
Article:
Paller, A.S., Ramien, M. orcid.org/0000-0001-9191-3611, Cork, M.J. orcid.org/0000-0003-4428-2428 et al. (9 more authors) (2025) Low infection rates with long-term dupilumab treatment in patients aged 6 months to 5 years: an open-label extension study. Pediatric Dermatology, 42 (2). pp. 251-258. ISSN 0736-8046

https://doi.org/10.1111/pde.15781

Pediatric Dermatology

WILEY

Pediatric Dermatology

ORIGINAL ARTICLE OPEN ACCESS

Low Infection Rates With Long-Term Dupilumab Treatment in Patients Aged 6 Months to 5 Years: An Open-Label Extension Study

Amy S. Paller[1,2] | Michele Ramien[3,4] | Michael J. Cork[5,6] | Eric L. Simpson[7] | Lara Wine Lee[8] | Lawrence F. Eichenfield[9,10] | Faisal A. Khokhar[11] | Anna Coleman[12] | Guy Gherardi[13] | Zhen Chen[11] | Annie Zhang[14] | Sonya L. Cyr[11]

[1]Department of Dermatology, Northwestern University Feinberg School of Medicine, Chicago, Illinois, USA | [2]Ann and Robert H. Lurie Children's Hospital, Chicago, Illinois, USA | [3]Division of Dermatology, Department of Medicine, University of Calgary, Calgary, Alberta, Canada | [4]Section of Community Pediatrics, Department of Pediatrics, Alberta Children's Hospital, Calgary, Alberta, Canada | [5]Sheffield Dermatology Research, University of Sheffield, Sheffield, UK | [6]Sheffield Children's Hospital, Sheffield, UK | [7]Department of Dermatology, Oregon Health & Science University, Portland, Oregon, USA | [8]Dermatology and Dermatologic Surgery, Medical University of South Carolina, Charleston, South Carolina, USA | [9]Department of Dermatology and Pediatrics, University of California San Diego, La Jolla, California, USA | [10]Division of Pediatric and Adolescent Dermatology, Rady Children's Hospital, San Diego, California, USA | [11]Regeneron Pharmaceuticals Inc., Tarrytown, New York, USA | [12]Regeneron Pharmaceuticals Inc., Dublin, Ireland | [13]Sanofi, Reading, UK | [14]Sanofi, Cambridge, Massachusetts, USA

Correspondence: Sonya L. Cyr (sonya.cyr@regeneron.com)

Received: 25 July 2024 | **Revised:** 23 September 2024 | **Accepted:** 29 September 2024

Funding: This work was supported by Sanofi and Regeneron Pharmaceuticals Inc.

Keywords: atopic dermatitis | dupilumab | eczema | infections | pediatric dermatology

ABSTRACT

Objective: To evaluate long-term infection rates in children aged 6 months to 5 years with moderate-to-severe atopic dermatitis (AD) treated with dupilumab.

Methods: This was a post hoc analysis of an ongoing open-label extension (OLE) study of dupilumab. Pediatric patients aged 6 months to 5 years with moderate-to-severe AD who had previously taken part in the LIBERTY AD PRESCHOOL phase 2 and 3 clinical trials received weight-based subcutaneous dupilumab every 2 or 4 weeks. Exposure-adjusted infection rates after a median dupilumab exposure of 52 weeks are compared with data from the earlier randomized, placebo-controlled, 16-week LIBERTY AD PRESCHOOL phase 3 trial.

Results: Infection rates were overall lower in the OLE study compared with the dupilumab and placebo groups in the earlier 16-week trial, including total infections (101.0 patients/100 patient-years [PY]), nonherpetic skin infections (22.7 patients/100PY), herpetic infections (7.3 patients/100PY), and nonskin infections (92.9 patients/100PY). The frequency of severe and serious infections was low (3.1 patients/100PY), compared with 17.1 placebo-treated patients/100PY and 0 dupilumab-treated patients in the earlier 16-week trial, and no infections leading to treatment discontinuation were observed. Systemic anti-infective medication use (58.9 patients/100PY) was lower in the OLE study compared with both the dupilumab and placebo groups in the 16-week trial.

Conclusion: Overall, reduced infection rates are observed in infants and young children with moderate-to-severe AD treated with dupilumab long-term, supporting the known safety profile of dupilumab.

This article includes a comparison with data from a separate, previously published study (Paller et al. 2022, Lancet 400: 908–919; and Paller et al. 2024, Pediatric Drugs 26: 163–173).

1 | Introduction

Atopic dermatitis (AD) is a chronic skin condition caused by dysregulation of type 2 immune response [1, 2]. Patients with AD, particularly infants and young children, are at higher risk of developing both cutaneous and noncutaneous infections, including herpetic infections, molluscum contagiosum, and bacterial infections primarily caused by *Staphylococcus aureus* [3–6]. Skin colonization by *S. aureus* may exacerbate AD inflammation and skin barrier defects, which further increase the risk of infections [6].

Dupilumab is a fully human monoclonal antibody that blocks signaling of interleukin (IL)-4 and IL-13 type 2 cytokines [7]. As bacterial, viral, and fungal infections are not primarily targeted by type 2 immune responses [8], dupilumab is unlikely to interfere with the primary host defenses against these organisms. The efficacy and safety of dupilumab in improving AD signs and symptoms in children aged 6 months to 5 years have been evaluated in a placebo-controlled 16-week clinical trial (LIBERTY AD PRESCHOOL) [9] and in a long-term, open-label extension (OLE) study (LIBERTY AD PED-OLE) [10]. A post hoc analysis of the 16-week trial showed that dupilumab treatment did not increase overall infection rates and was associated with a significantly lower rate of bacterial infections and nonherpetic skin infections compared with placebo [11].

The aim of this analysis was to evaluate the long-term impact of dupilumab treatment on infections in children aged 6 months to 5 years with moderate-to-severe AD who had previously participated in the earlier, short-term LIBERTY AD PRESCHOOL study and subsequently enrolled in the LIBERTY AD PED-OLE study.

2 | Materials and Methods

2.1 | Study Design

This was a post hoc analysis of data from an ongoing phase 3 OLE study (LIBERTY AD PED-OLE, NCT02612454) in patients aged 6 months to 5 years with moderate-to-severe AD, who had previously participated in the LIBERTY AD PRESCHOOL phase 2 and 3 clinical trials (NCT03346434 Part A and B, respectively). The study design, efficacy, and safety results of both clinical trials [9, 12] and the OLE study [10] have been previously reported. In the OLE study, patients received weight-based subcutaneous dupilumab every 4 weeks (200 mg if body weight was 5 to < 15 kg; 300 mg if 15 to < 30 kg) or every 2 weeks (200 mg if body weight was 30 to < 60 kg). Concomitant topical corticosteroids, antihistamines, and topical calcineurin inhibitors were permitted without restriction. This analysis presents results through week 52 of the OLE study, with a data cutoff date of March 10, 2022. Mean (standard deviation) and median (interquartile range) treatment exposure were 64.1 (42.7) and 52 (44–60) weeks, respectively.

Infection results from a post hoc analysis of LIBERTY AD PRESCHOOL Part B are included for comparison. In this randomized, double-blind, placebo-controlled, phase 3 clinical trial, pediatric patients aged 6 months to 5 years with moderate-to-severe AD received subcutaneous dupilumab (200 mg if baseline weight ≥ 5 to < 15 kg, 300 mg if ≥ 15 to < 30 kg) or matched placebo, every 4 weeks for 16 weeks. Details of this analysis have been previously reported [11].

The study was conducted in accordance with the Declaration of Helsinki, the International Conference on Harmonization Good Clinical Practice Guideline, and applicable regulatory requirements. An independent data and safety monitoring committee conducted blinded monitoring of patient safety data. The local institutional review board or ethics committee at each study center oversaw trial conduct and documentation. All patients, or their parents/guardians, provided written informed consent before participating in the trial. Pediatric patients provided assent according to the ethics committee (institutional review board/independent ethics committee)-approved standard practice for pediatric patients at each participating center.

2.2 | Endpoints

Endpoints were based on treatment-emergent adverse events reported during the study and described according to the System Organ Class (SOC), High-Level Group Term (HLGT), High-Level Term (HLT), and Preferred Term (PT) of the Medical Dictionary for Regulatory Activities (MedDRA). Endpoints included total infections (SOC), infections leading to treatment discontinuation, severe or serious infections (severe: events that may interfere with the patient's normal daily activities; serious: events that may threaten the patient's life or normal functioning), nonherpetic skin infections (manually adjudicated by the study's clinical director), herpes viral infections (HLT, including PTs: herpes virus, eczema herpeticum, herpes zoster), nonskin infections (including all adverse events in the SOC "total infections" minus manually adjudicated nonherpetic skin infections and HLT herpes viral infections), skin structure and soft-tissue infections (HLT; this term only represents infections that fall within an HLGT category of "pathogens unspecified"), bacterial infections (HLGT), viral infections (HLGT), fungal infections (HLGT), and helminthic infections (HLGT).

2.3 | Analysis

The analysis included all patients who received at least one dose of dupilumab (safety set). The exposure-adjusted number of patients with ≥ 1 event per 100 patient-years (100PY) is presented for each endpoint. Analyses were descriptive; no formal statistical hypothesis was tested. All observed values were used for analysis, and no missing values were imputed.

3 | Results

The OLE study included 180 patients (mean age 3.86 years, 64.4% male), of whom 19 were younger than 2 years of age. Exposure-adjusted incidence rates of total infections (SOC infections and infestations) were lower in the OLE study after median dupilumab exposure of 52 weeks compared with both the dupilumab- and placebo-treated groups in the earlier 16-week trial (Table 1, Figure 1a). In the OLE study, 101.0 patients/100PY

TABLE 1 | Exposure-adjusted number of patients with treatment-emergent infections during the study treatment period.

	PRESCHOOL part B week 16[a]				OLE 52 weeks[b]	
	Placebo + TCS (*n* = 78)		Dupilumab 200/300 mg q4w + TCS (*n* = 83)		Dupilumab 200/300 mg q4w/q2w (*n* = 180)	
	***n* (%)**	***n*P/100PY**	***n* (%)**	***n*P/100PY**	***n* (%)**	***n*P/100PY**
Total infections (SOC)	40 (51.3)	245.7	35 (42.2)	185.2	114 (63.3)	101.0
Infections leading to treatment discontinuation (SOC)	0	0	0	0	0	0
Serious or severe infections	4 (5.1)	17.1	0	0	7 (3.9)	3.1
Serious infections	3 (3.8)	12.7	0	0	6 (3.3)	2.7
Severe infections	4 (5.1)	17.1	0	0	2 (1.1)	0.9
Nonherpetic skin infections (manually adjudicated)	19 (24.4)	92.7	10 (12.0)	42.7	41 (22.8)	22.7
Herpes viral infections (HLT)	4 (5.1)	17.1	5 (6.0)	20.0	16 (8.9)	7.3
Herpes virus infections (PT)	0	0	2 (2.4)	7.8	1 (0.6)	0.4
Eczema herpeticum (PT)	1 (1.3)	4.2	0	0	0	0
Herpes zoster (PT)	0	0	0	0	1 (0.6)	0.4
Herpes simplex (PT)	1 (1.3)	4.2	0	0	5 (2.8)	2.2
Oral herpes (PT)	2 (2.6)	8.4	1 (1.2)	3.9	4 (2.2)	1.8
Varicella (PT)	0	0	2 (2.4)	7.9	4 (2.2)	1.8
Nonskin infections[c]	36 (46.2)	207.4	31 (37.3)	152.7	109 (60.6)	92.9
Skin structures and soft-tissue infections (HLT)	9 (11.5)	40.2	6 (7.2)	24.7	17 (9.4)	8.3
Bacterial infectious disorders (HLGT)	10 (12.8)	45.6	1 (1.2)	3.9	20 (11.1)	9.6
Viral infectious disorders (HLGT)	12 (15.4)	55.2	15 (18.1)	64.8	65 (36.1)	35.6
Fungal infectious disorders (HLGT)	1 (1.3)	4.2	0	0	8 (4.4)	3.7
Helminthic infectious disorders (HLGT)	0	0	0	0	1 (0.6)	0.4

Abbreviations: HLGT, MedDRA High-Level Group Term; HLT, MedDRA High-Level Term; MedDRA, Medical Dictionary for Regulatory Activities; nP/100PY, number of patients per 100 patient-years; OLE, open-label extension; PT, MedDRA Preferred Term; q2w, every 2 weeks; q4w, every 4 weeks; SOC, MedDRA System Organ Class; TCS, topical corticosteroids.

[a]Paller et al. 2022, *Lancet* 400: 908–919; Paller et al. 2024, *Pediatric Drugs* 26: 163–173.

[b]Median treatment exposure.

[c]Includes all adverse events in the SOC "total infections" minus manually adjudicated nonherpetic skin infections and HLT herpes viral infections.

had ≥1 infections, compared with 185.2 dupilumab-treated patients/100PY and 245.7 placebo-treated patients/100PY in the 16-week trial (Table 1, Figure 1a). Severe and serious infections were infrequent in the OLE study, with a lower incidence than in the placebo group in the 16-week trial (3.1 patients/100PY in the OLE study vs. 17.1 placebo-treated patients/100PY and 0 dupilumab-treated patients). No infections leading to treatment discontinuation were observed in the OLE study (Table 1).

The incidence of nonherpetic adjudicated skin infections was lower in the OLE study compared with the dupilumab and placebo groups in the earlier 16-week trial, affecting 22.7 patients/100PY in the OLE study versus 42.7 and 92.7 patients/100PY in the dupilumab and placebo groups from the 16-week trial, respectively (Table 1, Figure 1a). Herpes viral infections (HLT) were also less frequent in the OLE study compared to both treatment groups in the 16-week trial, with 7.3 patients/100 PY having ≥1 herpetic infections in the OLE study versus 20.0 and 17.1 patients/100 PY in the dupilumab and placebo groups, respectively (Table 1, Figure 1a). No patients in the OLE study had eczema herpeticum; one patient had herpes zoster (Table 1). Furthermore, cases of molluscum contagiosum were less frequent in the OLE study compared with both the dupilumab and placebo groups in the 16-week trial, with 2.7 patients/100PY in the OLE study versus 15.9 dupilumab-treated and 8.4 placebo-treated patients/100PY (Table 2, Figure 1b).

Nonskin infections were less frequent in the OLE study (92.9 patients/100PY) compared with both the dupilumab (152.7

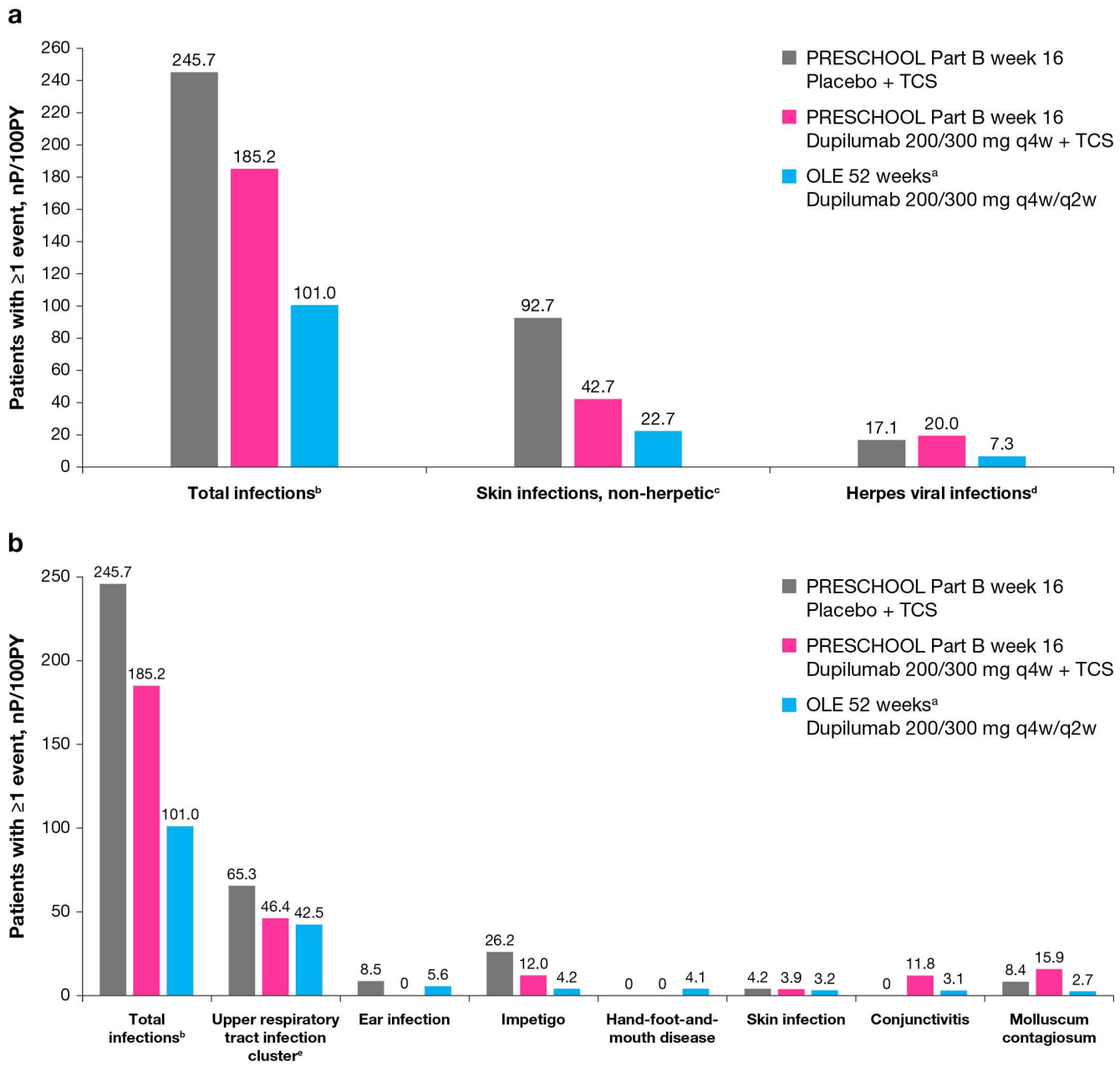

FIGURE 1 | Exposure-adjusted numbers of patients with ≥1 treatment-emergent infection events during the study treatment period. [a]Median treatment exposure. [b]SOC infections and infestations. [c]Adjudicated from the SOC infections and infestations. [d]HLT under the SOC infections and infestations. [e]Preferred Terms: Upper respiratory tract infection, pharyngitis streptococcal, viral upper respiratory tract infection, rhinitis, nasopharyngitis, and sinusitis. HLT, MedDRA High-Level Term; nP/100PY, number of patients per 100 patient-years; OLE, open-label extension; q2w, every 2 weeks; q4w, every 4 weeks; SOC, MedDRA System Organ Class; TCS, topical corticosteroids.

patients/100PY) and placebo group (207.4 patients/100PY) in the earlier 16-week trial (Table 1). Nasopharyngitis and upper respiratory tract infection were the most common treatment-emergent infections in the OLE study; however, their incidence was lower compared with both the dupilumab and placebo groups in the 16-week trial (Table 2). A total of 3.1 patients/100PY in the OLE study had PT conjunctivitis, compared with 11.8 patients/100PY in the dupilumab group and 0 patients in the placebo group from the 16-week trial (Table 2, Figure 1b). A small increase in the incidence of hand-foot-and-mouth disease (4.1 patients/100PY), streptococcal pharyngitis (3.2 patients/100PY), rhinitis (2.7 patients/100PY), bacterial conjunctivitis (2.2 patients/100PY), sinusitis (1.8 patients/100PY), and hordeolum (1.8 patients/100PY) was observed in the OLE study, compared with an incidence of 0 in both the dupilumab and placebo groups in the 16-week trial (Table 2).

The incidence of viral infections was lower in the OLE study compared with the dupilumab and placebo groups in the earlier 16-week trial (Table 1). In the OLE study, 35.6 patients/100PY had ≥1 viral infections, compared with 64.8 dupilumab-treated patients/100PY and 55.2 placebo-treated patients/100PY in the 16-week trial (Table 1). Bacterial and fungal infections were less frequent in the OLE study (9.6 patients/100PY and

TABLE 2 | Exposure-adjusted numbers of patients with treatment-emergent infections during the study treatment period.

	PRESCHOOL part B week 16[a]		OLE[b] 52 weeks[c]
	Placebo + TCS ($n = 78$)	Dupilumab 200/300 mg q4w + TCS ($n = 83$)	Dupilumab 200/300 mg q4w/q2w ($n = 180$)
	N (*n*P/100PY)	*N* (*n*P/100PY)	*N* (*n*P/100PY)
Patients with at least one TEAE	58 (514.3)	53 (361.2)	143 (195.3)
Infections and infestations	40 (245.7)	35 (185.2)	114 (101.0)
Upper respiratory tract infection cluster[d]	14 (65.3)	11 (46.4)	65 (42.5)
Upper respiratory tract infection	6 (26.2)	5 (20.1)	29 (15.0)
Nasopharyngitis	7 (30.9)	7 (28.6)	40 (21.7)
Pharyngitis streptococcal	0	0	7 (3.2)
Viral upper respiratory tract infection	2 (8.5)	0	7 (3.2)
Rhinitis	0	0	6 (2.7)
Sinusitis	0	0	4 (1.8)
Other infections and infestations[e]			
COVID-19[f]	1 (4.2)	1 (3.9)	26 (11.9)
Ear infection	2 (8.5)	0	12 (5.6)
Impetigo	6 (26.2)	3 (12.0)	9 (4.2)
Hand-foot-and-mouth disease	0	0	9 (4.1)
Skin infection	1 (4.2)	1 (3.9)	7 (3.2)
Conjunctivitis	0	3 (11.8)	7 (3.1)
Molluscum contagiosum	2 (8.4)	4 (15.9)	6 (2.7)
Croup infectious	1 (4.2)	1 (3.9)	5 (2.2)
Herpes simplex	1 (4.2)	0	5 (2.2)
Conjunctivitis bacterial	0	0	5 (2.2)
Otitis media	0	1 (3.9)	5 (2.2)
Bronchitis	0	1 (3.9)	4 (1.8)
Hordeolum	0	0	4 (1.8)
Oral herpes	2 (8.4)	1 (3.9)	4 (1.8)
Varicella	0	2 (7.9)	4 (1.8)

Note: Date ranges for data collection: [a]AD-1539 Part B: June 30, 2020–July 8, 2021. [b]AD-1434 OLE: January 15, 2018–March 10, 2022 (data cutoff). [c]Median treatment exposure. [d]Preferred Terms: upper respiratory tract infection, pharyngitis streptococcal, viral upper respiratory tract infection, rhinitis, nasopharyngitis, and sinusitis. [e]Treatment-emergent infections with ≥2% incidence in OLE (from SOC infections and infestations). [f]OLE vs. PRESCHOOL data were collected during different pandemic periods, impacting quarantine requirements, diagnosis, and testing capabilities, and therefore, these data should not be compared directly.
Abbreviations: nP/100PY, number of patients per 100 patient-years; OLE, open-label extension; q2w, every 2 weeks; q4w, every 4 weeks; SOC, MedDRA System Organ Class; TCS, topical corticosteroids; TEAE, treatment-emergent adverse event.
[a]Paller et al. 2022, *Lancet* 400: 908–919; Paller et al. 2024, *Pediatric Drugs* 26: 163–173.

3.7 patients/100PY, respectively) than in the placebo group from the earlier 16-week trial (45.6 patients/100PY and 4.2 patients/100PY, respectively) but slightly higher than in the dupilumab group (3.9 patients/100PY and 0, respectively) (Table 1). All bacterial and fungal infections in the OLE study were mild or moderate in severity. One patient in the OLE study had a helminthic infection (enterobiasis, commonly known as pinworm) of moderate severity, which was resolved by the end of the study (Table 1).

Systemic anti-infective medication use was lower in the OLE study compared with both the dupilumab and placebo groups

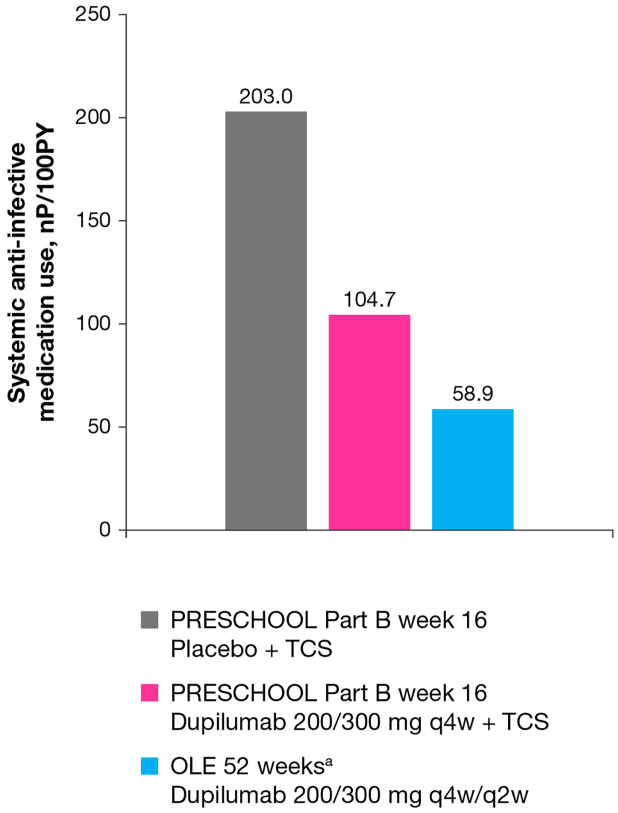

FIGURE 2 | Exposure-adjusted number of patients using anti-infective medication during the study treatment period. [a]Median treatment exposure. nP/100PY, number of patients per 100 patient-years; OLE, open-label extension; q2w, every 2 weeks; q4w, every 4 weeks; TCS, topical corticosteroids.

in the earlier 16-week trial (Figure 2). In the OLE study, 58.9 patients/100PY were administered systemic anti-infective medication during the study, compared with 104.7 patients/100PY in the dupilumab group and 203.0 patients/100PY in the placebo group from the 16-week trial. The most frequently used systemic anti-infective medications in the OLE study were amoxicillin, clindamycin, and cefalexin (Supporting Information S1).

4 | Discussion

In this analysis of data from a long-term OLE study in children aged 6 months to 5 years with moderate-to-severe AD, infection rates were compared with results from an earlier randomized, placebo-controlled, phase 3 trial of 16 weeks. Infection rates were generally lower in the OLE study after a median dupilumab treatment exposure of 52 weeks compared with both the dupilumab and placebo groups in the 16-week trial, including total infections, nonherpetic skin infections, herpetic infections, and nonskin infections. Although rates of herpetic infections were similar between the dupilumab and placebo groups in the 16-week trial (20.0 and 17.1 patients/100PY, respectively), only 7.3 patients/100PY had one or more herpetic infection in the OLE study. Severe and serious infections were infrequent, and the use of systemic anti-infective medication was lower in the OLE study than in both the dupilumab and placebo groups in the 16-week trial.

In the earlier 16-week trial, cases of conjunctivitis and molluscum contagiosum were more frequent in the dupilumab group compared with placebo; however, a substantial decrease in both was observed in the OLE study. Although conjunctivitis rates in the OLE study were still higher than in the placebo group in the 16-week study, conjunctivitis events were mild or moderate in severity. Furthermore, the reported cases of conjunctivitis may not be representative of infectious conjunctivitis rates, as the MedDRA PT conjunctivitis does not distinguish between infectious and noninfectious conjunctivitis (ocular surface disease) [13].

The consistently low skin infection rates in the OLE study reflect an acceptable long-term safety profile of dupilumab as seen in the primary study [11]. Dupilumab may decrease the incidence of skin infections in patients with AD by enhancing and normalizing skin barrier function through the reduction of dysregulated type 2 cytokines. The restored balance enables an effective expression of IL-17 and neutrophil responses, which in turn significantly reduce the risk of colonization of the skin by *S. aureus* [6, 14]. *S. aureus* skin colonization, which is often abundant in patients with AD, increases the risk of skin infections by producing cytotoxins and superantigens that contribute to skin barrier dysfunction and inflammation [6].

In addition, because dupilumab selectively targets type 2 immunity, it is not expected to interfere with host defense mechanisms against bacterial, viral, and fungal infections, which are typically type 1- and type 3-mediated [8, 15]. This differs from other immunomodulators such as Janus kinase inhibitors, which have been reported to increase the risk of infections, including herpetic infections [15, 16]. The low risk of serious infections with dupilumab is comparable to immunosuppressants such as cyclosporine and methotrexate in the treatment of AD [17, 18]; however, treatment with dupilumab, in contrast to cyclosporine, decreases *S. aureus* abundance and tends to restore a healthy skin microbiome independently of the clinical response, suggesting potential effects of IL-4RA blockade on the microbiome [19].

These results further support the long-term continuous use of dupilumab in pediatric patients aged 6 months to 5 years with moderate-to-severe AD. Overall, infection rates were lower following longer dupilumab treatment exposure, supplementing comparable results observed in short-term clinical trials in children, adolescents, and adults [11, 13, 20]. The main strength of this study is that it is the first long-term analysis of the impact of dupilumab on infections in this young population. Regarding limitations, the study was open-label and nonrandomized, the concomitant use of topical corticosteroids and other AD therapies was not standardized, and only a small sample of patients was younger than 2 years. In addition, data are descriptive and do not account for potential confounding factors. Further studies in pediatric patients are ongoing to evaluate longer-term safety and efficacy of dupilumab.

Author Contributions

Paller, Cork, and Simpson acquired data. Chen conducted the statistical analyses on the data. All authors interpreted the data, provided

critical feedback on the manuscript, approved the final manuscript for submission, and are accountable for the accuracy and integrity of the manuscript.

Acknowledgments

This research was sponsored by Sanofi and Regeneron Pharmaceuticals Inc. (ClinicalTrials.gov Identifiers: NCT02612454 and NCT03346434). Medical writing/editorial assistance was provided by Alessandra Iannino, PhD, of Excerpta Medica, and was funded by Sanofi and Regeneron Pharmaceuticals Inc., according to the Good Publication Practice guidelines. The authors would like to thank the patients and their families for their participation, and publications managers Purvi Smith of Regeneron Pharmaceuticals Inc. and Adriana Mello of Sanofi for their input and support.

Consent

All patients, or their parents/guardians, provided written informed consent before participating in the trial. Pediatric patients provided assent according to the ethics committee (institutional review board/independent ethics committee)-approved standard practice for pediatric patients at each participating center.

Conflicts of Interest

Dr. Paller reported serving as an investigator, consultant, and/or data and safety monitoring board member for AbbVie, Abeona Therapeutics, Amryt Pharma, Azitra, BioCryst, BMS, Boehringer Ingelheim, Castle Creek Biosciences, Catawba Research, Dermavant, Eli Lilly, Galderma, Incyte, InMed Pharmaceuticals, Janssen, Krystal Biotech, LEO Pharma, Novartis, Regeneron Pharmaceuticals Inc., Sanofi, Seanergy, TWi Biotechnology, and UCB. Dr. Ramien reported serving as a consultant, speaker, and/or investigator for AbbVie, Eli Lilly, LEO Pharma, Pfizer, Regeneron Pharmaceuticals Inc., and Sanofi. Dr. Cork reported serving as an investigator and/or consultant for AbbVie, Astellas Pharma, Boots, Dermavant, Galapagos, Galderma, Hyphens Pharma, Johnson & Johnson, LEO Pharma, L'Oréal, Menlo Therapeutics, Novartis, Oxagen, Pfizer, Procter & Gamble, Reckitt Benckiser, Regeneron Pharmaceuticals Inc., and Sanofi. Dr. Simpson has received personal fees from AbbVie, Advances in Cosmetic and Medical Dermatology Hawaii, Amgen, AOBiome, Arcutis Biotherapeutics, Arena Pharmaceuticals, Aslan Pharmaceuticals, BMS, Boehringer Ingelheim, Boston Consulting Group, Collective Acumen, CorEvitas, Dermira, Eli Lilly, Evelo Biosciences, Evidera, Excerpta Medica, Forté Biosciences, Fraunhofer, Galderma, GSK, Incyte, Janssen, Johnson & Johnson, Kyowa Kirin, LEO Pharma, Maui Derm, Medscape, Merck, MJH Life Sciences, MLG Operating, Pfizer, Physicians World, PRImE, Regeneron Pharmaceuticals Inc., Revolutionizing Atopic Dermatitis, Roivant Sciences, Sanofi, Trevi Therapeutics, Valeant, Vindico Medical Education, and WebMD; and received grants from (or undertook a principal investigator role with) AbbVie, Amgen, Arcutis Biotherapeutics, Aslan Pharmaceuticals, Castle Creek Biosciences, CorEvitas, Dermavant, Dermira, Eli Lilly, Incyte, Kymab, Kyowa Kirin, National Jewish Health, LEO Pharma, Pfizer, Regeneron Pharmaceuticals Inc., Sanofi, and Target RWE. Dr. Wine Lee has acted as an advisory board member consultant, investigator, data and safety monitoring board member, and/or speaker for AbbVie, Amgen, Amryt Pharma, Arcutis Biotherapeutics, BMS, Castle Creek Biosciences, Celgene, Eli Lilly, Galderma, Incyte, Kimberly-Clark, Krystal Biotech, Mayne Pharma, Novartis, Pfizer, Pyramid Biosciences, Regeneron Pharmaceuticals Inc., Sanofi, Target Pharma, Trevi Therapeutics, and UCB. Dr. Eichenfield reported receiving honoraria for consulting services and/or research support from AbbVie, Amgen, Arcutis, Aslan Pharmaceuticals, Bausch, BMS, Castle Biosciences, Dermavant, Eli Lilly, Forté Pharma, Galderma, Incyte, Novartis, Otsuka, Pfizer, Regeneron Pharmaceuticals Inc., Sanofi, and UCB. Drs Khokhar, Chen, and Cyr are employees and shareholders of Regeneron Pharmaceuticals Inc. Drs Coleman, Gherardi, and Zhang are employees of and may hold stock and/or stock options in Sanofi.

Data Availability Statement

Qualified researchers may request access to study documents (including the clinical study report, study protocol with any amendments, blank case report form, statistical analysis plan) that support the methods and findings reported in this manuscript. Individual anonymized participant data will be considered for sharing 1) once the product and indication has been approved by major health authorities (e.g., FDA, EMA, PMDA, etc) or development of the product has been discontinued globally for all indications on or after April 2020 and there are no plans for future development, 2) if there is legal authority to share the data, and 3) there is not a reasonable likelihood of participant re-identification. Submit requests to https://vivli.org/.

References

1. P. O. Fiset, D. Y. M. Leung, and Q. Hamid, "Immunopathology of Atopic Dermatitis," *Journal of Allergy and Clinical Immunology* 118, no. 1 (2006): 287–290, https://doi.org/10.1016/j.jaci.2006.03.046.

2. S. Garcovich, M. Maurelli, P. Gisondi, K. Peris, G. Yosipovitch, and G. Girolomoni, "Pruritus as a Distinctive Feature of Type 2 Inflammation," *Vaccines* 9, no. 3 (2021): 303, https://doi.org/10.3390/vaccines9030303.

3. C. N. Ellis, A. J. Mancini, A. S. Paller, E. L. Simpson, and L. F. Eichenfield, "Understanding and Managing Atopic Dermatitis in Adult Patients," *Seminars in Cutaneous Medicine and Surgery* 31, no. 3 Suppl (2012): S18–S22, https://doi.org/10.1016/j.sder.2012.07.006.

4. J. I. Silverberg and N. B. Silverberg, "Childhood Atopic Dermatitis and Warts Are Associated With Increased Risk of Infection: A US Population-Based Study," *Journal of Allergy and Clinical Immunology* 133, no. 4 (2014): 1041–1047, https://doi.org/10.1016/j.jaci.2013.08.012.

5. P. Y. Ong and D. Y. M. Leung, "Bacterial and Viral Infections in Atopic Dermatitis: A Comprehensive Review," *Clinical Reviews in Allergy & Immunology* 51, no. 3 (2016): 329–337, https://doi.org/10.1007/s12016-016-8548-5.

6. E. L. Simpson, P. M. Schlievert, T. Yoshida, et al., "Rapid Reduction in *Staphylococcus aureus* in Atopic Dermatitis Subjects Following Dupilumab Treatment," *Journal of Allergy and Clinical Immunology* 152, no. 5 (2023): 1179–1195, https://doi.org/10.1016/j.jaci.2023.05.026.

7. A. Le Floc'h, J. Allinne, K. Nagashima, 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* 75, no. 5 (2020): 1188–1204, https://doi.org/10.1111/all.14151.

8. F. Annunziato, C. Romagnani, and S. Romagnani, "The 3 Major Types of Innate and Adaptive Cell-Mediated Effector Immunity," *Journal of Allergy and Clinical Immunology* 135, no. 3 (2015): 626–635, https://doi.org/10.1016/j.jaci.2014.11.001.

9. A. S. Paller, E. L. Simpson, E. C. Siegfried, et al., "Dupilumab in Children 6 Months to Younger Than 6 Years With Uncontrolled Atopic Dermatitis: A Randomised, Double-Blind, Placebo-Controlled Phase 3 Trial," *Lancet* 400, no. 10356 (2022): 908–919, https://doi.org/10.1016/S0140-6736(22)01539-2.

10. A. S. Paller, E. C. Siegfried, E. L. Simpson, et al., "Dupilumab Efficacy and Safety up to 1 Year in Children Aged 6 Months to 5 Years With Atopic Dermatitis: Results From a Phase 3 Open-Label Extension Study," *American Journal of Clinical Dermatology* 25 (2024): 655–668, https://doi.org/10.1007/s40257-024-00859-y.

11. A. S. Paller, E. C. Siegfried, M. J. Cork, et al., "Infections in Children Aged 6 Months to 5 Years Treated With Dupilumab in a Placebo-Controlled Clinical Trial of Moderate-To-Severe Atopic Dermatitis," *Pediatric Drugs* 26 (2024): 163–173, https://doi.org/10.1007/s40272-023-00611-9.

12. A. S. Paller, E. C. Siegfried, E. L. Simpson, et al., "A Phase 2, Open-Label Study of Single-Dose Dupilumab in Children Aged 6 Months to

< 6 Years With Severe Uncontrolled Atopic Dermatitis: Pharmacokinetics, Safety and Efficacy," *Journal of the European Academy of Dermatology and Venereology* 35, no. 2 (2021): 464–475, https://doi.org/10.1111/jdv.16928.

13. A. S. Paller, L. A. Beck, A. Blauvelt, et al., "Infections in Children and Adolescents Treated With Dupilumab in Pediatric Clinical Trials for Atopic Dermatitis – A Pooled Analysis of Trial Data," *Pediatric Dermatology* 39, no. 2 (2022): 187–196, https://doi.org/10.1111/pde.14909.

14. J. M. Leyva-Castillo, A. McGurk, M. Strakosha, et al., "IL-4 Receptor Alpha Blockade Dampens Allergic Inflammation and Upregulates IL-17A Expression to Promote *S aureus* Clearance in Antigen Sensitized Mouse Skin," *Journal of Allergy and Clinical Immunology* 152, no. 4 (2023): 907–915, https://doi.org/10.1016/j.jaci.2023.05.025.

15. E. Haddad, S. L. Cyr, K. Arima, R. A. McDonald, N. A. Levit, and F. O. Nestle, "Current and Emerging Strategies to Inhibit Type 2 Inflammation in Atopic Dermatitis," *Dermatology and Therapy (Heidelb)* 12, no. 7 (2022): 1501–1533, https://doi.org/10.1007/s13555-022-00737-7.

16. M. A. Adas, E. Alveyn, E. Cook, M. Dey, J. B. Galloway, and K. Bechman, "The Infection Risks of JAK Inhibition," *Expert Review of Clinical Immunology* 18, no. 3 (2022): 253–261, https://doi.org/10.1080/1744666X.2022.2014323.

17. M. C. Schneeweiss, L. Perez-Chada, and J. F. Merola, "Comparative Safety of Systemic Immunomodulatory Medications in Adults With Atopic Dermatitis," *Journal of the American Academy of Dermatology* 85, no. 2 (2021): 321–329, https://doi.org/10.1016/j.jaad.2019.05.073.

18. M. C. Schneeweiss, S. C. Kim, R. Wyss, S. Schneeweiss, and J. F. Merola, "Dupilumab and the Risk of Conjunctivitis and Serious Infections in Patients With Atopic Dermatitis: A Propensity Score-Matched Cohort Study," *Journal of the American Academy of Dermatology* 84, no. 2 (2021): 300–311, https://doi.org/10.1016/j.jaad.2020.09.084.

19. J. Hartmann, L. Moitinho-Silva, N. Sander, et al., "Dupilumab but Not Cyclosporine Treatment Shifts the Microbiome Toward a Healthy Skin Flora in Patients With Moderate-To-Severe Atopic Dermatitis," *Allergy* 78, no. 8 (2023): 2290–2300, https://doi.org/10.1111/all.15742.

20. L. F. Eichenfield, T. Bieber, L. A. Beck, et al., "Infections in Dupilumab Clinical Trials in Atopic Dermatitis: A Comprehensive Pooled Analysis," *American Journal of Clinical Dermatology* 20, no. 3 (2019): 443–456, https://doi.org/10.1007/s40257-019-00445-7.

Supporting Information

Additional supporting information can be found online in the Supporting Information section.