SMALL MOLECULE IMMUNOSUPPRESSANTS **METHOTREXATE** We **suggest against** adding methotrexate	**Conditional** against	**Low** certainty evidence
	MODERATE, SEVERE	SMALL MOLECULE IMMUNOSUPPRESSANTS **MYCOPHENOLATE** We **suggest against** adding mycophenolate	**Conditional** against	**Low** certainty evidence
Chu et al Network meta-analysis	MILD, MODERATE, SEVERE	**SYSTEMIC CORTICOSTEROIDS** We **suggest against** systemic corticosteroids for all patients with atopic dermatitis	**Conditional** against	**Low** certainty evidence
TOPICAL TREATMENTS	MILD, MODERATE, SEVERE	**PRESCRIPTION MOISTURIZERS** We **suggest against** using prescription moisturizers rather than a fragrance-free over-the-counter moisturizer	**Conditional** against	**Low** certainty evidence
If refractory to moisturizers	MILD, MODERATE, SEVERE	**TOPICAL CORTICOSTEROIDS** (Age 3 mo+) We **recommend** adding a topical corticosteroid	**Strong** in favor	**High** certainty evidence
	MILD, MODERATE, SEVERE	**TOPICAL CALCINEURIN INHIBITORS** (Age 3 mo+) We **recommend** adding a topical calcineurin inhibitor	**Strong** in favor	**High** certainty evidence
	MILD, MODERATE	**TOPICAL PDE4 INHIBITORS** (Age 3 mo+) We **suggest** adding crisaborole	**Conditional** in favor	**Moderate** certainty evidence
	MILD, MODERATE	**TOPICAL JAK INHIBITORS** (Age 12 yo+) We **suggest against** adding topical ruxolitinib	**Conditional** against	**Low** certainty evidence
	MILD, MODERATE, SEVERE	**APPLICATION FREQUENCY** We **suggest** applying mid- to high-potency topical medicines once per day over twice per day	**Conditional** in favor	**Low** certainty evidence
Localized lesions refractory to mid- to high-potency topical treatment	MODERATE, SEVERE	**OCCLUSIVE APPLICATION** (WET WRAPS) We **suggest** a time and body surface area-limited trial of occlusive low- to mid-potency topical steroid	**Conditional** in favor	**Very low** certainty evidence
	MILD, MODERATE, SEVERE	**TOPICAL ANTIMICROBIALS** We **suggest against** adding topical antimicrobials to topical anti-inflammatories in patients with no clear signs of infection	**Conditional** against	**Very low** certainty evidence
Chu et al Network meta-analysis Devasenapathy & Chu meta-analysis	MILD, MODERATE, SEVERE	**MAINTENANCE OF REMISSION** We **recommend** use of proactive therapy to areas that flare with a topical calcineurin inhibitor or mid-potency topical steroid	**Strong** in favor	**Moderate** certainty evidence

INTERVENTION Treatment or category of treatments considered	SEVERITY Severity of dermatitis that this recommend-ation applies to	RECOMMENDATION Text summary of recommendation	STRENGTH The strength of the recommendation	CERTAINTY GRADE rating for the certainty of evidence
BLEACH BATHS  Bakaa et al 2022. Systematic review	MODERATE, SEVERE	We **suggest** adding dilute bleach bathing	**Conditional** in favor	**Low** certainty evidence
	MILD	We **suggest against** adding dilute bleach bathing	**Conditional** against	**Low** certainty evidence
ELIMINATION DIETS  Oykhman et al Systematic review	MILD, MODERATE, SEVERE	We **suggest against** the use of elimination diets	**Conditional** against	**Low** certainty evidence
ALLERGEN IMMUNOTHERAPY  Sublingual · Subcutaneous · Best evidence for dust mite allergy Ypes-Nuñez & Chu et al Systematic review	MODERATE, SEVERE	We **suggest** adding allergen immunotherapy If refractory, intolerant, or unable to use mid-potency topical treatments	**Conditional** in favor	**Moderate** certainty evidence
	MILD	We **suggest against** adding allergen immunotherapy See conditions to consider, eg, comorbidities, values and preferences	**Conditional** against	**Moderate** certainty evidence

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Systemic Treatment Recommendations for AD

	Dupilumab	Tralokinumab	Lebrikizumab	Abrocitinib		Baricitinib		Upadacitinib	
	Standard dose	Standard dose	Standard dose	Low dose (100 mg)	High dose (200 mg)	Low dose (1 mg)	High dose (2–4 mg)	Low dose (15 mg)	High dose (30 mg)
EASI	✓✓	✓	✓	✓	✓	–	✓	✓✓	✓✓
POEM	✓✓	✓	✓	✓	✓✓	–	✓	✓✓	✓✓
Itch NRS	✓	–	✓	✓	✓	–	–	✓	✓✓
Sleep NRS	✓✓	–	✓✓	–	✓✓	–	✓✓	N/A	N/A
DLQI	✓	–	✓	–	✓	–	–	✓✓	✓✓
AD flares	✓	✓	?	✓	✓✓	?	?	✓✓	✓✓
Any AE	–	–	?	–	✗	–	✗	✗	✗✗
SAE	–	–	?	?	?	?	?	?	?

High- to moderate-certainty evidence

- ✓✓ Among the most effective
- ✓ Among the intermediate (superior) effective
- ✓ Among the intermediate (inferior) effective
- – Not clearly different from placebo
- ✗ Among the intermediate harmful
- ✗✗ Among the most harmful

Low- to very-low-certainty evidence

- ? Possibly not clearly different from placebo

- **Dupilumab:** In patients aged 6 months or older with moderate-to-severe AD refractory, intolerant, or unable to use mid-potency or greater topical treatment, the JTF panel recommends adding dupilumab over continued standard topical treatment without dupilumab ***(Strong recommendation, high-certainty evidence)***
- **Tralokinumab:** In patients aged ≥12 years with moderate-to-severe AD refractory, intolerant, or unable to use mid-potency topical treatment, the JTF panel recommends adding tralokinumab over continued topical treatment without tralokinumab ***(Strong recommendation, high-certainty evidence)***

> *"Although the panel provides strong recommendations for dupilumab or tralokinumab, available evidence does not address combination therapy, and as such, the panel recommends using either agent, based on contextual factors, rather than both agents together. The panel did not yet issue a formal recommendation for one agent over the other. The evidence for benefits, however, provides stronger support for dupilumab compared with agents targeting solely IL-13, such as tralokinumab or lebrikizumab"*

- **Oral JAK inhibitors (abrocitinib, baricitinib, upadacitinib):** In adults and adolescents with moderate-to-severe AD refractory, intolerant, or unable to use mid- to high-potency topical treatment and systemic treatment inclusive of a recommended biologic (dupilumab or tralokinumab), the panel suggests replacing the systemic treatment with one of the following, over not using one of these JAK inhibitors ***(Conditional recommendation, low-certainty evidence)***
  - **Abrocitinib** 100–200 mg (aged ≥12 years)
  - **Baricitinib** 2–4 mg (aged ≥18 years)
  - **Updacitinib** 15–30 mg (aged ≥12 years)

Abbreviations, References, and Additional Resources

Abbreviations:

AAAAI, American Academy of Allergy, Asthma, and Immunology; ACAAI, American College of Allergy, Asthma, and Immunology; AD, atopic dermatitis; AE, adverse event; DLQI, Dermatology Life Quality Index; EASI, Eczema Area and Severity Index; GRADE, Grading of Recommendations Assessment, Development, and Evaluation; IL, interleukin; JAK, Janus kinase; JTF, Joint Task Force; mo, months; NRS, numeric rating scale; PCP, primary care physician; PDE4, phosphodiesterase-4; POEM, Patient-Oriented Eczema Measure; SAE, serious adverse event; UV, ultraviolet; yo, years old.

Reference:

- Chu DK, et al. *Ann Allergy Asthma Immunol*. 2023 Dec 18:S1081–1206(23):01455–2. [click here for full text article]

Additional resources:

- Supplemental information on the AD guidelines can be downloaded here

DUPILUMAB PRESCRIBING INFORMATION

https://www.regeneron.com/downloads/dupixent_fpi.pdf

Please reach out if you have questions or would like additional information.

Warm regards,

Sanofi Medical Value & Outcomes (MVO) Team

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Appendix 2: Clinical and Economic Value of Dupixent® (Dupilumab)

Atopic Dermatitis

Atopic dermatitis (AD) is a type 2 immune-mediated skin disease with a multifactorial etiology, characterized by chronic systemic inflammation and skin barrier dysfunction (Gandhi 2016). AD onset can occur during infancy or childhood; in most patients with AD, disease onset occurs between ages 3 months to 2 years (Bieber 2017, Weidinger 2016). Particularly in children with severe disease, this chronic disease can persist through adolescence and into adulthood. After diagnosis, 20% of childhood-onset AD cases persist for 8 years and 5% persist for 20 years (Kim 2016). In the United States (US), the prevalence of AD is estimated to be 10.2% in young children aged 6 months to 5 years, 10.0% in children aged 6 to 11 years, 9.3% in adolescents, and 3.2% in adults (Silverberg 2017, Silverberg 2021). Uncontrolled moderate-to-severe disease is estimated to occur in 274,000 young children aged 6 months to 5 years, 320,000 children aged 6 to 11 years, 389,000 adolescents, and 1.6 million adults (Sanofi and Regeneron, Data on file, Infant and young childhood AD epidemiology funnel; Sanofi and Regeneron, Data on file, Childhood AD epidemiology funnel; Sanofi and Regeneron, Data on file, Adolescent AD epidemiology funnel; Sanofi and Regeneron, Data on file, Adult AD epidemiology funnel).

In the US, the 1-year prevalence of hand eczema is estimated to be 10%, with a lifetime prevalence of 15% (Thyssen 2010). In patients with a history of AD, the proportion of patients with current or previous hand dermatitis was 34.4% in adults and 79.9% in children and adolescents (Quaade 2021). For patients with active AD, the prevalence of hand dermatitis can be as high as 60% overall (age 0–2 years, 43.7%; 3–12 years, 54.1%; >12 years, 63.9%) (Simpson 2006). A total of 30% of patients present with foot dermatitis (Agner 2015).

Dupilumab is indicated for the treatment of adult and pediatric patients aged ≥6 months with moderate-to-severe AD, whose disease is not adequately controlled with topical prescription therapies or when those therapies are not advisable. Dupilumab can be used with or without topical corticosteroids (TCS) (Dupixent US Prescribing Information [USPI] 2024).

In several randomized, double-blinded clinical trials (6 in adults and 4 in pediatric patients), dupilumab provided significant, rapid, sustained, and clinically meaningful improvements in AD signs, symptoms, and health-related quality of life (HRQOL) in patients aged ≥6 months with moderate-to-severe AD.

Note: Study results for approved dose regimens are summarized below.

- **Adults aged ≥18 years**
  - Pooled analysis of Week 16 data from two phase 3 randomized trials (SOLO 1 and SOLO 2) (Thaçi 2019):
    - The proportion of patients achieving an Investigator's Global Assessment (IGA) score of 0 or 1 (clear or almost clear skin) and a ≥2-point reduction from baseline in IGA was statistically significantly greater in the dupilumab 300 mg once every 2 weeks (q2w) arm than in the placebo arm (37.0% vs 9.3%, respectively; *P*<0.0001)
    - The proportion of patients achieving ≥75% improvement from baseline in lesion extent and severity, measured by the Eczema Area and Severity Index (EASI-75), was statistically significantly greater in the dupilumab 300 mg q2w arm than in the placebo arm (47.7% vs 13.3%, respectively; *P*<0.0001)
    - The proportion of patients with improvement in itch based on achieving a ≥4- or ≥3-point reduction from baseline in the weekly average of the daily Peak Pruritus Numerical Rating Scale (PP-NRS) scores were statistically significantly greater in the dupilumab 300 mg q2w arm than in the placebo arm (≥4-point reduction: 38.4% vs 10.9%, respectively; ≥3-point reduction: 48.8% vs 15.0%, respectively; *P*<0.0001 for both comparisons)

- CHRONOS (Blauvelt 2017):
  - At Week 16, the proportion of patients achieving an IGA score of 0 or 1 and a ≥2-point reduction from baseline in IGA score was statistically significantly greater in the dupilumab 300 mg q2w + TCS arm than in the placebo + TCS arm (39% vs 12%, respectively; *P*<0.0001)
  - At Week 16, the proportion of patients achieving EASI-75 was statistically significantly greater in the dupilumab 300 mg q2w + TCS arm than in the placebo + TCS arm (69% vs 23%, respectively; *P*<0.0001)
  - At Week 16, the proportion of patients with ≥4- or ≥3-point reduction from baseline in the weekly average of the daily PP-NRS scores was statistically significantly greater in the dupilumab 300 mg q2w + TCS arm than in the placebo + TCS arm (≥4-point reduction: 59% vs 20%, respectively; ≥3-point reduction: 66% vs 28%, respectively; *P*<0.0001 for both comparisons)
  - At Week 52, the proportion of patients achieving an IGA score of 0 or 1 and a reduction from baseline of ≥2 points was statistically significantly greater in the dupilumab 300 mg q2w + TCS arm than in the placebo + TCS arm (36% vs 13%, respectively; *P*<0.0001)
  - At Week 52, the proportion of patients achieving EASI-75 was statistically significantly greater in the dupilumab 300 mg q2w + TCS arm than in the placebo + TCS arm (65% vs 22%, respectively; *P*<0.0001)
  - At Week 52, the proportion of patients with ≥4- or ≥3-point reduction from baseline in the weekly average of the daily PP-NRS scores was statistically significantly greater in the dupilumab 300 mg q2w + TCS arm than in the placebo + TCS arm (≥4-point reduction: 51% vs 13%, respectively; ≥3-point reduction: 56% vs 16%, respectively; *P*<0.0001 for both comparisons)

- **Adolescents aged 12 to 17 years**
  - The proportion of patients achieving an IGA score of 0 or 1 at Week 16 was statistically significantly greater in the dupilumab 200 mg/300 mg (weight-based dosing) q2w arm than in the placebo arm (24% vs 2%, respectively; *P*<0.001) (Simpson 2020)
  - The proportion of patients achieving EASI-75 at Week 16 was statistically significantly greater in the dupilumab 200 mg/300 mg q2w arm than in the placebo arm (41% vs 8%, respectively; *P*<0.001) (Simpson 2020)
  - The proportion of patients achieving a ≥4-point reduction in PP-NRS scores at Week 16 was statistically significantly greater in the dupilumab 200 mg/300 mg q2w arm than in the placebo arm (37% vs 5%, respectively; *P*<0.001) (Simpson 2020)
  - Efficacy was sustained in the adolescent population through Week 52 (Blauvelt 2022)
- **Children aged 6 to 11 years**
  - In the general study population, the proportion of patients achieving IGA 0 or 1 at Week 16 was statistically significantly greater in the dupilumab once every 4 weeks (q4w) + TCS and dupilumab q2w + TCS arms than in the placebo + TCS arm (*P*<0.001 for both comparisons) (Paller 2020)
    - Among patients weighing <30 kg, the proportion achieving IGA 0 or 1 at Week 16 was significantly greater in those treated with dupilumab 300 mg q4w + TCS than in those treated with placebo + TCS (29.5% vs 13.1%, respectively; nominal *P*<0.05)
    - Among patients weighing ≥30 kg, the proportion achieving IGA 0 or 1 at Week 16 was significantly greater in those treated with dupilumab 200 mg q2w + TCS than in those treated with placebo + TCS (39.0% vs 9.7%, respectively; nominal *P*<0.001)

- In the general study population, the proportion of patients achieving EASI-75 at Week 16 was statistically significantly greater in the dupilumab q4w + TCS and dupilumab q2w + TCS arms than in the placebo + TCS arm (*P*<0.0001 for both comparisons) (Paller 2020)
    - Among patients weighing <30 kg, the proportion achieving EASI-75 at Week 16 was significantly greater in those treated with dupilumab 300 mg q4w + TCS than in those treated with placebo + TCS (75.4% vs 27.9%, respectively; nominal *P*<0.0001)
    - Among patients weighing ≥30 kg, the proportion achieving EASI-75 at Week 16 was significantly greater in those treated with dupilumab 200 mg q2w + TCS than in those treated with placebo + TCS (74.6% vs 25.8%, respectively; nominal *P*<0.0001)
- In the general study population, the proportion of patients achieving a ≥4-point reduction in the weekly average of daily PP-NRS scores at Week 16 was statistically significantly greater in the dupilumab q4w + TCS and dupilumab q2w + TCS arms than in the placebo + TCS arm (*P*<0.0001 for both comparisons) (Paller 2020)
    - Among patients weighing <30 kg, the proportion achieving a ≥4-point reduction in the weekly average of daily PP-NRS scores at Week 16 was significantly greater in those treated with dupilumab 300 mg q4w + TCS than in those treated with placebo + TCS (54.1% vs 11.7%, respectively; nominal *P*<0.0001)
    - Among patients weighing ≥30 kg, the proportion achieving a ≥4-point reduction in the weekly average of daily PP-NRS scores at Week 16 was significantly greater in those treated with dupilumab 200 mg q2w + TCS than in those treated with placebo + TCS (61.4% vs 12.9%, respectively; nominal *P*<0.0001)

- **Infants and young children aged 6 months to 5 years**
    - The proportion of patients achieving an IGA score of 0 or 1 at Week 16 was statistically significantly greater in the dupilumab 200 mg/300 mg (weight-based dosing) q4w + TCS arm than in the placebo + TCS arm (28% vs 4%, respectively; *P*<0.0001) (Paller 2022a)
    - The proportion of patients achieving EASI-75 at Week 16 was statistically significantly greater in the dupilumab 200 mg/300 mg + TCS arm than in the placebo + TCS arm (53% vs 11%, respectively; *P*<0.0001) (Paller 2022a)
    - The proportion of patients with a ≥4-point reduction in the weekly average of daily Worst Scratch/Itch scores at Week 16 was statistically significantly greater in the dupilumab 200 mg/300 mg + TCS arm than in the placebo + TCS arm (48% vs 9%, respectively; *P*<0.0001) (Paller 2022a)
- **AD with hand and/or foot involvement in adult and adolescent patients aged ≥12 years**
    - The proportion of patients achieving an IGA score (hand and foot) of 0 or 1 at Week 16 was statistically significantly greater in the dupilumab 200 mg/300 mg q2w arm than in the placebo arm (40.3% vs 16.7%, respectively; *P*=0.003), with separation between groups evident from Week 4 through Week 16 (Simpson 2023)
    - The proportion of patients achieving ≥75% reduction in hand eczema severity index-75 at Week 16 was statistically significantly greater in the dupilumab 200 mg/300 mg q2w arm than in the placebo arm (46.9% vs 21.5%, respectively; *P*<0.01) (Simpson 2023)
    - The proportion of patients achieving a ≥4-point reduction in the weekly average of daily PP-NRS scores (hand and foot) at Week 16 was statistically significantly greater in the dupilumab 200 mg/300 mg arm than in the placebo arm (52.2% vs 13.6%, respectively; *P*<0.0001) (Simpson 2023)

Dupilumab had a positive benefit-risk ratio and was generally well tolerated in patients with moderate-to-severe AD, supported by data from clinical trials of infants and young children (aged 6 months–5 years), children (aged 6–11 years), and adolescents (aged 12–17 years) treated for up to 52 weeks and adults treated for up to 3 years.

- According to data released in May 2023, more than 600,000 patients are being treated with dupilumab globally (Sanofi Press Release 2023).
  - The most common adverse events (AEs) with dupilumab (incidence ≥1%) in AD clinical trials were injection site reactions, conjunctivitis, blepharitis, oral herpes, keratitis, eye pruritus, other herpes simplex virus infections, dry eye, and eosinophilia (Dupixent USPI 2024)
  - AEs reported with dupilumab were generally mild or moderate and occurred with an overall similar incidence compared with that of placebo (Blauvelt 2017, Simpson 2023, Thaçi 2019, Worm 2020); the long-term safety/tolerability profile observed in adult patients treated for up to 4 years and adolescent patients treated for up to 1 year were consistent with that seen in studies of shorter treatment duration (Beck 2022, Blauvelt 2022)
  - In adult patients, lower risk of serious and severe infections, as well as nonherpetic skin infections, were observed with dupilumab vs placebo; no increase in the incidence of overall infections was observed with dupilumab vs placebo (Eichenfield 2019). In pediatric patients, lower risk of total skin infections (patients aged 6–17 years) and nonherpetic skin infections (patients aged 6 months–17 years) was observed with dupilumab vs placebo; no increase in the incidence of overall infections or serious and severe infections was observed with dupilumab vs placebo (Paller 2022b, Siegfried 2022)
  - Conjunctivitis, including conjunctivitis, allergic conjunctivitis, bacterial conjunctivitis, and viral conjunctivitis, in patients with moderate-to-severe AD was generally mild to moderate and mostly resolved while patients continued dupilumab treatment; treatment discontinuation was rarely required for adults and not required for adolescents (Akinlade 2019, Bansal 2021, Simpson 2023)

Asthma

Asthma is a heterogeneous, chronic inflammatory disease characterized by chronic airway inflammation, a history of variable symptoms (wheezing, shortness of breath, chest tightness, and/or coughing), and variable expiratory airflow limitation with poor lung function (Global Initiative for Asthma [GINA] 2022).

In the US, asthma prevalence by age group is as follows:

- **Children:** The overall prevalence of asthma in the US is estimated to be 8.1% in children aged 5 to 11 years, according to 2018 National Health Interview Survey data (Centers for Disease Control and Prevention [CDC] 2020). According to an internal analysis, the prevalence of moderate-to-severe persistent asthma among children aged 6 to 11 years with asthma is estimated to be 8%. Among these patients, the prevalence of uncontrolled disease despite asthma treatments is estimated to be 37%. By extrapolating these prevalence rates to the US childhood asthma population aged 6 to 11 years (2.4 million), the number of children estimated to have uncontrolled moderate-to-severe asthma (including the eosinophilic phenotype) despite current therapies is approximately 75,000 (Data on file 2015a)
- **Adolescents and adults:** The overall prevalence of asthma is estimated to be 9.9% in adolescents aged 12 to 17 years and 7.7% in adults (CDC 2020). According to an internal analysis, 6.4%–7.0% of adolescents and adults aged ≥12 years with asthma are estimated to have moderate-to-severe persistent asthma. Among these patients, 51.2% to 54.9% are estimated to have uncontrolled disease despite asthma treatments. By extrapolating these prevalence rates to the US adolescent and adult asthma population aged ≥12 years (23.5–24.5 million patients), the number of adolescent and adult patients estimated to have moderate-to-severe asthma is 1.5 million to 1.6 million; of these patients, approximately 775,000 to 899,000 have uncontrolled disease despite current therapies. These patients are candidates for treatment with biologic therapy for asthma as recommended by GINA 2022 guidelines; 621,000 to 746,000 are eligible for dupilumab, according to the approved indication (Data on file 2015b)

Long-term asthma treatment goals are to achieve symptom control, minimize the risk of exacerbations, and normalize lung function while minimizing the risk of side effects associated with treatments (eg, long-term, high-dose inhaled corticosteroids and chronic use of oral corticosteroids [OCS]) (GINA 2022, National Heart, Lung, and Blood Institute [NHLBI] 2007). Patients with uncontrolled moderate-to-severe asthma continue to have an unmet need for treatment options to achieve comprehensive asthma control.

Dupilumab is indicated as an add-on maintenance treatment for adult and pediatric patients aged ≥6 years with moderate-to-severe asthma characterized by an eosinophilic phenotype or with OCS-dependent asthma (Dupixent USPI 2024).

The efficacy and safety of dupilumab have been studied in 3 randomized, double-blind, placebo-controlled trials (phase 2b dose-ranging clinical trial: Study DRI12544; phase 3 trials: LIBERTY ASTHMA QUEST and LIBERTY ASTHMA VENTURE) that enrolled a total of 2888 adult and adolescent patients aged ≥12 years with uncontrolled moderate-to-severe asthma (Study DRI12544 enrolled adult patients aged ≥18 years, and the other 2 studies enrolled adult and adolescent patients aged ≥12 years). The efficacy and safety of dupilumab have also been studied in a phase 3 randomized, double-blind, placebo-controlled, parallel-group trial (LIBERTY ASTHMA VOYAGE) in 408 children aged 6 to 11 years with uncontrolled moderate-to-severe asthma (Dupixent USPI 2024).

Dupilumab significantly improved lung function and significantly reduced the rate of severe asthma exacerbations vs placebo in adults, adolescents, and children aged 6 to 11 years; in adult and adolescent patients, dupilumab also reduced the rate of severe exacerbations that result in hospitalizations or emergency department (ED) visits. In addition, in an indirect treatment comparison of asthma biologics, dupilumab had a greater reduction in annualized severe asthma exacerbation rates (AERs) and improvement in lung function than other biologics approved for the treatment of moderate-to-severe asthma in adult and adolescent patients.

- **Adult and adolescent asthma**
  - For the subgroup with baseline blood eosinophil counts ≥300 cells/μL in the phase 2b dose-ranging clinical trial (Study DRI12544, N=776) in patients with uncontrolled moderate-to-severe asthma, the greatest increases in pre-bronchodilator (BD) forced expiratory volume in 1 second (FEV_1) from baseline to Week 12 were observed in the dupilumab 300 mg q2w group (least-squares mean [LSM] change, 0.39 L; LSM difference vs placebo, 0.21; 95% CI, 0.06–0.36; *P*=0.0063) and in the dupilumab 200 mg q2w group (LSM change, 0.43 L; LSM difference vs placebo, 0.26; 95% CI, 0.11–0.40; *P*=0.0008) compared with placebo (LSM change, 0.18 L) (Wenzel 2016)
  - In the LIBERTY ASTHMA QUEST phase 3 clinical trial of patients with uncontrolled moderate-to-severe asthma (N=1902), dupilumab statistically significantly decreased the AERs during the 52 weeks of treatment, with relative risk reductions (RRRs) for dupilumab vs matched placebo of 47.7% with 200 mg q2w and 46.0% with 300 mg q2w (*P*<0.001 for each comparison) in the overall intention-to-treat (ITT) population. The AERs for severe asthma exacerbations resulting in a hospitalization or ED visit during the 52 weeks of treatment was reduced in the combined dupilumab arm compared with the combined matched placebo arm, with an RRR of 46.8% (95% CI, 18.4–65.3) in the overall ITT population (Castro 2018)
  - In the LIBERTY ASTHMA VENTURE phase 3 clinical trial of patients with OCS-dependent asthma (N=210), the percentage change in the OCS dose was statistically significantly greater in the dupilumab 300 mg q2w arm than in the placebo arm (−70.1% vs −41.9%, respectively; *P*<0.001). Despite reductions in the OCS dose, dupilumab 300 mg q2w resulted in an AER that was 59% (95% CI, 37–74) lower than with placebo and a pre-BD FEV_1 that was 0.22 L (95% CI, 0.09–0.34) higher after 24 weeks of treatment. Reductions in the risk for severe asthma exacerbations with dupilumab 300 mg q2w vs placebo were observed regardless of baseline eosinophil count (Rabe 2018)
  - In an indirect treatment comparison, 14 randomized controlled trials were included in the analyses. The matched dupilumab subgroups were associated with greater reductions in AERs

compared with benralizumab, mepolizumab, reslizumab, and omalizumab (54%, 28%, 38%, and 26% greater reduction, respectively). A greater improvement in FEV_1 was also observed for dupilumab at Week 12 and/or Week 24/52 than for the other biologics (0.06–0.14 L) (Bateman 2020)

- **Childhood asthma**
  - In the LIBERTY ASTHMA VOYAGE phase 3 clinical trial of patients with uncontrolled moderate-to-severe asthma (N=408), dupilumab 100 mg or 200 mg q2w (based on body weight ≤30 kg or >30 kg, respectively) statistically significantly decreased AERs during the 52 weeks of treatment, with RRRs for dupilumab vs matched placebo of 59.3% in the population with type 2 inflammatory asthma phenotype (defined as baseline blood eosinophil count ≥150 cells/µL or baseline fractional exhaled nitric oxide ≥20 parts per billion) and 64.7% in the population with baseline blood eosinophil count ≥300 cells/µL (P<0.0001 for each comparison). Dupilumab 100 mg or 200 mg q2w statistically significantly increased pre-BD FEV_1 percent predicted from baseline to Week 12, with LSM differences for dupilumab vs matched placebo of 5.21% (95% CI, 2.14–8.27) in the population with type 2 inflammatory asthma phenotype and 5.32% (95% CI, 1.76–8.88) in the population with baseline blood eosinophil count ≥300 cells/µL (P<0.01 for each comparison) (Bacharier 2021)

Dupilumab had a positive benefit-risk ratio and was generally well tolerated in patients aged ≥6 years with moderate-to-severe asthma.

- **Dupilumab asthma clinical trial program**
  - The most common AEs with dupilumab (incidence ≥1%) in asthma clinical trials were injection site reactions, oropharyngeal pain, and eosinophilia. Injection site reactions were most common with the loading (initial) dose. The safety profile of dupilumab through Week 52 was generally consistent with the safety profile observed at Week 24 (Dupixent USPI 2024)
  - There were no indications that dupilumab increased the overall occurrence of any malignancy (Data on file 2017)
- **Adult and adolescent asthma**
  - In LIBERTY ASTHMA QUEST, the most frequent AE occurring in ≥5% of patients was injection site reaction in both dupilumab doses (200 mg q2w, 15.2%; 300 mg q2w, 18.4%) vs matched placebo (5.4% and 10.3%, respectively). Treatment-emergent eosinophilia occurred in 4.1% of patients treated with dupilumab vs 0.6% of patients treated with placebo. The rate of persistent antidrug antibody (ADA) responses was 4.2% with dupilumab 200 mg q2w and 2.1% with dupilumab 300 mg q2w compared with 1.1% in the combined placebo groups. Persistent ADA responses had no meaningful effect on efficacy or safety. During the 52-week treatment period, there were no meaningful between-group differences in AEs of conjunctivitis (2.3% of patients receiving dupilumab and 3.3% of those receiving placebo) (Castro 2018)
  - In LIBERTY ASTHMA TRAVERSE, the long-term open-label extension (OLE) study of patients with moderate-to-severe asthma who participated in a previous dupilumab asthma clinical trial (N=2282), the overall safety profile was consistent with the safety profile observed in placebo-controlled trials, and no new safety concerns were identified (Wechsler 2022), thus supporting the long-term safety of dupilumab
- **Childhood asthma**
  - In LIBERTY ASTHMA VOYAGE, the safety profile of dupilumab in children aged 6 to 11 years through Week 52 was similar to the safety profile of dupilumab from studies in adults and adolescents aged ≥12 years with moderate-to-severe asthma with the addition of helminth infections. Helminth infections were reported in 6 patients (2.2%) in the dupilumab group and 1 patient (0.7%) in the placebo group. The majority of cases were enterobiasis, reported in 5 patients (1.8%) in the dupilumab arm and 0 patients in the placebo arm. There was 1 case of ascariasis in the dupilumab arm. All helminth infection cases were mild-to-moderate and patients

recovered with anthelmintic treatment without dupilumab treatment discontinuation (Data on file 2020a, Dupixent USPI 2024)

- In LIBERTY ASTHMA EXCURSION, the ongoing long-term OLE study of patients with moderate-to-severe asthma who participated in LIBERTY ASTHMA VOYAGE (N=365), the overall safety profile of dupilumab was consistent with the safety profile observed in the LIBERTY ASTHMA VOYAGE placebo-controlled trial, and no new safety concerns were identified (Data on file 2020b), thus supporting the long-term safety of dupilumab

Chronic Rhinosinusitis With Nasal Polyps

Chronic rhinosinusitis with nasal polyps (CRSwNP) is defined as chronic rhinosinusitis with ≥2 of the following symptoms persisting for ≥12 weeks: facial pressure or pain, decreased or absent sense of smell, nasal obstruction and congestion, and mucopurulent discharge (rhinorrhea or postnasal drip); and ≥1 of the following findings: evidence of inflammation on paranasal sinus examination or computed tomography, evidence of purulence coming from paranasal sinuses or ostiomeatal complex, and presence of bilateral polyps (Orlandi 2016, Peters 2014, Rosenfeld 2015).

Among patients diagnosed with CRSwNP in the US, approximately 55,000 to 90,000 patients have uncontrolled CRSwNP despite prior sinus surgery or oral steroid use (CDC 2017; Data on file 2018a, Stevens 2015). The symptoms of CRSwNP are often moderate-to-severe and lead to a substantial HRQOL burden, with adverse effects on sleep quality, mood, and activities of daily living (Abdalla 2012, DeConde 2015a, Palmer 2019). In addition, patients with CRSwNP have a particularly high prevalence of type 2 atopic comorbidities (ie, 26% to 48% with asthma and 10% to 16% with aspirin-exacerbated respiratory disease); and patients with these comorbidities have more severe disease than those without these comorbidities, resulting in higher rates of polyp recurrence and an increased need for revision sinus surgeries (Bachert 2018, Batra 2013, Cahill 2017, Khan 2020, Promsopa 2016, Stevens 2016, Stevens 2017, White 2018).

For patients with CRSwNP, standard of care medical therapies, such as intranasal corticosteroids (INCS), may have limited effects and systemic corticosteroids are suitable only for short-term use (Li 2015, Orlandi 2016). Surgical interventions can have limited benefit, as they do not correct the underlying pathology of CRSwNP (DeConde 2017, van der Veen 2017). Symptoms in patients with CRSwNP who receive endoscopic sinus surgery (ESS) often persist, with frequent polyp and edema recurrence (DeConde 2015b, DeConde 2017, Wynn 2004).

As such, patients with inadequately controlled CRSwNP despite conventional pharmaceutical or surgical therapies, including those with comorbid asthma, lack a treatment option that provides robust and durable symptom relief combined with an acceptable safety profile.

Dupilumab is the first biologic approved as an add-on maintenance treatment in adult patients with inadequately controlled CRSwNP. Dupilumab has been studied in the largest clinical development program in CRSwNP, with nearly 500 patients with CRSwNP treated with dupilumab across clinical trials to date (Bachert 2016, Bachert 2019, Dupixent USPI 2024).

In patients with CRSwNP whose disease has not been adequately managed by current standard of care treatments, dupilumab demonstrated rapid and consistent benefits on all disease outcome measures, including improvement in objective measures of CRSwNP, key disease symptoms, and HRQOL, as well as reduction in the use of sinonasal surgery and systemic corticosteroids.

- In two phase 3 trials (SINUS-24 [N=276] and SINUS-52 [N=448]), dupilumab met both primary end points, statistically significantly reducing nasal polyp size (endoscopic nasal polyp score [NPS]) and nasal congestion (NC)/obstruction score from baseline vs placebo at Week 24 in SINUS-24 and SINUS-52 (P<0.0001 for each comparison), with improvements observed as early as the first postbaseline assessment at Week 4. In addition, patients treated with dupilumab in SINUS-52 continued to improve in NPS and NC score through Week 52 (Bachert 2019)

- Dupilumab also produced statistically significant improvements from baseline in sinus opacification, loss of smell, and total symptom score vs placebo at Week 24 in SINUS-24 and SINUS-52 (P<0.0001 for each comparison) (Bachert 2019)
- Patients treated with dupilumab had clinically meaningful improvement in disease-specific HRQOL (22-item Sinonasal Outcome Test [SNOT-22]), with key dimensions of improvement on SNOT-22 subscores, including loss of smell/taste, sleep impairment, lack of energy, and productivity loss (Data on file 2018b; Data on file 2018c)
- In a prespecified multiplicity-adjusted pooled analysis of SINUS-24 and SINUS-52, treatment with dupilumab resulted in significant reductions in systemic corticosteroid use and the need for sinonasal surgery vs treatment with placebo (hazard ratio [HR], 0.24; 95% CI, 0.17–0.35). The proportion of patients who required systemic corticosteroids was reduced by 74% (HR, 0.26; 95% CI, 0.18–0.38). The total number of systemic corticosteroid courses per year was reduced by 75% (RR, 0.25; 95% CI, 0.17–0.37). The proportion of patients who required surgery was reduced by 83% (HR, 0.17; 95% CI, 0.07–0.46) (Bachert 2019)
- In patients with CRSwNP and comorbid asthma, dupilumab produced rapid and continuous improvement in lung function (FEV_1) and asthma control (Asthma Control Questionnaire 6-items) vs placebo, observed by the first postbaseline assessment and sustained through 52 weeks of treatment (Data on file 2018b; Data on file 2018c)
- In an indirect treatment comparison, dupilumab had statistically significantly greater improvements in nasal polyp burden and symptoms according to NPS, NC, loss of smell, total symptom, and University of Pennsylvania Smell Identification Test scores than omalizumab q2w/q4w at Week 24 (statistical significance based on 95% CI of mean difference not containing 0). Dupilumab also had a greater improvement in SNOT-22 scores than omalizumab, but this difference was not statistically significant (Peters 2021)

Dupilumab had a positive benefit-risk ratio and was generally well tolerated in combination with INCS in patients with CRSwNP.

- In two phase 3 trials, patients receiving dupilumab had a lower overall incidence of treatment-emergent AEs (TEAEs), serious AEs (SAEs), and discontinuation rates vs patients receiving placebo; the most frequent TEAEs in both trials were nasopharyngitis and nasal polyps, both of which occurred less frequently in patients treated with dupilumab than with placebo (Data on file 2018b; Data on file 2018c)
- The most frequent TEAE considered to be related to study treatment was injection site erythema, which also occurred less frequently in the dupilumab group vs the placebo group (Data on file 2018b; Data on file 2018c)

Eosinophilic Esophagitis

Eosinophilic esophagitis (EoE) is a chronic, progressive, type 2 inflammatory disease characterized by esophageal dysfunction and eosinophilic inflammation in the esophagus (Furuta 2015). The pathogenesis is related to a type 2 immune response involving immune dysregulation and epithelial barrier dysfunction (Gómez-Aldana 2019, Hill 2016, O'Shea 2018). Patients with coexisting type 2 inflammatory diseases are at a greater risk of EoE (Hill 2018). The predominant symptom of EoE in adults and adolescents is dysphagia, which is characterized by a sensation of difficulty when swallowing liquids, foods, or saliva (Furuta 2015, NIH 2017). The most common symptoms of EoE in children are feeding difficulties, vomiting, abdominal pain, dysphagia, food impaction, reflux-like symptoms, and failure to thrive (Lucendo 2017, Martin 2015). In the US, the estimated prevalence of diagnosed EoE for adult and adolescent patients (aged ≥12 years) is 0.114%, or 322,000 patients. Of these patients, 42,000 have uncontrolled disease on proton-pump inhibitors (PPIs) and swallowed topical corticosteroids (STCs). In children (aged 1–11 years), the estimated US prevalence of diagnosed EoE is 0.077%, or 34,000. Of these children, 7000 have uncontrolled disease on PPIs and STCs (Data on file 2021). The incidence of disease is more common in males with a 2- to 3-fold increase in risk for the male sex for both children and adults (Lucendo 2017).

Patients with EoE have persistent debilitating symptoms of dysphagia, chest and abdominal pain, heartburn, and vomiting. The underlying inflammatory and fibrostenotic process can lead to food impaction that may require medical intervention. In all age groups, the disease is associated with social challenges and a considerably reduced HRQOL, in addition to incurring higher health care utilization costs and economic burden.

The current standard of care for the treatment of EoE includes dietary therapy, use of medications (STCs and PPIs), and esophageal dilation. PPI therapy is one of the first-line therapeutic options (Hirano 2018). STCs are used to coat the esophagus and provide anti-inflammatory effects (Dellon 2018). Even though symptom control can be achieved with these therapies in some patients, they do not have a targeted impact on the underlying pathophysiology of EoE that leads to esophageal remodeling. Lastly, esophageal dilation is reserved for patients who require dilation of the esophagus to treat dysphagia and food impaction, but similar to the other therapies, it does not treat the underlying inflammation associated with EoE (Hirano 2020).

Management of EoE is challenging because of the limited treatment options and the high frequency of initial treatment failure and recurrence of symptoms (Dellon 2020). There is an unmet need for a treatment modality that improves treatment response while targeting the underlying pathophysiology of EoE. Dupilumab is indicated for the treatment of adult and pediatric patients aged ≥1 year, weighing ≥15 kg, with EoE (Dupixent USPI 2024).

In two 3-part, phase 3 studies in adult and adolescent (aged ≥12 years) and pediatric (aged 1–11 years) patients with EoE, dupilumab resulted in significant improvements in histologic and endoscopic outcomes compared with placebo.

Note: Results reported below do not include Part C data in the pediatric population as it is not yet reported.

Adult and Adolescent EoE

In Part A of a study in adult and adolescent patients with EoE, dupilumab met the coprimary end points of the proportion of patients achieving peak esophageal intraepithelial eosinophil count ≤6 eosinophils/high-power field (eos/hpf) at Week 24 and absolute change from baseline in the dysphagia symptom questionnaire (DSQ) total score.

- The proportion of patients who achieved peak esophageal intraepithelial eosinophil count ≤6 eos/hpf at Week 24 was significantly greater in the dupilumab 300 mg once weekly (qw) arm (25/42 [60%] patients) than the placebo arm (2/39 [5%] patients) (adjusted between-group difference of 55 percentage points; 95% CI, 40–71; *P*<0.001) (Dellon 2022)
- The change from baseline DSQ total score was better in the dupilumab 300 mg qw arm than in the placebo arm at Week 24 (LSM change −21.92 vs −9.60 points; 95% CI, −19.11 to −5.54; *P*<0.001) (Dellon 2022)

In Part B of a study in adults and adolescents with EoE, the proportion of patients treated with dupilumab 300 mg qw achieving peak esophageal intraepithelial eosinophil count of ≤6 eos/hpf at Week 24 and absolute change from baseline in DSQ total score significantly improved. The dupilumab 300 mg q2w dosing regimen showed numerical, but not significant, improvement in the histologic coprimary end point and symptom end point of absolute change from baseline in DSQ total score. The dupilumab 300 mg q2w dosing also did not significantly improve other EoE disease symptoms or HRQOL measures. All other secondary histologic, endoscopic, and molecular end points of EoE showed a similar degree of improvement to those observed with the dupilumab 300 mg qw dosing regimen.

- The proportion of patients who achieved peak esophageal intraepithelial eosinophil count ≤6 eos/hpf at Week 24 was greater in the dupilumab 300 mg qw arm (47/80 [59%]) and 300 mg q2w arm (49/81 [60%]) than in the placebo arm (5/79 [6%]; difference between weekly dupilumab and placebo: 54 percentage points; 95% CI, 41–66; *P*<0.001; difference between dupilumab q2w and placebo: 56 percentage points; 95% CI, 43–69; not significant per hierarchical plan to adjust for multiple testing) (Dellon 2022)

- Treatment with dupilumab 300 mg qw resulted in a greater reduction from baseline in DSQ total score compared with treatment with placebo at Week 24 (LSM change −23.78 points vs −13.86 points; 95% CI, −14.81 to −5.02; *P*<0.001). The reduction from baseline in the DSQ score at Week 24 did not differ significantly between patients who received dupilumab 300 mg q2w compared with those who received placebo (LSM change −14.37 points vs −13.86 points; 95% CI, −5.42 to 4.41; *P*=0.84) (Dellon 2022)

In Part C of the study that enrolled participants from Part A (Part A–C) and participants from Part B (Part B–C), improvements in efficacy outcomes were observed for an additional 28 weeks of dupilumab treatment.

- In Part A–C, the proportion of patients who achieved peak esophageal intraepithelial eosinophil count ≤6 eos/hpf at Week 52 was as follows: dupilumab 300 mg qw/dupilumab 300 mg qw (19/34 [56%]) and placebo/dupilumab 300 mg qw (18/30 [60%]) (Dellon 2022)
- In Part A–C, improvements in DSQ score were maintained to Week 52 in the dupilumab 300 mg qw/dupilumab 300 mg qw arm (mean change from baseline −23.44 points; 95% CI, −29.58 to −17.30) and were achieved in patients who switched to dupilumab in the placebo/dupilumab 300 mg qw arm (mean change from baseline −21.71 points; 95% CI, −29.13 to −14.30) (Dellon 2022)
- In Part B–C, peak esophageal intraepithelial eosinophil count ≤6 eos/hpf at Week 52 was achieved by 55 (85%) patients in the dupilumab 300 mg qw/dupilumab 300 mg qw arm, 54 (74%) patients in the dupilumab 300 mg q2w/dupilumab 300 mg q2w arm, 25 (68%) patients in the placebo/dupilumab 300 mg qw arm, and 23 (72%) patients in the placebo/dupilumab 300 mg q2w arm (Rothenberg 2023)
- In Part B–C, improvements in DSQ score were maintained to Week 52 in patients in the dupilumab 300 mg qw/dupilumab 300 mg qw arm and the dupilumab 300 mg q2w/dupilumab 300 mg q2w arm, with the absolute change from Part B baseline in DSQ total score (mean [95% CI]) of −30.3 points [−34.5 to −26.1] and −20.9 points [−25.4 to −16.3], respectively. In patients who switched to dupilumab in the placebo/dupilumab 300 mg qw arm and placebo/dupilumab 300 mg q2w arm, improvements in DSQ total score (mean [95% CI]) were experienced from Part B baseline to Week 52: −27.3 points [−32.1 to −22.4] and −23.7 [−29.1, −18.3], respectively (Rothenberg 2023)

Pediatric EoE

In Part A of EoE KIDS, a study in pediatric patients with EoE who remain symptomatic despite treatment with PPIs, patients in both the higher-exposure and lower-exposure dupilumab arms met the primary end point of patients achieving peak esophageal intraepithelial eosinophil count of ≤6 eos/hpf at Week 16. Patients also achieved improvements in key secondary outcomes related to histologic and endoscopic improvement.

- The proportion of patients achieving peak esophageal eosinophil counts ≤6 eos/hpf at Week 16 was higher in the dupilumab arm than in the placebo arm (higher-exposure dupilumab 68% vs lower-exposure dupilumab 58% vs placebo 3%; *P*<0.0001) (Chehade 2023a)
- Patients in the higher-exposure dupilumab arm had reduced peak esophageal intraepithelial eosinophil counts at Week 16 compared with baseline, relative to those in the placebo arm (LSM percent change: −86% vs 21%, respectively; *P*<0.0001) (Chehade 2023a)
- Patients in the higher-exposure dupilumab arm also achieved a reduction in histologic scores at Week 16 compared with placebo (absolute change from baseline in Eosinophilic Esophagitis Histology Scoring System (EoE-HSS) grade score: −0.88 vs 0.02, respectively; *P*<0.0001; absolute change from baseline EoE-HSS stage score: −0.84 vs 0.05, respectively; *P*<0.0001) (Chehade 2023a)
- Patients in the higher-exposure dupilumab arm achieved improved endoscopic features of EoE at Week 16 compared with placebo (LSM absolute change from baseline in Eosinophilic Esophagitis Endoscopic Reference Score (EoE-EREFS) total score: −3.5 vs 0.3, respectively; *P*<0.0001) (Chehade 2023a)
- Results were generally comparable in the lower-exposure dupilumab arm (Chehade 2023a)

In Part B of the study, patients who switched to or continued in the higher-exposure dupilumab arm experienced or maintained improvements in histologic disease remission to Week 52.

- The proportion of patients who achieved peak esophageal counts ≤6 eos/hpf at Week 52 was 62.9% in patients who continued in the higher-exposure dupilumab arm and 52.9% in patients who were switched from placebo to the higher-exposure dupilumab arm (Chehade 2023b)
- Patients who switched from placebo to the higher-exposure dupilumab arm and those who continued in the higher-exposure dupilumab arm improved and maintained, respectively, histologic scores at Week 52 (absolute change from baseline in EoE-HSS grade scores: −0.89, −0.97, respectively; absolute change from baseline EoE-HSS stage scores: −0.86, −0.89, respectively) (Chehade 2023b)
- Patients who switched from placebo to the higher-exposure dupilumab arm and those who continued in the higher-exposure dupilumab arm improved and maintained, respectively, endoscopic features of EoE at Week 52 (LSM absolute change from baseline in EoE-EREFS total score: −3.6, −4.8, respectively) (Chehade 2023b)
- Patients who switched from placebo to the lower-exposure dupilumab arm and those who continued in the lower-exposure dupilumab arm also experienced or maintained histologic and endoscopic outcome improvements to Week 52 but to a numerically lower extent than those in the higher-exposure dupilumab arm (Chehade 2023b)
- Part C of the study is still ongoing, and full results are not yet available

Dupilumab was well tolerated in adult, adolescent, and pediatric patients with EoE, as supported by two, 3-part phase 3 trials.

Adult and Adolescent EoE

- In Part A–C of the study, most AEs were mild or moderate in intensity (placebo/dupilumab 300 mg qw [73%] vs dupilumab 300 mg qw/dupilumab 300 mg qw [60%]). During Part A–C, among patients who received placebo in Part A and dupilumab in Part C, 2 patients had AEs that led to discontinuation of dupilumab, and 1 patient had an SAE during the Part C treatment period. ADA responses were observed during the treatment period in 0% to 3% of the patients across the active treatment groups. No deaths were reported in any treatment arm (Dellon 2022)
- In Part B–C of the study, the most common TEAEs in the dupilumab/dupilumab and placebo/dupilumab treatment arms were injection-site reactions. Treatment-emergent SAEs occurred in 3 (4%) patients in the dupilumab 300 mg qw/dupilumab 300 mg qw arm and in 2 (5%) patients in the placebo/dupilumab 300 mg qw arm during Part B–C and none of them were considered to be related to study drug by the investigator. The TEAE of COVID-19 occurred in 18 (8%) patients, and all were nonserious, unrelated to study drug, and none led to permanent discontinuation of study drug. No deaths were reported in any treatment arm (Rothenberg 2023)

Pediatric EoE

- In Part A of the study, dupilumab was well tolerated in pediatric patients with EoE. There were 0 and 2 AEs leading to discontinuation in the dupilumab and placebo groups, respectively. The most common TEAEs among all arms were injection-site reactions and COVID-19. Most TEAEs were mild or moderate (Chehade 2023b)
- In Part B of the study, dupilumab was well tolerated in pediatric patients with EoE. Among the treatment arms, the incidence of AEs was 73%–100%. There was 1 AE leading to discontinuation in the dupilumab-dupilumab higher-exposure group. The most common TEAEs among all arms were similar to Part A, injection-site reactions and COVID-19. Most TEAEs were mild or moderate (Chehade 2023b)
- Part C of the study is still ongoing, and full results are not yet available

Prurigo Nodularis

Prurigo nodularis (PN), a chronic inflammatory skin condition characterized by intensely pruritic papulonodular lesions, substantially affects quality of life (QOL) and mental health (Elmariah 2021, Huang 2020, Whang 2020). According to a private insurance claims database, estimated PN prevalence in the US is 72 per 100,000 (Wongvibulsin 2021). According to an internal analysis, the prevalence of PN in the US adult population is 0.12% and the estimated number of adults with PN uncontrolled on topical prescription therapy is 139,000 (Data on file 2022). PN can occur in all age groups but primarily affects middle-aged and older adults (Hughes 2020). PN can arise without any concomitant comorbidities or separate underlying conditions; however, a range of comorbidities are often associated with PN that may contribute to initiation or perpetuation of itch (Elmariah 2021, Kwatra 2020, Kwon 2019). In an international cross-sectional survey study including adults with PN, coexisting type 2 inflammatory diseases were highly prevalent, with allergic rhinitis reported in 71%, eczema reported in 50%, and asthma reported in 31% (Aggarwal 2019). PN imposes a substantial economic and societal burden because of the high levels of health care resource utilization (Aggarwal 2021, Whang 2019, Whang 2020, Whang 2021).

Dupilumab is indicated for the treatment of adults with PN (Dupixent USPI 2024).

During the dupilumab PN clinical development program, the clinical efficacy and safety of dupilumab were studied in two phase 3 trials (Dupixent USPI 2024, Yosipovitch 2023).

Dupilumab provided significant and clinically meaningful improvements in itch and nodule clearance as well as both itch and nodule clearance in the same patients at 24 weeks. Improvements were also observed in skin pain, HRQOL, and symptoms of anxiety and depression. Safety was consistent with the known dupilumab safety profile (Yosipovitch 2023).

Dupilumab demonstrated significant and clinically meaningful improvement in itch, as measured by worst itch numerical rating scale (WI-NRS)

- In the PRIME and PRIME2 trials, itch severity was reduced by a clinically meaningful degree, as assessed by a ≥4-point reduction in weekly average WI-NRS from baseline, in a significantly greater proportion of patients treated with dupilumab than those treated with placebo (Dupixent USPI 2024, Yosipovitch 2023):
  - Week 12: PRIME, 44.0% dupilumab vs 15.8% placebo (treatment difference: 29.2%; *P*-value NR); PRIME2, 37.2% vs 22.0%, respectively (treatment difference: 16.8%; *P*=0.0216)
  - Week 24: PRIME, 60.0% dupilumab vs 18.4% placebo (treatment difference: 42.7%; *P*<0.0001); PRIME2, 57.7% vs 19.5%, respectively (treatment difference: 42.6%; *P*<0.0001)

Dupilumab demonstrated significant and clinically meaningful improvement of lesions, as measured by IGA PN-Stage (IGA PN-S)

- In the PRIME and PRIME2 trials, the number of lesions was reduced by a clinically meaningful degree, as assessed by achievement of IGA PN-S 0 or 1 (clear or almost clear) at Week 24, in a significantly greater proportion of patients treated with dupilumab than those treated with placebo (PRIME: 48.0% vs 18.4%, respectively [treatment difference: 28.3%; *P*=0.0004]; PRIME2: 44.9% vs 15.9%, respectively [treatment difference: 30.8%; *P*<0.0001]) (Dupixent USPI 2024, Yosipovitch 2023)

Dupilumab demonstrated clinically meaningful improvements in both itch and lesions, as measured by WI-NRS and IGA PN-S, respectively

- In the PRIME and PRIME2 trials, a greater proportion of patients achieved clinically meaningful responses in both itch and lesions, as assessed by the composite of ≥4-point reduction in weekly average WI-NRS from baseline and IGA PN-S 0 or 1 at Week 24, with dupilumab vs placebo (PRIME:

38.7% vs 9.2%, respectively [treatment difference: 29.6%]; PRIME2: 32.1% vs 8.5%, respectively [treatment difference: 25.5%]) (Dupixent USPI 2024)

Dupilumab had a safety profile in the PN indication that was consistent with the safety profile of dupilumab in other approved indications (Yosipovitch 2023)

- In the PRIME trial, dupilumab was evaluated through Week 24 and was generally well tolerated, with an overall acceptable safety profile
  - The overall rate of TEAEs in the dupilumab arm was similar to that of the placebo arm (70.7% vs 62.7%, respectively). The rate of TEAEs was also similar between the dupilumab and placebo arms (6.7% vs 10.7%, respectively). No TEAEs lead to treatment discontinuation in the dupilumab arm, whereas 3 (4.0%) patients in the placebo arm had a TEAE leading to treatment discontinuation
  - The incidence of conjunctivitis (narrow term) was similar between the dupilumab and placebo arms (4.0% vs 2.7%, respectively)
  - The incidence of injection site reactions was similar between the dupilumab and placebo arms (5.3% vs 6.7%, respectively)
  - The incidence of adjudicated nonherpetic skin infections was numerically lower in the dupilumab arm than the placebo arm (4.0% vs 9.3%, respectively)
  - No herpes viral infections were reported in either treatment arm
- In the PRIME2 trial, dupilumab was evaluated through Week 24 and was generally well tolerated, with an overall acceptable safety profile
  - The overall rate of TEAEs in the dupilumab arm was similar to that of the placebo arm (57.1% vs 51.2%, respectively)
  - The incidence of conjunctivitis (narrow term) was numerically higher in the dupilumab arm than in the placebo arm (3.9% vs 0%, respectively)
  - The incidence of adjudicated nonherpetic skin infections was numerically lower in the dupilumab arm than the placebo arm (5.2% vs 8.5%, respectively)
  - The incidence of herpes viral infections was higher in the dupilumab arm than in the placebo arm (6.5% vs 0%, respectively); none of the herpes viral infection events were severe or led to permanent treatment discontinuation

Economic Benefits

A pharmacy budget impact model from the health plan perspective was developed to assess the pharmacy-cost impact of including dupilumab on a US health plan's formulary. Eligible patients and treatments for uncontrolled AD, asthma, CRSwNP, EoE, and PN were included for evaluation. The budget impact model estimates the budget for dupilumab by indication and across all 5 indications.

For a hypothetical plan of 1 million patient lives, the budget impact results are presented in **Table 1**.

Table 1. Budget for dupilumab by indication and across all 5 indications

Outcome	Year	
	2022	2025
AD		
Total annual budget for dupilumab	$10,179,212	$15,613,787
Budget impact PMPM	$0.85	$1.30
Budget impact PMPY	$10.18	$15.61
Asthma		
Total annual budget for dupilumab	$3,472,267	$5,135,237
Budget impact PMPM	$0.29	$0.43
Budget impact PMPY	$3.47	$5.14
CRSwNP		
Total annual budget for dupilumab	$2,284,458	$4,864,592
Budget impact PMPM	$0.19	$0.41
Budget impact PMPY	$2.28	$4.86
EoE		
Total annual budget for dupilumab	$74,444	$1,097,065
Budget impact PMPM	$0.01	$0.09
Budget impact PMPY	$0.07	$1.10
PN		
Total annual budget for dupilumab	$291,020	$1,891,057
Budget impact PMPM	$0.02	$0.16
Budget impact PMPY	$0.29	$1.89
All 5 indications combined[a]		
Total annual budget for dupilumab	$16,301,400	$28,601,738
Budget impact PMPM	$1.36	$2.38
Budget impact PMPY	$16.30	$28.60

[a]These estimations account for patients with multimorbid indications.
AD, atopic dermatitis; CRSwNP, chronic rhinosinusitis with nasal polyps; EoE, eosinophilic esophagitis; PMPM, per member per month; PMPY, per member per year; PN, prurigo nodularis.

References

Abdalla S, Alreefy H, Hopkins C. Prevalence of sinonasal outcome test (SNOT-22) symptoms in patients undergoing surgery for chronic rhinosinusitis in the England and Wales National prospective audit. *Clin Otolaryngol*. 2012;37(4):276–282.

Aggarwal P, Choi J, Sutaria N, et al. Clinical characteristics and disease burden in prurigo nodularis. *Clin Exp Dermatol.* 2021;46(7):1277–1284.

Agner T, Aalto-Korte K, Andersen KE, et al. Classification of hand eczema. *J Eur Acad Dermatol Venereol.* 2015;29(12):2417–2422.

Akinlade B, Guttman-Yassky E, de Bruin-Weller M, et al. Conjunctivitis in dupilumab clinical trials. *Br J Dermatol*. 2019;181(3):459–473.

Bacharier LB, Maspero JF, Katelaris CH, et al. Dupilumab in children with uncontrolled moderate-to-severe asthma. *N Engl J Med*. 2021;385(24):2230–2240.

Bachert C, Mannent L, Naclerio RM, et al. Effect of subcutaneous dupilumab on nasal polyp burden in patients with chronic sinusitis and nasal polyposis: a randomized clinical trial. *JAMA*. 2016;315(5):469–479.

Bachert C, Hellings PW, Mullol J, et al. Atopic comorbidities and biomarkers of type 2 inflammation in patients with chronic rhinosinusitis with nasal polyposis (CRSwNP) who failed intranasal corticosteroids . Presented at: 2018 American Academy of Allergy, Asthma and Immunology (AAAAI)/World Allergy Organization (WAO) Joint Congress; March 2–5, 2018; Orlando, FL.

Bachert C, Hellings PW, Mullol J, et al. Dupilumab improves patient-reported outcomes in patients with chronic rhinosinusitis with nasal polyps and comorbid asthma. *J Allergy Clin Immunol Pract*. 2019;7(7):2447–2449.e2.

Bansal A, Simpson EL, Paller AS, et al. Conjunctivitis in dupilumab clinical trials for adolescents with atopic dermatitis or asthma. *Am J Clin Dermatol*. 2021;22(1):101–115.

Bateman E, Khan AH, Xu Y, et al. Pairwise indirect treatment comparison of dupilumab versus other biologics in patients with uncontrolled persistent asthma. *Respir Med*. 2022;191:105991.

Batra PS, Tong L, Citardi MJ. Analysis of comorbidities and objective parameters in refractory chronic rhinosinusitis. *Laryngoscope*. 2013;123(Suppl 7):S1–S11.

Beck LA, Deleuran M, Bissonnette R, et al. Dupilumab provides acceptable safety and sustained efficacy for up to 4 years in an open-label study of adults with moderate-to-severe atopic dermatitis. *Am J Clin Dermatol*. 2022;23(3):393–408.

Bieber T, D'Erme AM, Akdis CA, et al. Clinical phenotypes and endophenotypes of atopic dermatitis: where are we, and where should we go? *J Allergy Clin Immunol.* 2017;139(4S):S58–S64.

Blauvelt A, de Bruin-Weller M, Gooderham M, et al. Long-term management of moderate-to-severe atopic dermatitis with dupilumab and concomitant topical corticosteroids (LIBERTY AD CHRONOS): a 1-year, randomised, double-blinded, placebo-controlled, phase 3 trial. *Lancet.* 2017;389(10086):2287–2303.

Blauvelt A, Guttman-Yassky E, Paller AS, et al. Long-term efficacy and safety of dupilumab in adolescents with moderate-to-severe atopic dermatitis: results through week 52 from a phase III open-label extension trial (LIBERTY AD PED-OLE). *Am J Clin Dermatol*. 2022;23(3):365–383.

Cahill KN, Johns CB, Cui J, et al. Automated identification of an aspirin-exacerbated respiratory disease cohort. *J Allergy Clin Immunol*. 2017;139(3):819–825.e816.

Castro M, Corren J, Pavord ID, et al. Dupilumab efficacy and safety in moderate-to-severe uncontrolled asthma. *N Engl J Med*. 2018;378(26):2486–2496.

Centers for Disease Control and Prevention (CDC). Chronic sinusitis. Last updated January 20, 2017. Accessed December 2018. https://www.cdc.gov/nchs/fastats/sinuses.htm

Centers for Disease Control and Prevention (CDC). Most recent asthma data. Last updated October 26, 2020. Accessed February 2021. https://www.cdc.gov/asthma/most_recent_data.htm

Chehade M, Dellon ES, Spergel JM, et al. Dupilumab improves histological and endoscopic features of eosinophilic esophagitis in children aged 1–11 years in the phase 3 EoE KIDS trial. Presented at: Digestive Diseases Week (DDW) 2023 Annual Meeting; May 7–9, 2023a; Chicago, IL.

Chehade M, Dellon ES, Spergel JM, et al. Dupilumab improves histological, endoscopic, and symptomatic aspects of eosinophilic esophagitis in children aged 1–11 years in the phase 3 EoE KIDS trial. Poster presented at: North American Society for Pediatric Gastroenterology, Hepatology & Nutrition (NASPGHAN) 2023; October 4–7, 2023b; San Diego, CA.

DeConde AS, Mace JC, Ashby S, Smith TL, Orlandi RR, Alt JA. Characterization of facial pain associated with chronic rhinosinusitis using validated pain evaluation instruments. *Int Forum Allergy Rhinol*. 2015a;5(8):682–690.

DeConde AS, Mace JC, Alt JA, Soler ZM, Orlandi RR, Smith TL. Investigation of change in cardinal symptoms of chronic rhinosinusitis after surgical or ongoing medical management. *Int Forum Allergy Rhinol*. 2015b;5(1):36–45.

DeConde AS, Mace JC, Levy JM, Rudmik L, Alt JA, Smith TL. Prevalence of polyp recurrence after endoscopic sinus surgery for chronic rhinosinusitis with nasal polyposis. *Laryngoscope.* 2017;127(3):550–555.

Dellon ES, Liacouras CA, Molina-Infante J, et al. Updated international consensus diagnostic criteria for eosinophilic esophagitis: proceedings of the AGREE conference. *Gastroenterology*. 2018;155(4):1022–1033.e10.

Dellon ES, Woosley JT, Arrington A, et al. Rapid recurrence of eosinophilic esophagitis activity after successful treatment in the observation phase of a randomized, double-blind, double-dummy trial. *Clin Gastroenterol Hepatol*. 2020;18(7):1483–1492.e2.

Dellon ES, Rothenberg ME, Collins MH, et al. Dupilumab in adults and adolescents with eosinophilic esophagitis. *N Engl J Med*. 2022;387(25):2317–2330.

Dupixent (dupilumab). US Prescribing Information. Sanofi-Aventis US, Regeneron Pharmaceuticals; 2024.

Eichenfield LF, Bieber T, Beck LA, et al. Infections in dupilumab clinical trials in atopic dermatitis: a comprehensive pooled analysis. *Am J Clin Dermatol.* 2019;20(3):443–456.

Elmariah S, Kim B, Berger T, et al. Practical approaches for diagnosis and management of prurigo nodularis: United States expert panel consensus. *J Am Acad Dermatol.*2021;84:747–760.

Furuta GT, Katzka DA. Eosinophilic esophagitis. *N Engl J Med*. 2015;373(17):1640–1648.

Gandhi NA, Bennett BL, Graham NM, Pirozzi G, Stahl N, Yancopoulos GD. Targeting key proximal drivers of type 2 inflammation in disease. *Nat Rev Drug Discov*. 2016;15(1):35–50.

Global Initiative for Asthma (GINA). Global strategy for asthma management and prevention, 2022. Accessed May 2024. https://ginasthma.org/wp-content/uploads/2022/07/GINA-Main-Report-2022-FINAL-22-07-01-WMS.pdf

Gómez-Aldana A, Jaramillo-Santos M, Delgado A, Jaramillo C, Lúquez-Mindiola A. Eosinophilic esophagitis: current concepts in diagnosis and treatment. *World J Gastroenterol*. 2019;25(32):4598–4613.

Hill DA, Spergel JM. The immunologic mechanisms of eosinophilic esophagitis. *Curr Allergy Asthma Rep*. 2016;16(2):9.

Hill DA, Grundmeier RW, Ramos M, Spergel JM. Eosinophilic esophagitis is a late manifestation of the allergic march. *J Allergy Clin Immunol Pract*. 2018;6(5):1528–1533.

Hirano I. How to approach a patient with eosinophilic esophagitis. *Gastroenterology*. 2018;155(3):601–606.

Hirano I, Chan ES, Rank MA, et al. AGA institute and the joint task force on allergy-immunology practice parameters clinical guidelines for the management of eosinophilic esophagitis. *Ann Allergy Asthma Immunol*. 2020;124(5):416–423.

Huang AH, Williams KA, Kwatra SG. Prurigo nodularis: epidemiology and clinical features. *J Am Acad Dermatol*. 2020;83:1559–1565.

Khan AH, Gouia I, Kamat S, et al. Type 2 inflammation-related comorbidities among patients with asthma, chronic rhinosinusitis with nasal polyps and atopic dermatitis. Poster presented at: European Respiratory Society (ERS) International Congress 2020; September 7–9, 2020; virtual meeting.

Kim JP, Chao LX, Simpson EL, Silverberg JI. Persistence of atopic dermatitis (AD): a systematic review and meta-analysis. *J Am Acad Dermatol.* 2016;75(4):681–687.e611.

Kwatra SG. Breaking the itch-scratch cycle in prurigo nodularis. *N Engl J Med*. 2020;382(8):757–758.

Kwon CD, Khanna R, Williams KA., et al. Diagnostic workup and evaluation of patients with prurigo nodularis. *Medicines (Basel)*. 2019;6(4):97.

Li N, Peters AT. Chronic rhinosinusitis management beyond intranasal steroids and saline solution irrigations. *Allergy Asthma Proc*. 2015;36(5):339–343.

Lucendo AJ, Molina-Infante J, Arias Á, et al. Guidelines on eosinophilic esophagitis: evidence-based statements and recommendations for diagnosis and management in children and adults. *United European Gastroenterol J*. 2017;5(3):335–358.

Martin LJ, Franciosi JP, Collins MH, et al. Pediatric Eosinophilic Esophagitis Symptom Scores (PEESS v2.0) identify histologic and molecular correlates of the key clinical features of disease. *J Allergy Clin Immunol*. 2015;135(6):1519–1528.e8.

National Heart, Lung, and Blood Institute (NHLBI). Expert Panel Report 3: Guidelines for the Diagnosis and Management of Asthma. Published August 28, 2007. Accessed May 2024. https://www.nhlbi.nih.gov/sites/default/files/media/docs/EPR-3_Asthma_Full_Report_2007.pdf.

National Institute of Health (NIH). Dysphagia. Published March 2017. Accessed July 2022. https://www.nidcd.nih.gov/health/dysphagia

Orlandi RR, Kingdom TT, Hwang PH, et al. International Consensus Statement on Allergy and Rhinology: Rhinosinusitis. *Int Forum Allergy Rhinol*. 2016;6(Suppl 1):S22–S209.

O'Shea KM, Aceves SS, Dellon ES, et al. Pathophysiology of eosinophilic esophagitis. *Gastroenterology.* 2018;154(2):333–345.

Paller AS, Siegfried EC, Thaçi D, et al. Efficacy and safety of dupilumab with concomitant topical corticosteroids in children 6 to 11 years old with severe atopic dermatitis: a randomized, double-blinded, placebo-controlled phase 3 trial. *J Am Acad Dermatol*. 2020;83(5):1282–1293.

Paller AS, Simpson EL, Siegfried EC, et al. Dupilumab in children aged 6 months to younger than 6 years with uncontrolled atopic dermatitis: a randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet*. 2022a;400(10356):908-919.

Paller AS, Beck LA, Blauvelt A, et al. Infections in children and adolescents treated with dupilumab in pediatric clinical trials for atopic dermatitis—a pooled analysis of trial data. *Pediatr Dermatol*. 2022b;39(2):187–196.

Palmer JN, Messina JC, Biletch R, Grosel K, Mahmoud RA. A cross-sectional, population-based survey of U.S. adults with symptoms of chronic rhinosinusitis. *Allergy Asthma Proc*. 2019;40(1):48–56.

Peters AT, Spector S, Hsu J, et al. Diagnosis and management of rhinosinusitis: a practice parameter update. *Ann Allergy Asthma Immunol*. 2014;113(4):347–385.

Peters AT, Han J, Hellings P, et al. Indirect treatment comparison of biologics in chronic rhinosinusitis with nasal polyps. *J Allergy Clin Immunol Pract*. 2021;9(6):2461–2471.e5.

Promsopa C, Kansara S, Citardi MJ, Fakhri S, Porter P, Luong A. Prevalence of confirmed asthma varies in chronic rhinosinusitis subtypes. *Int Forum Allergy Rhinol*. 2016;6(4):373–377.

Quaade AS, Simonsen AB, Halling AS, Thyssen JP, Johansen JD. Prevalence, incidence, and severity of hand eczema in the general population—a systematic review and meta-analysis. *Contact Dermatitis.* 2021;84(6):361–374.

Rabe KF, Nair P, Brusselle G, et al. Efficacy and safety of dupilumab in glucocorticoid-dependent severe asthma. *N Engl J Med*. 2018;378(26):2475–2485.

Rosenfeld RM, Piccirillo JF, Chandrasekhar SS, et al. Clinical practice guideline (update): adult sinusitis. *Otolaryngol Head Neck Surg*. 2015;152(Suppl 2):S1–S39.

Rothenberg ME, Dellon ES, Collins MH, et al. Efficacy and safety of dupilumab up to 52 weeks in adults and adolescents with eosinophilic oesophagitis (LIBERTY EoE TREET study): a multicentre, double-blind, randomised, placebo-controlled, phase 3 trial. *Lancet Gastroenterol Hepatol.* 2023;8(11):990–1004.

Sanofi. Data on file. A randomized, 24-week treatment, double-blind, placebo-controlled efficacy and safety study of dupilumab 300 mg every other week, in patients with bilateral nasal polyposis on a background therapy with intranasal corticosteroids (SINUS-24 [EFC14146]). Clinical study report. December 10, 2018b.

Sanofi. Data on file. A randomized, double-blind, 52-week, placebo-controlled efficacy and safety study of dupilumab, in patients with bilateral nasal polyposis on a background therapy with intranasal corticosteroids (SINUS-52 [EFC14280]). Clinical study report. December 11, 2018c.

Sanofi. Data on file. A randomized, double blind, placebo-controlled, parallel group study to evaluate the efficacy and safety of dupilumab in children 6 to <12 years of age with patients with uncontrolled persistent asthma (LIBERTY ASTHMA VOYAGE [EFC14153]). Clinical study report. December 7, 2020a.

Sanofi. Data on file. One-year study to evaluate the long-term safety and tolerability of dupilumab in pediatric patients with asthma who participated in a previous dupilumab asthma clinical study (LIBERTY ASTHMA EXCURSION [LTS14424]). Clinical study report interim analysis. December 3, 2020b.

Sanofi and Regeneron. Data on file. Truven claims database study in children. 2015a

Sanofi and Regeneron. Data on file. Truven claims database study in adolescents and adults]. 2015b.

Sanofi and Regeneron. Data on file. Summary of clinical safety [asthma]. 2017.

Sanofi and Regeneron. Data on file. Truven MarketScan database analysis, Adelphi DSP, and Galen 2010 description. 2018a.

Sanofi and Regeneron. Data on file. Truven MarketScan database analysis and uncontrolled EoE calculations, ACG. 2021.

Sanofi and Regeneron. Data on file. Optum Clinformatics 2019 prevalence. 2022.

Sanofi and Regeneron. Data on file. Adolescent AD epidemiology funnel.

Sanofi and Regeneron. Data on file. Adult AD epidemiology funnel.

Sanofi and Regeneron. Data on file. Childhood AD epidemiology funnel.

Sanofi and Regeneron. Data on file. Infant and young childhood AD epidemiology funnel.

Sanofi Press Release. Press Release: Dupixent® (dupilumab) late-breaking Phase 3 COPD results presented at ATS and simultaneously published in the *New England Journal of Medicine*. May 2023. https://www.sanofi.com/en/media-room/press-releases/2023/2023-05-21-18-17-12-2672904. Accessed May 2024.

Siegfried EC, Cork MJ, Arkwright PD, et al. Dupilumab treatment is not associated with an increased overall risk of infections in patients aged 6 months to 5 years with moderate-to-severe atopic dermatitis. Poster presented at: 47th Annual Meeting of the Society for Pediatric Dermatology (SPD); July 7–10, 2022; Indianapolis, IN.

Silverberg JI, Barbarot S, Gadkari A, et al. Atopic dermatitis in the pediatric population: a cross-sectional, international epidemiologic study. *Ann Allergy Asthma Immunol*. 2021;126(4):417–428.e412.

Silverberg JI. Public health burden and epidemiology of atopic dermatitis. *Dermatol Clin*. 2017;35(3):283–289.

Simpson EL, Thompson MM, Hanifin JM. Prevalence and morphology of hand eczema in patients with atopic dermatitis. *Dermatitis.* 2006;17(3):123–127.

Simpson EL, Paller AS, Siegfried EC, et al. Efficacy and safety of dupilumab in adolescents with uncontrolled moderate to severe atopic dermatitis: a phase 3 randomized clinical trial. *JAMA Dermatol*. 2020;156(1):44–56.

Simpson EL, Silverberg JI, Worm M, et al. Dupilumab treatment in patients with atopic hand and foot dermatitis: Results from a phase 3, randomized, double-blind, placebo-controlled trial [oral presentation]. Presented at: 81st American Academy of Dermatology (AAD) Annual Meeting; March 17-21, 2023; New Orleans, LA.

Stevens WW, Lee RJ, Schleimer RP, Cohen NA. Chronic rhinosinusitis pathogenesis. *J Allergy Clin Immunol*. 2015;136(6):1442–1453.

Stevens WW, Schleimer RP, Kern RC. Chronic rhinosinusitis with nasal polyps. *J Allergy Clin Immunol Pract*. 2016;4(4):565–572.

Stevens WW, Peters AT, Hirsch AG, et al. Clinical characteristics of patients with chronic rhinosinusitis with nasal polyps, asthma, and aspirin-exacerbated respiratory disease. *J Allergy Clin Immunol Pract*. 2017;5(4):1061–1070. e1063.

Thaçi D, Simpson EL, Deleuran M, et al. Efficacy and safety of dupilumab monotherapy in adults with moderate-to-severe atopic dermatitis: a pooled analysis of two phase 3 randomized trials (LIBERTY AD SOLO 1 and LIBERTY AD SOLO 2). *J Dermatol Sci*. 2019;94(2):266–275.

Thyssen JP, Johansen JD, Linneberg A, Menné T. The epidemiology of hand eczema in the general population—prevalence and main findings. *Contact Dermatitis.* 2010;62(2):75–87.

van der Veen J, Seys SF, Timmermans M, et al. Real-life study showing uncontrolled rhinosinusitis after sinus surgery in a tertiary referral centre. *Allergy*. 2017;72(2):282–290.

Wechsler ME, Ford LB, Maspero JF, et al. Long-term safety and efficacy of dupilumab in patients with moderate-to-severe asthma (TRAVERSE): an open-label extension study. *Lancet Respir Med*. 2022;10(1):11–25.

Weidinger S, Novak N. Atopic dermatitis. *Lancet*. 2016;387(10023):1109–1122.

Wenzel S, Castro M, Corren J, et al. Dupilumab efficacy and safety in adults with uncontrolled persistent asthma despite use of medium-to-high-dose inhaled corticosteroids plus a long-acting β_2 agonist: a randomised double-blind placebo-controlled pivotal phase 2b dose-ranging trial. *Lancet.* 2016;388(10039):31–44.

Whang KA, Kang S, Kwatra SG. Inpatient burden of prurigo nodularis in the United States. *Medicines (Basel)*. 2019;6(3)88.

Whang KA, Mahadevan V, Bakhshi PR, et al. Prevalence of prurigo nodularis in the United States. *J Allergy Clin Immunol Pract*. 2020;8(9):3240–3241.

Whang KA, Gabriel S, Chavda R, Kwatra SG. Emergency department use by patients with prurigo nodularis in the United States. *J Am Acad Dermatol*. 2021;84(4):1138–1140.

White AA, Stevenson DD. Aspirin-exacerbated respiratory disease. *N Engl J Med*. 2018;379(11):1060–1070.

Wongvibulsin S, Sutaria N, Williams KA, et al. A Nationwide study of prurigo nodularis: disease burden and healthcare utilization in the United States. *J Invest Dermatol*. 2021;141(10):2530–2533.e1.

Worm M, Simpson EL, Thaçi D, et al. Efficacy and safety of multiple dupilumab dose regimens after initial successful treatment in patients with atopic dermatitis: a randomized clinical trial. *JAMA Dermatol*. 2020;156(2):131–143.

Wynn R, Har-El G. Recurrence rates after endoscopic sinus surgery for massive sinus polyposis. *Laryngoscope*. 2004;114(5):811–813.

Yosipovitch G, Mollanazar N, Ständer S, et al. Dupilumab in patients with prurigo nodularis: two randomized, double-blind, placebo-controlled phase 3 trials. *Nat Med*. 2023;29(5):1180–1190.