Dupilumab provides sustained effectiveness on patient-reported outcomes and favorable safety in patients with moderate-to-severe atopic dermatitis: Up to 5-year results from the daily practice BioDay registry

Junfen Zhang, MD,[a] Celeste M. Boesjes, MD,[b] Laura Loman, MD, PhD,[a] Esmé Kamphuis, MD,[a] Margreet L. E. Romeijn,[a] Lotte S. Spekhorst, MD,[b] Inge Haeck, MD, PhD,[c] Lian F. van der Gang, MD,[b] Coco C. Dekkers, MD,[b] Lisa P. van der Rijst, MD,[b] Albert J. Oosting, MD,[d] Paula van Lumig, MD, PhD,[e] Anneke M. T. van Lynden-van Nes, MD, PhD,[f] Ron A. Tupker, MD, PhD,[g] Annieke Nijssen, MD, PhD,[h] Annebeth Flinterman, MD, PhD,[i] Klaziena Politiek, MD, PhD,[j] Wouter R. H. Touwslager, MD,[k] Wianda A. Christoffers, MD, PhD,[l] Shiarra M. Stewart, MD,[m] Marijke Kamsteeg, MD, PhD,[n] Marlies de Graaf, MD, PhD,[b] Marjolein S. de Bruin-Weller, MD, PhD,[b] and Marie-Louise A. Schuttelaar, MD, PhD[a]

Background: Long-term daily practice data on patient-reported benefits of dupilumab for atopic dermatitis (AD) remains limited.

Objective: To evaluate patient-reported outcome measures (PROMs) and the safety of dupilumab in patients with moderate-to-severe AD over a follow-up period of up to 5 years.

Methods: Data were extracted from the prospective, multicenter BioDay registry (October 2017−2022) of patients with moderate-to-severe AD treated with dupilumab in daily practice.

Results: In total 1223 patients, 1108 adults and 115 pediatric patients were included. After ≥1 year of treatment, mean Patient-Oriented Eczema Measure (POEM), Dermatology Life Quality Index (DLQI),

From the Department of Dermatology, University Medical Center Groningen, Groningen, The Netherlands[a]; National Expertise Center for Atopic Dermatitis, Department of Dermatology and Allergology, University Medical Center Utrecht, Utrecht, The Netherlands[b]; Department of Dermatology, Reinier de Graaf Hospital, Delft, The Netherlands[c]; Department of Dermatology, Spaarne Gasthuis, Hoofddorp, The Netherlands[d]; Department of Dermatology, University Medical Center Maastricht, Maastricht, The Netherlands[e]; Department of Dermatology, Meander Medical Center, Amersfoort, The Netherlands[f]; Department of Dermatology, St Antonius Hospital, Nieuwegein, The Netherlands[g]; Department of Dermatology, Haga Hospital, Den Haag, The Netherlands[h]; Department of Dermatology, Diakonessenhuis, Utrecht, The Netherlands[i]; Department of Dermatology, Medical Center Leeuwarden, Leeuwarden, The Netherlands[j]; Department of Dermatology, Catharina Hospital, Eindhoven, The Netherlands[k]; Department of Dermatology, Isala Hospital, Zwolle, The Netherlands[l]; Department of Dermatology, IJsselland Hospital, Capelle aan den IJssel, The Netherlands[m]; and Department of Dermatology, Radboud University Medical Center, Nijmegen, The Netherlands.[n]

Authors Zhang and Boesjes share the first authorship.

Authors de Bruin-Weller and Schuttelaar share the last authorship.

Funding sources: Patients included in this manuscript participated in the BioDay registry sponsored by Sanofi, AbbVie, Eli Lilly and Company, Leo Pharma, and Pfizer. J.Z. is supported by the China Scholarship Council (CSC) Grant #201806200089.

Patient consent: Consent for the publication of recognizable patient photographs or other identifiable material was obtained by the authors and included at the time of article submission to the journal stating that all patients gave consent with the understanding that this information may be publicly available.

IRB approval status: Reviewed and approved by the Medical Research Ethics Committee of the University Medical Center Utrecht (reference number WAG/mb/18/011009).

Accepted for publication April 3, 2024.

Correspondence to: Marie-Louise A. Schuttelaar, MD, PhD, Dermatologist and Associate professor, Department of Dermatology, University Medical Center Groningen, PO Box 30 001, Groningen, 9700 RB, The Netherlands. E-mail: m.l.a.schuttelaar@umcg.nl.

Published online April 21, 2024.

0190-9622

https://doi.org/10.1016/j.jaad.2024.04.026

Numeric rating scale (NRS)-pruritus ranged between 7.8 and 8.7, 3.5 and 4.2, and 2.9 and 3.1 in adults, respectively, whilst these patient-reported outcome measures (PROMs) ranged between 8.9 and 10.9, 4.4 and 6.4, and 3.0 and 3.7 in pediatric patients, respectively. At follow-up, overall work impairment decreased from 40.1% to 16.3% to 13.3% in adults. Furthermore, class I obesity and itch-dominant patients generally had less favorable treatment response. Of all patients, 66.8% reported ≥1 adverse event, with conjunctivitis being the most common (33.7%).

Limitations: The overall percentage of missing values for selected PROMs was 26% in adults and 46% in pediatric patients.

Conclusion: In addition to favorable safety, dupilumab has demonstrated sustained effectiveness across various PROMs, underscoring the treatment benefits from patients' perspectives. (J Am Acad Dermatol 2024;91:300-11.)

Key words: atopic dermatitis; atopic eczema; daily practice; dupilumab; effectiveness; patient-reported outcomes; safety.

INTRODUCTION

The relapsing-remitting nature of atopic dermatitis (AD) necessitates appropriate treatment strategies, to ensure effective long-term management of the condition. Dupilumab, a fully human monoclonal IgG4 antibody inhibiting IL-4 and IL-13 signaling in the Th2 pathway, represents the first biologic approved for the treatment of patients with moderate-to-severe AD.[1] Previous placebo-controlled studies of up to 1 year[2] and open-label extension studies of up to 4 years[3,4] have demonstrated the long-term effectiveness and safety of dupilumab. However, clinical trial populations may not fully represent patients encountered in routine clinical practice due to the controlled conditions of trials. Daily practice data can bridge this gap; however, daily practice studies are only available up to 2 years of treatment[5-14] and most studies have focused on clinical outcomes. Relying solely on clinical measures may not adequately capture the comprehensive disease burden experienced by patients over time.

Therefore, by incorporating various patient-reported outcome measures (PROMs), we evaluated the real-life effectiveness of dupilumab in patients with moderate-to-severe AD during a follow-up of up to 5 years. Additionally, safety was assessed by adverse events (AEs).

CAPSULE SUMMARY

- Long-term daily practice data on patient-reported benefits of dupilumab for atopic dermatitis remain limited.
- In addition to favorable safety, dupilumab treatment has demonstrated sustained improvements in patient-reported measures of severity, symptoms, quality of life, overall well-being, and work productivity. However, some subpopulations, ie, baseline itch-dominant subset, and those with class I obesity, might exhibit a less favorable treatment response.

METHODS

Study design and population

This prospective, multicenter, observational cohort study was conducted within the Dutch BioDay registry, containing clinical and patient-reported data.[15] In this study, both adult and pediatric patients with moderate-to-severe AD treated with dupilumab between October 20th 2017, and September 30th 2022, were included. An outpatient visit was scheduled at baseline, after 4, 16, 28, and 52 weeks of treatment, followed every 3–6 months. Additional information regarding study design and population can be found in the Supplementary Material, available via Mendeley at https://data.mendeley.com/datasets/8bbwkw2xnd/1).

The BioDay registry was considered a noninterventional study by the local Medical Research Ethics Committee and was conducted according to the Declaration of Helsinki. All patients and if applicable caregivers provided written informed consent.

Outcome measures

A range of (proxy) PROMs, including the Patient-Oriented Eczema Measure (POEM),[16] Dermatology Life Quality Index (DLQI),[17,18] weekly average numeric rating scale (NRS) for pruritus[19] and pain,[20] Patient Global Assessment of Disease Status (PGADS),[21] Work Productivity and Activity Impairment

Abbreviations used:

AD:	atopic dermatitis
AEs:	adverse events
aOR:	adjusted odds ratio
BMI:	body mass index
DLQI:	dermatology life quality index
EASI:	eczema area and severity index
HND:	head and neck dermatitis
HR-QoL:	health-related quality of life
MI:	multiple imputation
MI-ML:	mild-moderate itch and mild-moderate lesions
NRS:	numeric rating scale
PGADS:	patient global assessment of disease status
POEM:	patient-oriented eczema measure
PROMs:	patient-reported outcome measures
PY:	patient-years
SI-ML:	severe itch and mild-moderate lesions
SI-SL:	severe itch and severe lesions
TCS:	topical corticosteroids

questionnaire general health,[22] sleep deprivation (yes/no) were employed in this study. Clinical severity was assessed using the Eczema Area and Severity Index (EASI)[23] and Investigator Global Assessment.[24]

Clinical phenotypes

As previously described,[25,26] AD severity was classified into 4 distinct clinical phenotypes based on the combination of NRS-pruritus≤4 and EASI≤21: mild-moderate itch and mild-moderate lesions (MI-ML), mild-moderate itch and severe lesions, severe itch and mild-moderate lesions (SI-ML), and severe itch and severe lesions (SI-SL).

Treatment response based on a combination of PROMs

Patients were identified as responders if they attained at least 2 of POEM≤7, NRS-pruritus≤4, and DLQI≤5, indicating well-controlled disease[27]; otherwise, they were identified as nonresponders. Moreover, patients who discontinued treatment due to insufficient effectiveness alone or a combination of insufficient effectiveness and side effects were also categorized as nonresponders.

Safety

AEs were reported during each visit and quantified in 2 ways: the rate of AEs per 100 patient-years (PY) and the proportion of patients who reported experiencing ≥1AE.

Statistical analysis

The pediatric population exhibited an overall percentage of missing values for selected PROMs of 45.9%. To address this issue and avoid bias and loss of statistical power, multiple imputation (MI) (n = 46) was employed,[28] with age, sex, EASI, concomitant systemic immunosuppressive treatment, and the presence of atopic comorbidities (ie, asthma, allergic rhinitis, allergic conjunctivitis, food allergy) used as predictors. Linear regression was utilized for continuous variables within the MI analysis. Notably, PROM data for the adult population (percent missing values of 26.0%) were analyzed without imputation to reflect the real-world data. Variables other than PROMs were analyzed without any imputation. To identify potential predictors of responders based on a combination of PROMs, binary logistic regression analysis was performed. The potential predictors included age, age of onset, sex, body mass index (BMI), use of systemic immunosuppressive treatment at baseline, history of systemic immunosuppressive treatment, presence of atopic comorbidities, investigator global assessment and EASI score at baseline, delta EASI (ie, EASI at week 4 − EASI at baseline), and baseline clinical phenotypes. A P-value of <.05 was considered statistically significant. Statistical analyses were performed using SPSS for Windows software (V 28.0; IBM SPSS).

RESULTS

Population

In total, 1223 patients were included at baseline analyses, comprising 1108 adults and 115 pediatric patients (mean age 38.5 years, 56.8% males, 2281 PY). The treatment duration extended up to 5 years in adults and 2.75 years in pediatric patients. Baseline characteristics are summarized in Supplementary Table I, available via Mendeley at https://data.mendeley.com/datasets/8bbwkw2xnd/1. As of the cutoff date for this analysis, 886 patients (72.4%) were receiving dupilumab, with 769 patients in the 1-year cohort and 2 in the 5-year cohort (Fig 1). After ≥1 year of treatment, up to 67.8% of patients had a prolonged dupilumab interval, primarily every 3 weeks or 4 weeks.

Long-term effectiveness on patient-reported outcomes

In adult patients, after ≥1 year of treatment, the mean scores for the POEM decreased from 19.9 to a range of 7.8−8.7, DLQI from 13.5 to 3.5−4.2, NRS-pruritus from 6.9 to 2.9−3.1, and NRS-pain from 4.1 to 0.9-1.2 (Table I, Fig 2, *A* and *B*). There was a progressive increase in the proportion of patients attaining POEM≤7, DLQI≤5, NRS-pruritus≤4, and NRS-pain≤4 after ≥1 year of treatment, reaching 44.2% to 55.4%, 73.3% to 79.3%, 74.7% to 77.8%, and 91.2% to 95.3%, respectively (Supplementary Fig 1, *A*

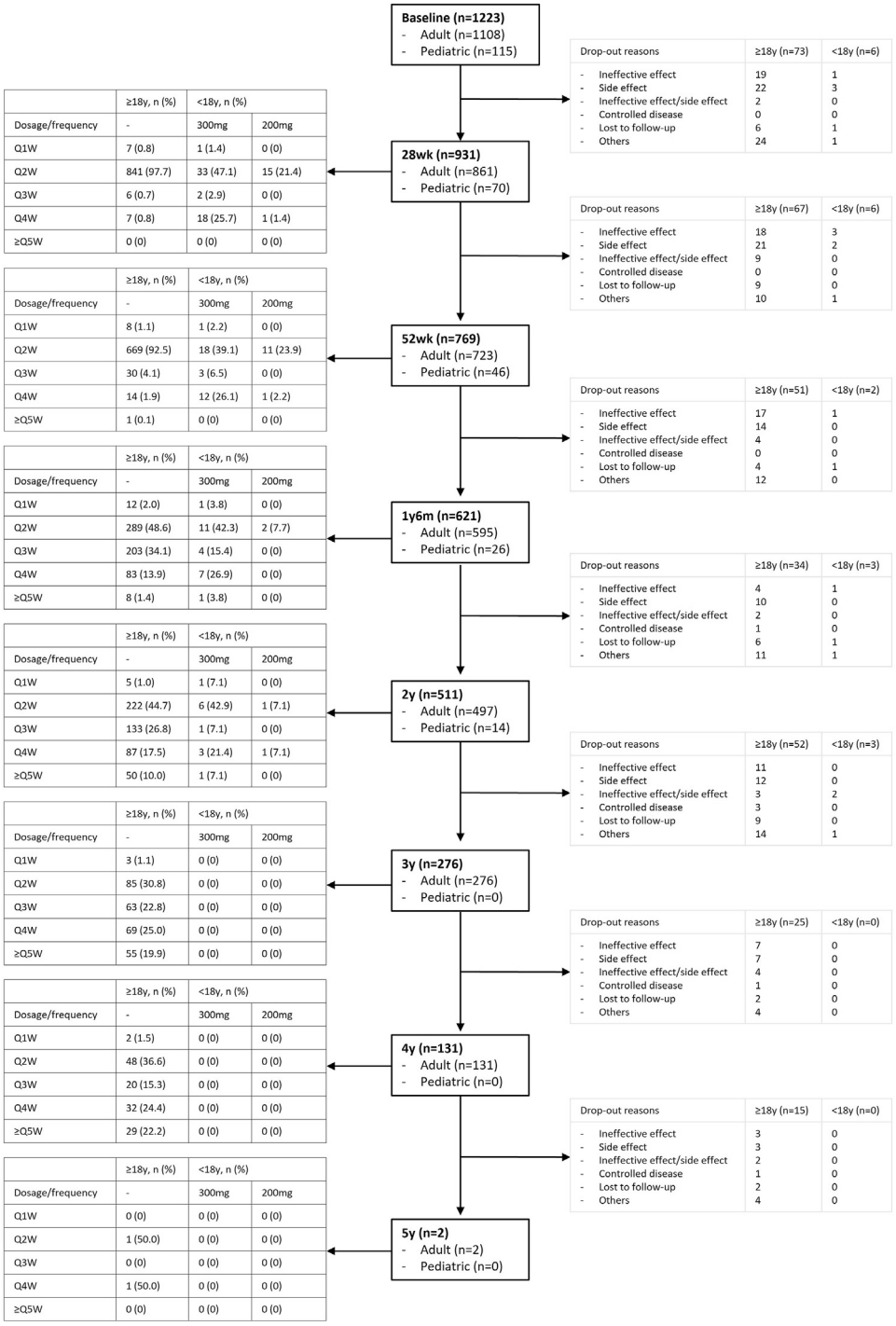


Fig 1. Flow chart of the included 1223 atopic dermatitis patients including dupilumab dosage and drop-out reasons. *mg*, Milligram; *n*, number; *Q1W*, every week; *wk*, week; *y*, year.

and *B*, available via Mendeley at https://data.mendeley.com/datasets/8bbwkw2xnd/1). At follow-up, 78.3% to 81.7% of patients rated their disease status (PGADS) as "good, very good, excellent", increasing from 23.2% at baseline. Reductions of ≥4-points in POEM, DLQI, and NRS-pruritus, and ≥2-points in NRS-pain, were achieved by 82% to 89.3%, 85.2% to 89.0%, 56.8% to 65.0%, and 82.4% to 87.8% of patients after ≥1 year of treatment, respectively (Supplementary Fig 2, *A* and *B*, available via Mendeley at https://data.mendeley.com/datasets/8bbwkw2xnd/1). Furthermore, 68.3% to 74.2% of

Table I. Long-term effectiveness based on the patient-reported outcome measures, and clinical phenotypes, stratified by the adult and pediatric cohort

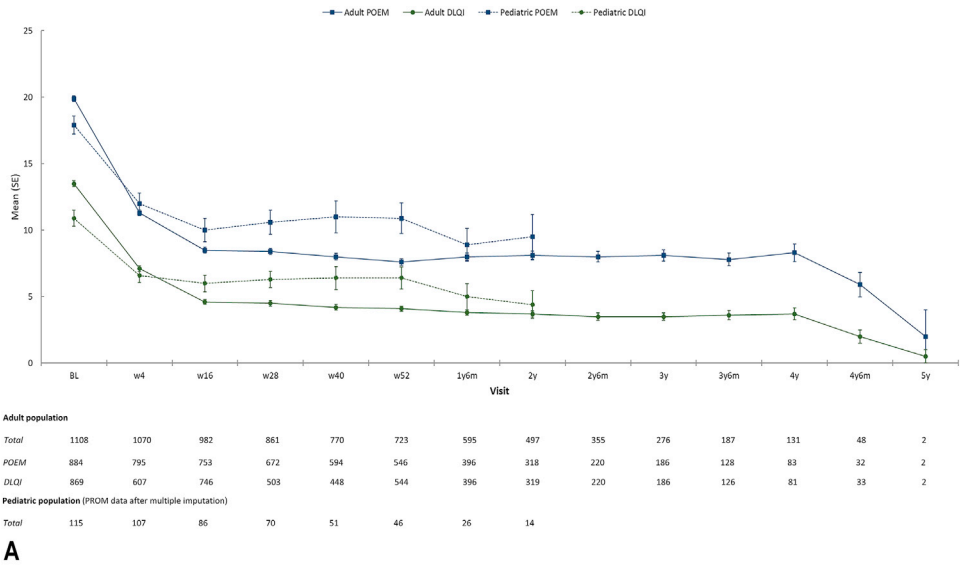
	Adult cohort*					Pediatric cohort†				
	BL (*N* = 1108) *N* (%)	1y (*N* = 723) *N* (%)	2y (*N* = 497) *N* (%)	3y (*N* = 276) *N* (%)	4y (*N* = 131) *N* (%)	BL (*N* = 115) *N* (%)	28 wk (*N* = 70) *N* (%)	1y (*N* = 46) *N* (%)	1y6m (*N* = 26) *N* (%)	2y (*N* = 14) *N* (%)
POEM score, mean (SD)	19.9 (6.0)	7.8 (5.7)	8.1 (5.9)	8.2 (6.0)	8.7 (6.2)	17.9 (7.3)	10.6 (7.6)	10.9 (7.8)	8.9 (6.3)	9.5 (6.3)
Missing, *n*	224	78	90	60	36					
POEM score of ≤7	36 (4.1)	354 (54.9)	210 (51.6)	118 (55.4)	42 (44.2)	8 (7.0)	22 (31.4)	14 (30.4)	11 (42.3)	4 (28.6)
ΔPOEM of ≥4 from BL (POEM≥4 at BL)	-	510 (89.3)	324 (87.1)	174 (86.6)	73 (82.0)	-	47 (72.3)	30 (69.8)	18 (72.0)	10 (76.9)
POEM item 1 (itch) = 0 (0 d)	127 (14.3)	442 (68.3)	283 (69.2)	158 (74.2)	68 (71.6)	5 (4.3)	10 (14.3)	8 (17.4)	7 (26.9)	6 (42.9)
POEM item 1 (itch) ≤1 (0-2d)	281 (31.7)	577 (89.2)	363 (88.8)	192 (90.1)	85 (89.5)	14 (12.2)	31 (44.3)	20 (43.5)	15 (57.7)	8 (57.1)
DLQI score, mean (SD)	13.5 (6.5)	4.2 (4.3)	3.7 (4.0)	3.5 (3.9)	3.8 (4.1)					
Missing, *n*	239	74	87	63	37	10.9 (6.3)	6.3 (5.2)	6.4 (5.6)	5.0 (5.0)	4.4 (3.9)
DLQI score of ≤5	98 (11.3)	476 (73.3)	313 (76.3)	169 (79.3)	73 (77.7)	17 (14.8)	33 (47.1)	21 (45.7)	15 (57.7)	9 (64.3)
ΔDLQI of ≥4 from BL (DLQI≥4 at BL)	-	455 (85.2)	309 (87.8)	168 (88.9)	73 (89.0)	-	38 (58.5)	23 (53.5)	16 (64.0)	9 (69.2)
Weekly average pruritus NRS, mean (SD)	6.9 (2.3)	2.9 (2.2)	3.1 (2.2)	2.9 (2.1)	2.9 (2.2)	6.2 (2.5)	3.8 (2.4)	3.7 (2.5)	3.1 (2.2)	3.0 (2.0)
Missing, *n*	158	59	58	18	5					
Weekly average pruritus NRS of ≤4	151 (15.9)	512 (77.1)	328 (74.7)	198 (76.7)	98 (77.8)	22 (19.1)	42 (60.0)	28 (60.9)	20 (76.9)	11 (78.6)
ΔPruritus NRS of ≥4 from BL (NRS-pruritus≥4 at BL)	-	334 (65.0)	192 (56.8)	127 (62.6)	67 (62.0)	-	23 (37.1)	14 (35.0)	9 (42.9)	4 (36.4)
≥2 of POEM≤7, DLQI≤5, and NRS-pruritus ≤4	53 (6.6)	444 (70.9)	278 (70.7)	169 (73.5)	64 (68.1)	13 (11.3)	33 (47.1)	23 (50.0)	17 (65.4)	8 (57.2)
Missing, *n*	307	97	104	46	37					
Weekly average pain NRS, mean (SD)	4.1 (3.1)	1.1 (1.8)	1.1 (1.9)	0.9 (1.6)	1.2 (1.9)	4.1 (3.1)	1.7 (2.0)	1.7 (2.2)	1.3 (2.0)	0.8 (1.5)
Missing, *n*	174	150	58	18	5					
Weekly average pain NRS of ≤4	388 (51.9)	524 (92.4)	396 (91.2)	246 (95.3)	115 (91.3)	62 (53.9)	62 (88.6)	41 (89.1)	24 (92.3)	14 (100)
ΔPain NRS of ≥2 from BL (NRS-pain≥2 at BL)	-	239 (87.2)	137 (84.0)	65 (87.8)	14 (82.4)	-	38 (73.1)	26 (74.3)	16 (80.0)	9 (90.0)
PGADS of ≥3 (good, very good, excellent)‡	173 (23.3)	479 (78.3)	320 (78.8)	174 (81.7)	79 (80.6)	33 (28.7)	30 (42.9)	21 (45.7)	10 (38.5)	8 (57.1)
Missing, *n*	225	79	91	63	33					

BL, Baseline; *DLQI*, dermatology life quality index; *N*, number; *NRS*, numeric rating scale; *PGADS*, patient global assessment of disease status; *POEM*, patient-oriented eczema measure; *SD*, standard deviation; *y*, year.

*For the adult cohort, if PROM data were missing at the year visit, PROM data from the closest visit (±3m) were used; if PROM data were available 3m before and after the year visit, randomly selected from one visit.

†For the pediatric cohort, PROM data after multiple imputation. Standard deviation was calculated as standard error or the mean (SEM) multiplied by $\sqrt{n}$.

‡PGADS was temporarily removed from the BioDay registry, roughly between December 2017 and August 2018.



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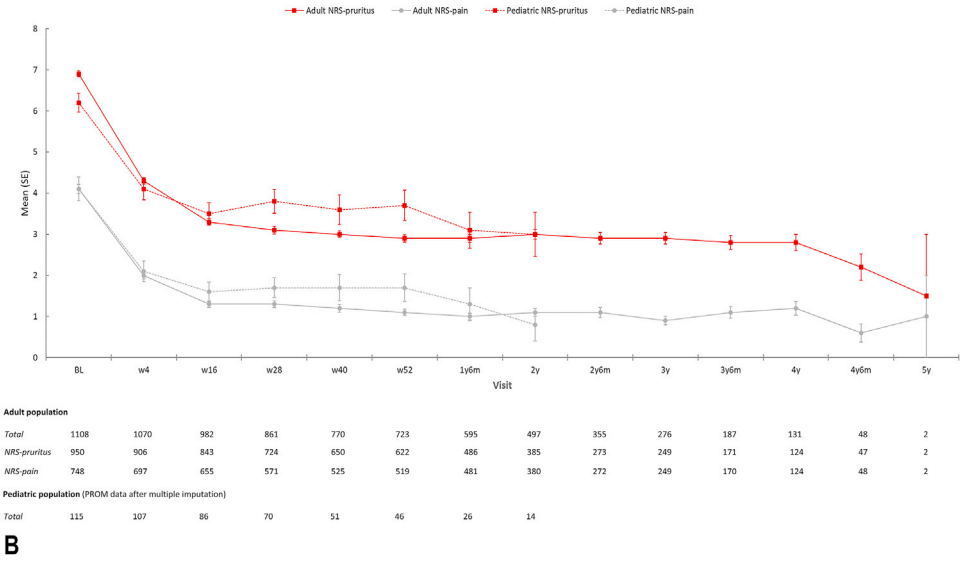

B

Fig 2. Mean score (SE) of patient-reported outcome measures during 5 years of dupilumab treatment, stratified by the adult and pediatric cohort. **A,** POEM and DLQI. **B,** NRS-pruritus and pain. *BL*, Baseline; *DLQI*, dermatology life quality index; *m*, month; *NRS*, numeric rating scale; *POEM*, patient-oriented eczema measure; *SE*, standard error; *w*, week; *y*, year.

patients reported experiencing "no days" of itching according to the individual POEM item (item 1), increasing from 14.3% at baseline. Regarding the Work Productivity and Activity Impairment questionnaire general health, patients reported a mean overall work impairment of 40.1% at baseline, significantly reducing to 13.3% to 16.3% (Supplementary Fig 3 available via Mendeley at https://data.mendeley.com/datasets/8bbwkw2xnd/1). Similar improvements were observed in activity impairment, absenteeism, and presenteeism.

In the pediatric cohort, after a follow-up duration of ≥1-year, mean scores for POEM decreased from 17.9 to a range of 8.9−10.9, DLQI from 10.9 to 4.4−6.4, NRS-pruritus from 6.2 to 3.0−3.7, and NRS-pain from 4.1 to 0.8−1.7. The proportion of patients achieving POEM≤7, DLQI≤5, NRS-pruritus≤4, and NRS-pain≤4 was 28.6% to 42.3%, 45.7% to 64.3%, 60.9% to 78.6%, and 89.1% to 100%, respectively. Among the pediatric patients, 38.5% to 57.1% rated their disease status (PGADS) as "good, very good, excellent". Improvements of ≥4-points in POEM, DLQI, and NRS-pruritus, and ≥2-points in NRS-pain, were achieved by 69.8% to 76.9%, 53.5% to 69.2%, 35.0% to 42.9%, and 74.3% to 90.0% of patients, respectively.

Concomitant treatment

At baseline, 85.5% of adults concomitantly used class III/IV topical corticosteroids (TCS), and 30.8% were treated with or in the washout of systemic treatment (Supplementary Table II, available via Mendeley at https://data.mendeley.com/datasets/8bbwkw2xnd/1). Following ≥1 year of treatment, this proportion decreased from 69.2% to 73.7% and 2.4% to 6.4%, respectively.

In the pediatric cohort, at baseline, 93.8% of patients received concurrent class III/IV TCS, mostly class III, whilst 25.4% were either using systemic treatment or undergoing systemic treatment washout. After ≥1 year of treatment, 53.9% to 68.9% still received concomitant class III/IV TCS, predominantly class III, and only 1 patient received concurrent systemic treatment, specifically methotrexate.

Clinical phenotypes

At baseline, the largest group was SI-ML, followed by SI-SL, and the smallest was MI-ML, despite age groups. After ≥1 year of treatment, most adults had MI-ML (74.6% to 77.4%), followed by SI-ML (22.2% to 24.5%). The distribution of clinical phenotypes in pediatric patients was similar compared to adults (Supplementary Fig 4, *A*, available via Mendeley at https://data.mendeley.com/datasets/8bbwkw2xnd/1).

Treatment response based on a combination of PROMs

After a treatment duration of ≥1 year, up to 73.5% of adults achieved ≥2 of POEM≤7, DLQI≤5, and NRS-pruritus≤4 (Table I). In the multivariate binary logistic regression analysis conducted at the 1-year mark (Supplementary Table III, available via Mendeley at https://data.mendeley.com/datasets/8bbwkw2xnd/1, model 2), females (adjusted odds ratio (aOR) 0.62, 95% CI 0.39-0.98) had a less favorable treatment response compared to males; adults with an early clinical response (ie, delta EASI at week 4 < 0) *versus* those without, exhibited a better treatment response (aOR 2.40, 95% CI 1.07-5.37). After additionally adjusting for clinical phenotypes at baseline (model 3), itch-dominant patients at baseline and those with class I obesity (BMI 30-34.99 kg/m^2) tended to have a less favorable treatment response (itch-dominant: aOR 0.44, 95% CI 0.20-0.96; class I obesity: aOR 0.47, 95% CI 0.23-0.97), whilst significant results did not remain in females.

Among pediatric patients, up to 65.4% achieved at least 2 of POEM≤7, DLQI≤5, and NRS-pruritus≤4, after ≥1 year of treatment. However, potential predictors were not examined due to the limited sample size.

Safety

In total, 1696 AEs were reported (74.4 events/100 PY), affecting 66.8% of patients (Table II). Compared to pediatric patients, adults generally reported AEs more often. Of the 1696 AEs, 122 cases (n = 122 (10%) patients, n = 94 solely due to AEs, n = 28 combined AEs/ineffectiveness) resulted in dupilumab discontinuation, and 124 (n = 78 (6.4%) patients) required dose adjustment. The most reported AE was conjunctivitis, affecting 35.2% of adults and 19.1% of pediatric patients. Among those affected, 69.7% of adults and 59.1% of pediatric patients had moderate-to-severe conjunctivitis, necessitating treatment with anti-inflammatory ophthalmic drugs. Specifically, 42 patients (3.4%) discontinued dupilumab due to dupilumab-associated conjunctivitis. Other common AEs included headache, fatigue, muscle or joint pain, alopecia/hair loss, injection site reaction, rosacea, and head and neck dermatitis (HND) (Table II/Supplementary Table V, available via Mendeley at https://data.mendeley.com/datasets/8bbwkw2xnd/1).

DISCUSSION

Main findings

In this large prospective study, although in many patients the dosage was tapered, significant and sustained improvement was observed in symptoms of itch and pain, health-related quality of life (HR-QoL), global disease status, and work/activity impairment outcomes for both adult and pediatric patients. After 1 year of treatment, early clinical responders exhibited better treatment response, while itch-dominant patients and those with class I obesity tended to have less favorable treatment response. At follow-up, clinical phenotypes distribution was similar in both cohorts, with the majority having MI-ML, followed by SI-ML. AEs were reported by 66.8% of patients, with conjunctivitis being the most common.

Long-term effectiveness

Our findings regarding the long-term effectiveness of dupilumab on patient-reported outcomes align with previous daily practice studies[6,8-11,13] that are comparable to a recent nationwide study conducted in Denmark,[11] ie, POEM, NRS-pruritus (mean/median of 6.0-8.7 and 2.0-3.1 at follow-up, respectively) and HR-QoL, ie, DLQI (mean/median of 2−4.2 during follow-up). Moreover, our study is in line with previous studies regarding significant reduction in work and activity impairment,[6,29] indicating potential economic implications for patients and society at large

Table II. Adverse events stratified by the adult and pediatric cohort

	No. event			No. event/100PY			Patients with individual adverse event, *n* (%)		
	Total	Adult	Pediatric	Total	Adult	Pediatric	Total	Adult	Pediatric
Total	1696	1619	77	74.4	74.5	72.6	817 (66.8)*	763 (68.9)*	54 (47.0)*
Death†	6	6	0	0.3	0.3	0	6 (0.5)	6 (0.5)	0 (0)
AEs leading to dupilumab discontinuation‡	122	115	7	5.3	5.3	6.6	122 (10.0)	115 (10.4)	7 (6.1)
AEs leading to dose Adjustment of dupilumab§	124	116	8	5.4	5.3	7.5	78 (6.4)	73 (6.6)	5 (4.4)
Ocular-related conditions									
Conjunctivitis (DAOSD)	499	475	24	21.9	21.8	22.6	**412 (33.7)**	**390 (35.2)**	**22 (19.1)**
Mild	147	138	9	6.4	6.3	8.8	**127 (10.4)**	**118 (10.6)**	**9 (7.8)**
Moderate-to-severe#	352	337	15	15.4	15.5	14.2	**285 (23.3)**	**272 (24.5)**	**13 (11.3)**
Keratitis (DAOSD)	11	11	0	0.5	0.5	0	8 (0.7)	8 (0.7)	0 (0)
Limbitis‖ (DAOSD)	24	23	1	1.1	1.1	0.9	22 (1.8)	21 (1.9)	1 (0.9)
Blepharitis and meibomian dysfunction	21	21	0	0.9	1.0	0	21 (1.7)	21 (1.9)	0 (0)
Uveitis	4	4	0	0.2	0.2	0	3 (0.2)	3 (0.3)	0 (0)
Cornea erosion/ulcer/ perforation	2	2	0	0.1	0.1	0	2 (0.2)	2 (0.2)	0 (0)
Skin-related conditions									
Alopecia/hair loss	61	57	4	2.7	2.6	3.8	**57 (4.7)**	**53 (4.8)**	**4 (3.5)**
Injection site reaction	52	49	3	2.3	2.3	2.8	50 (4.1)	47 (4.2)	3 (2.6)
Rosacea	48	47	1	2.1	2.2	0.9	44 (3.6)	43 (3.9)	1 (0.9)
Red face	18	16	2	0.8	0.7	1.9	18 (1.5)	16 (1.4)	2 (1.7)
Excessive sweating/ hyperhidrosis	13	13	0	0.6	0.6	0	11 (0.9)	11 (1.0)	0 (0)
Lymphoid reaction	6	6	0	0.3	0.3	0	5 (0.4)	5 (0.5)	0 (0)
Head and neck dermatitis	36	34	2	1.6	1.6	1.9	33 (2.7)	31 (2.8)	2 (1.7)
Gastrointestinal-related conditions									
Intestinal complaints	45	44	1	2.0	2.0	0.9	40 (3.3)	39 (3.5)	1 (0.9)
Nausea	15	13	2	0.7	0.6	1.9	14 (1.1)	12 (1.1)	2 (1.7)
Systemic hypersensitivity reaction	2	2	0	0.1	0.1	0	2 (0.2)	2 (0.2)	0 (0)
Diarrhea	8	6	2	0.4	0.3	1.9	7 (0.6)	5 (0.5)	2 (1.7)
Colitis ulcerosa	3	3	0	0.1	0.1	0	2 (0.2)	2 (0.2)	0 (0)

Continued

Table II. Cont'd

	No. event			No. event/100PY			Patients with individual adverse event, *n* (%)		
	Total	Adult	Pediatric	Total	Adult	Pediatric	Total	Adult	Pediatric
Crohn's disease	1	1	0	0.04	0.05	0	1 (0.1)	1 (0.1)	0 (0)
General conditions									
Headache	109	102	7	4.8	4.7	6.6	**93 (7.6)**	**86 (7.8)**	**7 (6.1)**
Fatigue	99	95	4	4.3	4.4	3.8	**88 (7.2)**	**84 (7.6)**	**4 (3.5)**
Weight gain	27	27	0	1.2	1.2	0	27 (2.2)	27 (2.4)	0 (0)
Malaise	12	12	0	0.5	0.6	0	12 (1.0)	12 (1.1)	0 (0)
Others									
Muscle or joint pain	97	95	2	4.3	4.4	1.9	**79 (6.5)**	**77 (6.9)**	**2 (1.7)**
Herpes simplex	35	35	0	1.5	1.6	0	31 (2.5)	31 (2.8)	0 (0)
Herpes zoster	10	9	1	0.4	0.4	0.9	10 (0.8)	9 (0.8)	1 (0.9)
Nasopharyngitis	3	3	0	0.1	0.1	0	3 (0.2)	3 (0.3)	0 (0)
Rheumatoid arthritis	1	1	0	0.04	0.05	0	1 (0.1)	1 (0.1)	0 (0)
Adrenal insufficiency	4	4	0	0.2	0.2	0	4 (0.3)	4 (0.4)	0 (0)
Blood eosinophilia[¶]	-	-	-	-	-	-			
Baseline, *n* (%)							414 (39.0)	355 (36.7)	59 (62.8)
Missing, *n*							162	141	21
28 wk, *n* (%)							317 (44.1)	279 (42.0)	38 (69.1)
Missing, *n*							212	197	15
1y, *n* (%)							222 (35.6)	199 (34.0)	23 (60.5)
Missing, *n*							146	138	8
1y6m, *n* (%)							119 (28.2)	108 (26.8)	11 (57.9)
Missing, *n*							199	192	7
2y, *n* (%)							108 (30.7)	99 (29.0)	9 (81.8)
Missing, *n*							159	156	3
3y, *n* (%)							43 (20.5)	43 (20.5)	-
Missing, *n*							66	66	
4y, *n* (%)							20 (19.4)	20 (19.4)	-
Missing, *n*							28	28	

Bold values indicates the most common adverse events.

AE, Adverse event; *DAOSD*, dupilumab-associated ocular surface disease; *L*, liter; *No.*, number; *PY*, patient-year; *y*, year.

*Patients who reported adverse events at least once during dupilumab treatment despite the types of adverse event.

[†]Six deaths were caused by myocardial infarction/heart failure, COVID-19 infection, COVID-19 infection with pancolitis, progressive amyotrophic lateral sclerosis, lung cancer, and euthanasia, respectively.

[‡]Discontinuation due to AEs solely (n = 94) or a combination of AEs and ineffectiveness (n = 28).

[§]Dose adjustment including increased, decreased, and interrupted.

[‖]Have been diagnosed/examined by an ophthalmologist.

[¶]Blood eosinophilia: <12y: $\geq 0.6 \times 10^9$/L; 12-17y: $\geq 0.4 \times 10^9$/L; ≥18y: $\geq 0.45 \times 10^9$/L.

[#]Moderate-to-severe conjunctivitis was defined as being treated with an anti-inflammatory ophthalmic drug.

because of dupilumab treatment. However, our results indicate a relatively lower disease control in pediatric patients after ≥1 year of treatment, as measured by NRS-pruritus (mean of 1.3−2.3 at 1-year follow-up) and DLQI (mean of 1.8 at 1-year follow-up), compared to previous studies in Italian adolescents aged ≥12 years.[8,9] This difference may be influenced by the relatively high amount of missing data (although covered by MI) and the inclusion of children (<12 years) in our pediatric cohort analysis.

Clinical phenotypes

Chovatiya et al[25,26] introduced a definition of AD subsets based on a combination of itch and lesional severity, recognizing that relying on either measure alone is insufficient to fully represent AD severity and phenotypes. Our results showed that approximately one-quarter of the population still belonged to the itch-dominant subset (SI-ML) after 1 year of treatment, exhibiting a significant impairment in HR-QoL and mental health, similar to those with severe lesions (ie, mild-moderate itch and severe lesions, SI-SL).[25] Itch-dominant patients may be overlooked due to milder skin lesions. Some may argue that the cutoff point of EASI≤21 is too high, thus we also employed EASI≤7. Nevertheless, we found quite similar results (Supplementary Fig 4, *B*, available via Mendeley at https://data.mendeley.com/datasets/8bbwkw2xnd/1), highlighting the importance of addressing both itch and lesional severity in treatment decision-making.

Treatment response based on a combination of PROMs

In this study, itch-dominant patients at baseline and those with class I obesity tended to have a less favorable treatment response, as measured by a combination of PROMs. Notably, the association between adult females and a less favorable treatment response, though initially significant, did not persist after additional adjustment for the baseline clinical phenotype. This could be attributed to the higher prevalence of itch-dominant AD among females in our results (Supplementary Table IV, available via Mendeley at https://data.mendeley.com/datasets/8bbwkw2xnd/1), consistent with findings by Chovatiya et al.[25,26] Previous studies and the current study based on clinical parameters (ie, EASI-75/90) yield conflicting results, with females exhibiting better treatment response, albeit without considering the itch-dominant phenotype.[9,30,31] Such discrepancy may stem from differences between patient-reported and physician-reported outcomes. The significant finding of patients with class I obesity exhibiting a less favorable treatment response needs further exploration as no significant *P*-values were found for class II/III obesity, which could be related to the sample size of this group, as several real-life studies reported on a negative correlation between treatment response and BMI.[32,33] Furthermore, we found that adults with early clinical response had a better treatment response compared to those without, which aligns with a previous study conducted by the BioDay registry.[34]

Safety

During follow-ups, a higher proportion of patients (66.8%) in our study reported ≥1 AE, compared to previous long-term daily practice studies (30% to 61%).[11,13,14] Consistent with previous research, we found that the most commonly reported AE was conjunctivitis, while the proportion of those affected (33.7%) is higher than the 25% reported in Danish and Italian adult populations.[11,35] Notably, despite the different proportions of adults and pediatric patients reporting conjunctivitis,[36] the development of conjunctivitis was quite similar when adjusted for patient-years, indicating the found disparities possibly due to different treatment durations between the groups. Moreover, a markedly higher proportion of patients with conjunctivitis in our study were classified as moderate-to-severe (69.2%) compared to previous studies.[11,35] This discrepancy may be attributed to heterogeneity in AE reporting patterns, treatment duration, easy access to ophthalmologists in the Netherlands, and diagnostic criteria used. Early recognition and treatment of dupilumab-associated ocular surface disease has shown to improve ocular inflammation during dupilumab treatment.[37] The rate of patients (2.7%) reporting HND in our study is lower than what has been reported in previous case series.[38,39] Moreover, when dupilumab is administered for other medical indications than AD, the occurrence of HND and conjunctivitis is lower.[40-42]

Strengths and limitations

This prospective, multicenter study expands on existing daily practice studies by incorporating a wide range of (proxy) PROMs in both adult and pediatric populations, and by extending the observational period up to 5 years. A limitation of the study is the amount of missing data on (proxy) PROMs in the pediatric cohort, which was addressed through multiple imputation. Another is the inclusion of merely 2 adults within the 5-year cohort. Additionally, patients with better treatment effectiveness may be more inclined to continue treatment, thereby introducing a potential bias toward favorable outcomes. Also, a subset of patients received

concomitant systemic treatment at baseline, possibly affecting the observed results. Lastly, this is a Dutch registry, possibly limiting its generalizability.

CONCLUSIONS

In addition to a favorable safety profile, dupilumab has shown rapid and sustained effectiveness in improving various aspects of patient-reported outcomes in both adult and pediatric populations in a long follow-up duration. This highlights the treatment benefits of dupilumab from patients' perspectives. However, itch-dominant patients, and those with class I obesity may experience less disease control during treatment, suggesting the need for future studies to identify optimal treatment approaches for these specific subgroups, such as exploring more effective treatment regimens and novel therapeutic options.

Conflicts of interest

C.M. Boesjes is a speaker for AbbVie and Eli Lilly. L.S. Spekhorst is a speaker for AbbVie. I.M. Haeck is a consultant, advisory board member, and/or speaker for Sanofi and Regeneron Pharmaceuticals, LEO Pharma, AbbVie, Janssen, and Eli Lilly. L.F. van der Gang is a speaker for AbbVie. L.P. van der Rijst is a speaker for AbbVie. R.A. Tupker is an advisory board member of Leo Pharma, Eli Lilly, and Novartis. K.Politiek was an advisory board member and/or speaker for AbbVie, LEO Pharma, Novartis, and Sanofi. W. Touwslager is an advisor, consultant, and speaker for Sanofi, Leo Pharma, AbbVie, and Novartis. WA Christoffers is an advisory board member of Leo Pharma. M. de Graaf is a consultant, advisory board member, and/or speaker for AbbVie, Almiral, Eli Lilly, Janssen, LEO Pharma, Novartis, Pfizer, Regeneron Pharmaceuticals, and Sanofi. M.S. de Bruin-Weller is a consultant, advisory board member, and/or speaker for AbbVie, Almirall, Aslan, Amgen, Eli Lilly, Galderma, Janssen, Leo Pharma, Pfizer, Regeneron, and Sanofi. M.L.A. Schuttelaar is an advisor, consultant, speaker, and/or investigator for AbbVie, Pfizer, LEO Pharma, Regeneron, Sanofi, Eli Lilly, and Galderma. She has received grants from Regeneron, Sanofi, Novartis, and Pfizer.

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