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# Dupilumab shows long-term effectiveness in a large cohort of treatment-refractory atopic dermatitis patients in daily practice: 52-Week results from the Dutch BioDay registry



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**Background:** Real-life data on long-term effectiveness and safety of dupilumab in atopic dermatitis patients are limited.

**Objective:** To study 52-week effectiveness and safety of dupilumab in a prospective multicenter cohort of adult patients with treatment-refractory atopic dermatitis.

**Methods:** Patients treated with dupilumab and participating in the Dutch BioDay registry were included. Clinical effectiveness and safety were evaluated.

**Results:** Two hundred ten atopic dermatitis patients were included. Mean percentage change in Eczema Area and Severity Index score after 16 weeks was  $-70.0\%$  (standard deviation  $33.2\%$ ) and further decreased to  $-76.6\%$  (standard deviation  $30.6\%$ ) by week 52. A greater than or equal to 75% improvement in the score was achieved by 59.9% of individuals by week 16 and by 70.3% by week 52. The most reported adverse effect was conjunctivitis (34%). Limited patients (17; 8.1%) discontinued dupilumab treatment.

**Limitations:** Because of the lack of a control group and observational design, factors of bias may have been induced.

**Conclusion:** Treatment with dupilumab resulted in a rapid improvement in clinical outcome measures, and effectiveness further improved during the 52-week follow-up period. (J Am Acad Dermatol 2021;84:1000-9.)

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Drs Ariëns, van der Schaft, Schuttelaar, and de Bruin-Weller contributed equally to this article.

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Kouwenhoven, Kamsteeg, Voorberg, Oosting, Haeck, and Thijs and Authors Romeijn, Ridder, and Sloeserwijn have no conflicts of interest to declare.

IRB approval status: The BioDay registry was considered non-interventional by the local medical ethics committee and collection of data was performed according to the Helsinki Declaration.

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**Key words:** atopic dermatitis; daily practice; disease severity; dupilumab; effectiveness; long-term; safety.

## INTRODUCTION

Dupilumab, a fully monoclonal antibody that targets the shared receptor component for interleukin (IL) 4 and IL-13, is the first biologic approved for the treatment of patients with moderate to severe atopic dermatitis. In phase 3 clinical trials including patients with moderate to severe atopic dermatitis, dupilumab with or without concomitant topical corticosteroids significantly improved disease severity and health-related quality of life until 16 and 52 weeks.<sup>1-4</sup> The most recent phase 3 open-label extension study showed that dupilumab treatment was effective and well tolerated up to 76 weeks.<sup>5</sup>

Data derived from daily practice provide important information, in addition to data from clinical trials, because there may be considerable differences in patient population and treatment conditions. Results from dupilumab treatment in daily practice show clinically relevant improvement of physician-reported outcome measures and patient-reported outcome measures after 3 to 6 months, which is in line with data from clinical trials.<sup>6-8</sup> The proportion of patients developing conjunctivitis during dupilumab treatment was higher in daily practice (34%-38%) compared with that in previous phase 3 clinical trials (9%-28%).<sup>1-3,6-8</sup> However, real-life data on the long-term effectiveness and safety of dupilumab treatment are limited and prospective large cohort studies are scarce.<sup>9,10</sup>

In this prospective real-life registry study, 52-week effectiveness and safety of dupilumab were studied in a multicenter cohort of adult patients with treatment-refractory atopic dermatitis.

## METHODS

### Study design

This prospective, multicenter, observational, longitudinal cohort study consecutively included all adult patients who started dupilumab for treatment-refractory atopic dermatitis, according to the criteria established by the Dutch Society of Dermatology and Venereology (treatment  $\geq 4$  months with  $\geq 1$  conventional systemic therapy in an adequate dose), from October 2017 to September 2018. These patients participated in the Dutch BioDay registry.<sup>8</sup> At baseline, all patients received a loading dose of

dupilumab 600 mg subcutaneously, followed by dupilumab 300 mg every other week. Interval adjustment was allowed in case of severe adverse effects or insufficient response. If possible, systemic immunosuppressive treatment was discontinued before the start of dupilumab treatment. The BioDay registry was considered noninterventional by the local medical ethics committee and collection of data was performed according to the Helsinki Declaration. All patients provided written informed consent.

### Patients and outcome measures

Patient characteristics were extracted from the BioDay registry. All patients were assessed at baseline until 52 weeks of treatment. Disease severity was assessed at baseline and after 4, 16, 28, 40, and 52 weeks (maximal visit window 4 weeks) of treatment by the Eczema Area and Severity Index (EASI) (range 0-72) and serum thymus and activation-regulated chemokine levels.<sup>11,12</sup> Patient-reported outcomes, including scores for the Patient-Oriented Eczema Measure (range 0-28), weekly average numeric rating scale (NRS) (range 0-10) for pruritus, Dermatology Life Quality Index (range 0-30), and generic 5-dimension 5-level EuroQoL scale (range 0-5 for each dimension), were collected.<sup>13-16</sup> To study longitudinal improvement and course of individual patients, the proportion of patients achieving absolute cutoff scores indicating controlled disease (EASI score  $\leq 7$  and NRS score  $\leq 4$ ) (weeks 16, 28, 40, and 52) and relative changes over time ( $\geq 50\%$  improvement in EASI score,  $\geq 75\%$  improvement in EASI score, and NRS score  $\geq 4$  points improvement from baseline) at 0 of 4 follow-up visits; greater than or equal to 1 of 4, 2 of 4, and 3 of 4 follow-up visits; and 4 of 4 follow-up visits were analyzed. Patients with baseline EASI score less than 7 and NRS score less than 4 were excluded from these analyses.

### Safety

Patients were asked about adverse effects and medication use during every visit. Ocular adverse effects and ocular medication use were assessed by standardized questionnaires during every visit, and included severity of redness, itching, tearing, pain, photophobia, burning sensation, and blepharitis of

## CAPSULE SUMMARY

- Prospective, real-life data on long-term effectiveness and safety of dupilumab in atopic dermatitis patients are limited.
- This study shows that treatment with dupilumab in daily practice shows a rapid improvement in clinical outcomes measures, and effectiveness sustains or further improves during long-term (52-week) treatment.

*Abbreviations used:*

EASI:	Eczema Area and Severity Index
IL:	interleukin
IQR:	interquartile range
LIBERTY AD CHRONOS:	Long-term management of moderate-to-severe atopic dermatitis with dupilumab and concomitant topical corticosteroids
NRS:	numeric rating scale

the eyes. In case of conjunctivitis with insufficient response to artificial tears, topical tacrolimus skin ointment on the eyelids, or both, patients were referred to an ophthalmologist for standardized examination and ophthalmologic follow-up. Laboratory parameters were monitored.

### Statistical analysis

Clinical outcome measures were compared with the Wilcoxon signed rank test. Missing data for patients who discontinued treatment during follow-up were imputed by the last observation carried forward method. Statistical analyses were conducted with SPSS (version 25.0, SPSS Inc) and Prism (version 7.4, GraphPad).

## RESULTS

### Population

Two hundred ten patients with moderate to severe atopic dermatitis were included (mean age 43.2 years [standard deviation 15.5 years]; 61.4% men). The majority of patients had been previously treated with oral immunosuppressive drugs (n = 208; 99.0%) (Table I). Two patients did not use prior oral immunosuppressive drugs because of contraindications. Treatment with oral immunosuppressive drugs (excluding systemic corticosteroids) was discontinued in almost all patients before the start of dupilumab treatment (99.5%). One patient was concomitantly treated with methotrexate (indication rheumatoid arthritis).

### Effectiveness of dupilumab treatment

Mean EASI score significantly improved from baseline (19.0; interquartile range [IQR] 12.6–27.7) to week 16 (3.6; IQR 1.8–7.2;  $P < .001$ ) and week 52 (2.7; IQR 1.4–5.4;  $P < .001$ ). Mean percentage change in EASI from baseline to week 16 was  $-70.0\%$  (standard deviation 33.2%) and further improved to  $-76.6\%$  (standard deviation 30.6%) in week 52 (Table II). The proportion of patients achieving greater than or equal to 50%, 75%, and 90% improvement in EASI score was 84.2% (n = 170), 58.9%

**Table I.** Baseline characteristics

Baseline characteristics	Total group (n = 210)
Age, mean (SD), y	43.2 (15.5)
Men, no. (%)	129 (61.4)
Atopic/allergic diseases at baseline, no. (%)	
Allergic rhinitis	145 (69.0)
Missing	4 (1.9)
Asthma	124 (59.0)
Missing	4 (1.9)
Food allergy	101 (48.1)
Missing	4 (1.9)
Allergic conjunctivitis	125 (59.5)
Missing	5 (2.4)
EASI score, median (IQR)	19.0 (12.6–27.7)
IGA score, median (IQR)	3 (3.0–4.0)
Weekly average pruritus NRS score, median (IQR)	7 (6.0–8.0)
POEM score, median (IQR)	20 (16.0–23.5)
DLQI score, median (IQR)	12 (8.0–18.0)
Previous use of oral immunosuppressive drugs for atopic dermatitis,* no. (%)	208 (99.0)
History of $\leq 1$ oral immunosuppressive drug, no. (%)	100 (47.6)
History of $\geq 2$ oral immunosuppressive drugs, no. (%)	110 (52.4)
Previous use of cyclosporine, no. (%)	201 (95.7)
Previous use of methotrexate, no. (%)	70 (33.3)
Previous use of azathioprine, no. (%)	59 (28.0)
Previous use of mycophenolate mofetil/enteric-coated mycophenolate sodium, no. (%)	48 (22.9)
Use of oral corticosteroids at start of dupilumab, no. (%)	53 (25.2)

DLQI, Dermatology Life Quality Index; EASI, Eczema Area and Severity Index; IGA, Investigator Global Assessment; IQR, interquartile range; no, number; NRS, numeric rating scale; POEM, Patient-Oriented Eczema Measure; SD, standard deviation. \*Treatment with oral immunosuppressive drugs for greater than or equal to 4 months.

(n = 119), and 21.9% (n = 46), respectively, at week 16 and 90.1% (n = 182), 70.3% (n = 142), and 34.7% (n = 70), respectively, at week 52 (Fig 1). Median serum thymus and activation-regulated chemokine levels significantly decreased from baseline (2231.0 pg/mL; IQR 810.0–4747.0 pg/mL) to week 16 (439.0 pg/mL; IQR 241.5–766.0 pg/mL;  $P < .001$ ) and week 52 (360.0 pg/mL; IQR 226.0–559.5 pg/mL;  $P < .001$ ).

Weekly average NRS pruritus score significantly decreased from baseline (median 7.0; IQR 6.0–8.0) to week 16 (3.0; IQR 1.3–4.0;  $P < .001$ ) and week 52

**Table II.** Effectiveness outcomes during dupilumab treatment in 210 patients

	Baseline	Week 4	Week 16	Week 28	Week 40	Week 52
EASI score, median (IQR)	19 (12.6 to 27.7)	7.5 (4.8 to 12.4)*	3.6 (1.8 to 7.2)*	3.4 (1.6 to 6.4)*	2.7 (1.2 to 6.2)*	2.7 (1.4 to 5.4)*
Missing	4 (1.9)	2 (1.0)	5 (2.4)	5 (2.4)	11 (5.2)	3 (1.4)
ΔEASI % from baseline, mean (±SD)	—	−48.9 (37.4)	−70.0 (33.2)	−72.5 (33.0)	−75.0 (33.4)	−76.6 (30.6)
EASI-50, no. (%)	—	125 (61.3)	170 (84.2)	175 (87.1)	173 (89.2)	182 (90.1)
Missing	—	6 (2.9)	8 (3.8)	9 (4.3)	16 (7.6)	8 (3.8)
EASI-75, no. (%)	—	42 (20.6)	119 (58.9)	131 (65.2)	132 (68.0)	142 (70.3)
Missing	—	6 (2.9)	8 (3.8)	9 (4.3)	16 (7.6)	8 (3.8)
EASI-90, no. (%)	—	6 (2.9)	46 (21.9)	61 (30.3)	72 (37.1)	70 (34.7)
Missing	—	6 (2.9)	8 (3.8)	9 (4.3)	16 (7.6)	8 (3.8)
Proportion of patients with EASI score ≤7, no. (%)	15 (7.3)	92 (44.2)	151 (73.3)	157 (76.6)	161 (81.3)	167 (81.1)
Missing	4 (1.9)	2 (1.0)	4 (1.9)	5 (2.4)	12 (5.7)	4 (1.9)
Serum TARC levels, median (IQR)	2231.0 (810.0 to 4747.0)	652.0 (374.5 to 1164.5)*	439.0 (241.5 to 766.0)*	389.0 (256.5 to 681.5)*	410.0 (252.5 to 559.0)*	360.0 (226.0 to 559.5)*
Weekly average pruritus NRS score, median (IQR)	7.0 (6.0 to 8.0)	4.0 (2.0 to 6.0)*	3.0 (1.3 to 4.0)*	3.0 (1.0 to 4.0)*	3.0 (1.0 to 5.0)*	2.0 (1.0 to 5.0)*
Missing	8 (3.8)	7 (3.3)	6 (2.9)	7 (3.3)	16 (7.6)	9 (4.3)
Weekly average pruritus NRS score, proportion of patients who achieved improvement (reduction) ≥4 points from baseline, no. (%) (n = 185)	—	75 (41.2)	109 (60.2)	109 (60.9)	107 (61.8)	110 (62.1)
Missing	—	3 (1.6)	4 (2.2)	6 (3.2)	12 (6.5)	8 (4.3)
Proportion of patients with NRS score ≤4, no. (%)	31 (15.3)	118 (58.1)	146 (71.6)	154 (76.2)	142 (74.3)	148 (75.5)
Missing	8 (3.8)	7 (3.3)	6 (2.9)	8 (3.8)	19 (9)	14 (6.7)
DLQI score, median (IQR)	12.0 (8.0 to 18.0)	—	3.0 (1.0 to 6.0)*	—	—	3.0 (2.0 to 5.0)*
Missing	10 (4.8)	—	8 (3.8)	—	—	24 (11.4)
Proportion of patients with ≥4-point improvement in DLQI score, no. (%) (n = 186)	—	—	155 (84.7)	—	—	145 (86.8)
Missing	—	—	3 (1.6)	—	—	19 (10.2)
Proportion of patients with DLQI score ≤5, no. (%)	28 (14.0)	—	152 (75.2)	—	—	189 (97.4)

Continued

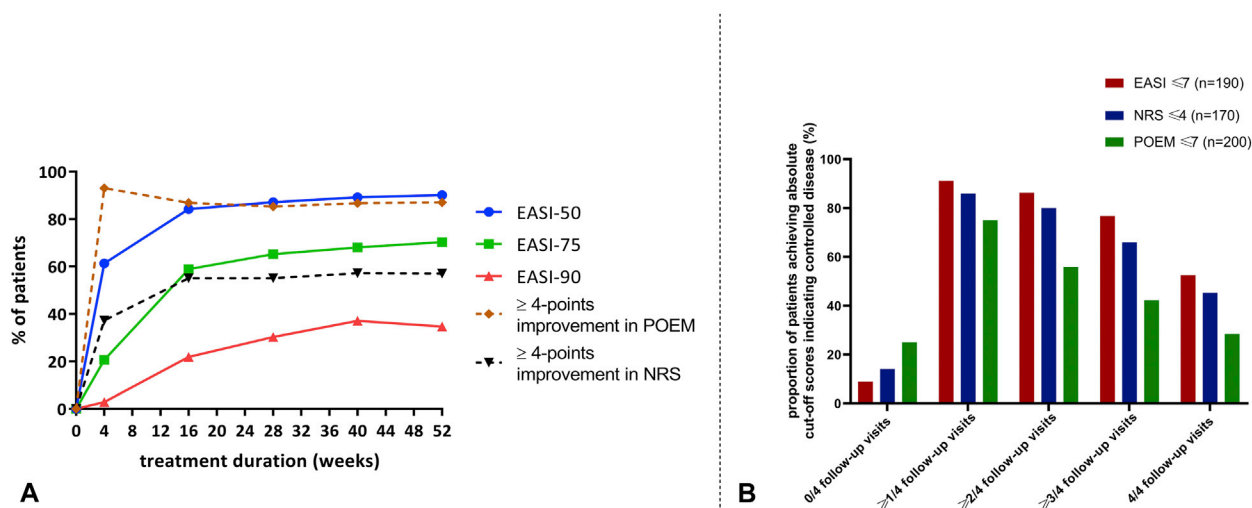
Table II. Cont'd

	Baseline	Week 4	Week 16	Week 28	Week 40	Week 52
Missing	10 (4.8)		8 (3.8)			16 (7.6)
POEM score, median (IQR)	20.0 (16.0 to 23.5)	7.0 (4.0 to 11.0)*	7.0 (3.0 to 11.0)*	6.0 (2.8 to 11.0)*	6.0 (2.8 to 11.0)*	6.0 (3.0 to 11.0)*
Missing	9 (4.3)	19 (9.0)	12 (5.7)	12 (5.7)	24 (11.4)	18 (8.6)
Proportion of patients with ≥4-point improvement in POEM score, no. (%) (n = 200)	—	173 (93.5)	166 (87.4)	163 (85.8)	156 (87.2)	161 (87.5)
Missing		15 (7.5)	10 (5.0)	10 (5.0)	21 (10.5)	16 (8.0)
ΔPOEM item 1 (itch) from baseline, mean (±SD)	—	−1.5 (1.4)	−1.8 (1.5)	−1.9 (1.5)	−1.9 (1.5)	−1.9 (1.5)
ΔPOEM item 2 (sleep) from baseline, mean (±SD)	—	−1.5 (1.5)	−1.8 (1.6)	−1.8 (1.6)	−1.8 (1.5)	−1.9 (1.6)
Proportion of patients with POEM score ≤7, no. (%)	7 (3.5)	108 (56.5)	99 (50.0)	110 (55.6)	99 (53.5)	111 (57.5)
Missing	9 (4.3)	19 (9.0)	12 (5.7)	12 (5.7)	25 (11.9)	17 (8.1)
EQ-5D item 4 (pain/ discomfort): proportion of patients reporting “no problem,” no. (%)	32 (16.1)	—	—	—	—	113 (59.8)
Missing	11 (5.2)	—	—	—	—	21 (10.0)
EQ-5D item 5 (anxiety/ depression): proportion of patients reporting “no problem,” no. (%)	86 (49.4)	—	—	—	—	136 (72.0)
Missing	10 (4.8)					21 (10.0)
Concomitant use of systemic prednisone, no. (%)	53 (25.2)	24 (11.4)	11 (5.2)	12 (5.7)	11 (5.2)	8 (3.8)

DLQI, Dermatology Life Quality Index; EASI, Eczema Area and Severity Index; EASI-50, greater than or equal to 50% improvement in EASI score; EASI-75, greater than or equal to 75% improvement in EASI score; EASI-90, greater than or equal to 90% improvement in EASI score; IGA, Investigator Global Assessment; IQR, interquartile range; no, number; NRS, numeric rating scale; POEM, Patient-Oriented Eczema Measure; SD, standard deviation; TARC, thymus and activation-regulated chemokine; —, not applicable.

Data were analyzed by using a Wilcoxon matched-pairs signed rank test. Missing data for patients who discontinued dupilumab treatment during follow-up were imputed by the last observation carried forward method.

\* $P < .001$  compared to baseline.



**Fig 1.** Clinician-reported outcomes, patient-reported outcomes, and longitudinal treatment effect of dupilumab. **A**, Relative changes over time in clinician-reported outcomes and patient-reported outcomes during dupilumab treatment (n = 210). **B**, Longitudinal treatment effect was evaluated by the proportion of patients achieving absolute cutoff scores indicating controlled disease. N is the number of patients with available outcome measure. Patients with baseline EASI score less than 7, NRS score less than 4, and POEM score less than 7 were excluded from these analyses. EASI, Eczema Area and Severity Index; EASI-50, greater than or equal to 50% improvement in EASI score; EASI-75, greater than or equal to 75% improvement in EASI score; EASI-90, greater than or equal to 90% improvement in EASI score; NRS, numeric rating scale; POEM, Patient-Oriented Eczema Measure.

(2.0; IQR 1.0-5.0;  $P < .001$ ). A greater than or equal to 4-point reduction in weekly average pruritus NRS score was achieved by 60.2% of patients (109/185; those with NRS score  $<4$  at baseline were excluded) at week 16 and 62.1% (110/185) at week 52. Dermatology Life Quality Index score significantly decreased from baseline (median 12.0; IQR 8.0-18.0) to week 16 (median 3.0; IQR 1.0-6.0;  $P < .001$ ) and to week 52 (median 3.0; IQR 2.0-5.0). Patient-Oriented Eczema Measure score significantly decreased from baseline (median 20.0; IQR 16.0-23.5) to week 16 (median 7.0; IQR 3.0-11.0;  $P < .001$ ) and to week 52 (median 6.0; IQR 3.0-11.0;  $P < .001$ ). The proportion of patients reporting “no problems” on the 5-dimension 5-level EuroQoL scale pain/discomfort and anxiety/depression subscale increased from baseline (16.1% and 49.4%, respectively) to week 52 (59.8% and 72.0%, respectively).

At baseline, 53 patients (25.2%) were treated with systemic corticosteroids. Use of concomitant systemic corticosteroids was successfully tapered and discontinued in the majority of patients (Table II). At week 52, 8 patients (3.8%) were still receiving systemic corticosteroids, 2 patients because of inadequately controlled atopic dermatitis, 3 because of a tertiary adrenal insufficiency, and 3 for the indication asthma.

### Longitudinal effectiveness of dupilumab treatment

EASI score less than or equal to 7 was achieved at all follow-up visits (4/4) by 100 of 190 patients

(52.6%), at greater than or equal to 3 of 4 visits by 146 of 190 (76.8%), at greater than or equal to 2 of 4 visits by 164 (86.3%), at greater than or equal to 1 of 4 by 173 of 190 (86.3%), and at 0 of 4 visits by 17 of 190 (8.9%) (Fig 1). NRS score less than or equal to 4 was achieved at 4 of 4 visits by 77 of 170 patients (45.3%), at greater than or equal to 3 of 4 visits by 112 of 170 (65.9%), at greater than or equal to 2 of 4 visits by 136 of 170 (80.0%), at greater than or equal to 1 of 4 visits by 146 of 170 (85.9%), and at 0 of 4 visits by 24 of 170 (14.1%).

### Adverse effects

The most common observed adverse effect was conjunctivitis in 34.1% of patients (n = 72) (Table III). Fourteen patients (6.6%) received a diagnosis of mild conjunctivitis, defined as signs and symptoms that could be controlled with artificial tears, antihistamine eye drops, or topical treatment with anti-inflammatory ointment on the eyelids. Patients received a diagnosis of moderate to severe conjunctivitis if treatment with ocular anti-inflammatory therapy was prescribed by an ophthalmologist (n = 58; 27.5%). Conjunctivitis during dupilumab treatment was associated with significantly higher EASI scores ( $P = .004$ ) and serum thymus and activation-regulated chemokine levels ( $P = .045$ ) at baseline; there were no other predictive factors (Supplemental Table I available via Mendeley at <https://doi.org/10.17632/j7mxxzbbhc5.1>).

Other reported adverse effects included headache (n = 20; 9.4%), muscle or joint pain (n = 16; 7.6%),

**Table III.** Adverse effects during dupilumab treatment in 210 patients

Patients with symptom, no. (%)	
Headache	20 (9.4)
Muscle or joint pain	16 (7.6)
Fatigue	10 (4.7)
Gastrointestinal complaints	10 (4.7)
Injection-site reaction	7 (3.3)
Hair loss	6 (2.8)
Facial redness	6 (2.8)
Herpes simplex	3 (1.4)
Herpes zoster	1 (0.5)
Nasopharyngitis	1 (0.5)
Skin infection	1 (0.5)
Conjunctivitis	72 (34.1)
Mild	14 (6.6)
Moderate to severe (treated with anti-inflammatory eyedrops/ointment)	58 (27.5)
Eosinophilia ( $\geq 0.45 \times 10^9/L$ ), wk	
Baseline	67 (33.0)
4	96 (47.5)
16	108 (54.5)
28	89 (46.4)
40	82 (45.3)
52	72 (40.2)

IGA, Investigator Global Assessment; no, number.

fatigue (n = 10; 4.7%), gastrointestinal complaints (n = 10; 4.7%), injection-site reaction (n = 7; 3.3%), hair loss (n = 6; 2.8%), and red face (n = 6; 2.8%). The proportion of patients with blood eosinophilia ( $\geq 0.45 \times 10^3/\mu L$ ) increased from baseline (n = 67; 33.0%) to week 16 (n = 108; 54.5%) and then decreased (n = 72; 40.2%) at week 52. No other clinically significant changes in laboratory parameters were observed during dupilumab treatment.

### Dupilumab dose adjustment

Dupilumab interval was prolonged in 12 patients (7.0%) because of adverse effects (300 mg/3 weeks: n = 8 [3.8%]; 300 mg/4 weeks: n = 4 [1.9%]). In 10 of 12 patients, dupilumab interval was prolonged because of persistent conjunctivitis despite treatment with ocular anti-inflammatory therapy. In 2 patients (1.2%), dupilumab interval was prolonged because of severe muscle or joint pain. Dupilumab interval was shortened in 2 patients (300 mg/week) because of ineffectiveness.

### Discontinuation of dupilumab treatment

Seventeen patients (8.1%) discontinued dupilumab treatment during follow-up (Supplemental

Table II), 8 (3.8%) because of adverse effects, of which 5 cases (2.4%) were caused by conjunctivitis during dupilumab treatment. Other adverse effects resulting in discontinuation of dupilumab included joint and muscle complaints (0.5%), enlargement of lymphoid cells (0.5%), and flare of rosacea (0.5%). Nine patients (4.3%) discontinued dupilumab treatment because of ineffectiveness.

### DISCUSSION

In this prospective observational 52-week study, data on long-term effectiveness and safety during dupilumab treatment in patients with moderate to severe atopic dermatitis in a real-life setting are presented. Clinical outcome measures rapidly improved in the first 16 weeks of treatment with dupilumab and further improved until week 52. Overall, dupilumab was well tolerated, with only 3.8% of patients discontinuing treatment because of adverse effects. However, 34% of the patients received a diagnosis of new-onset or worsening of conjunctivitis during dupilumab treatment.

Physician- and patient-reported outcomes at week 16 are consistent with those reported in previous phase 3 clinical trials and daily practice studies.<sup>1-3,6-8,17</sup> Concerning long-term outcome, the effectiveness in our daily practice study is comparable to clinical outcomes of the 52-week, randomized, double-blinded, placebo-controlled, phase 3 study that investigated long-term management of moderate-to-severe atopic dermatitis with dupilumab and concomitant topical corticosteroids (LIBERTY AD CHRONOS).<sup>1</sup> In contrast to LIBERTY AD CHRONOS, nearly all clinical outcome measures further improved after 16 weeks in the current study. Patients included in LIBERTY AD CHRONOS had a higher median baseline EASI score (29.6; IQR 22.2-40.8) compared with the patients included in this study (19.0; IQR 12.6-27.7), which can be explained by the washout period of oral immunosuppressive drugs and topical corticosteroids before the start of dupilumab in LIBERTY AD CHRONOS. In our study, follow-up visits were performed by specialized physicians and nurses paying specific and particular attention to adequate use of topical corticosteroids and compliance. This might explain the slightly better performance of this daily practice cohort compared with that in LIBERTY AD CHRONOS.

A recently published retrospective study including 52 patients treated with dupilumab in daily practice evaluated the long-term (52-week) efficacy, safety, and reasons for discontinuation.<sup>9</sup> At week 52, 54% of patients (n = 28) achieved the primary outcome of Investigator Global Assessment score 0 of 1 (clear to almost clear); 46% of patients were



defined as nonresponders, although dupilumab treatment was continued because of significant improvement in quality of life, pruritus, and sleep. Bosma et al<sup>10</sup> published a prospective cohort study including 221 patients treated with dupilumab in daily practice. Linear mixed models were used because not all patients reached the long-term end points. The models showed similar results in clinical outcome measures compared with our study. After starting dupilumab treatment, 46.6% of the patients continued treatment with conventional systemic therapy, which makes the interpretation of the effectiveness of dupilumab difficult in this bridging phase. In our study, we preferred discontinuation of systemic immunosuppressive drugs to evaluate effectiveness of dupilumab in the first weeks of treatment. To avoid exacerbations despite intensive treatment with topical steroids, short courses of systemic steroids were used for some patients before they started dupilumab treatment. Because the number of patients receiving this rescue medication was rather small and the treatment period in most patients was short, this might not have large effect on our results.

This study found low discontinuation rates of dupilumab treatment after 52 weeks (8.1%), mostly because of adverse effects (3.8%) and ineffectiveness (4.3%). This percentage of discontinuation is slightly lower compared with that in the retrospective daily practice study by Jo et al<sup>9</sup> (12%) and comparable to the discontinuation rate in the study by Bosma et al<sup>10</sup> (6.1%). In LIBERTY AD CHRONOS, discontinuation owing to adverse events was reported for 2% of patients treated with dupilumab every other week plus topical corticosteroids (n = 110) at week 52.<sup>1</sup> Long-term effectiveness and safety data of conventional systemic immunosuppressive drugs in atopic dermatitis show high discontinuation rates—up to 50%—in daily practice after 1 year because of adverse effects and ineffectiveness.<sup>18-20</sup> The low discontinuation rate of dupilumab in the current study, despite the relatively high rate of conjunctivitis, might be explained by the intensive and protocolled ophthalmologic care and the lack of alternative treatment options because most patients had already failed multiple oral immunosuppressive treatments.

In this study cohort, 34% of the patients received a diagnosis of conjunctivitis. Literature on patients treated with dupilumab in daily practice shows incidences of conjunctivitis up to 38%, which is higher than that in clinical trials.<sup>6-8,21</sup> Higher conjunctivitis rates during daily practice treatment with dupilumab can be explained by an increased

awareness, but can also be related to the differences in atopic dermatitis severity at baseline. The patient population treated with dupilumab shortly after market access represents an atopic dermatitis population with rather severe disease. In this study, conjunctivitis during dupilumab treatment was associated with significantly higher EASI baseline scores and serum thymus and activation-regulated chemokine levels, which is in accordance with the clinical trials data. In contrast to trial data, conjunctivitis was not associated with history of conjunctivitis in this study. Despite that moderate to severe conjunctivitis, indicated for ocular anti-inflammatory treatment, was observed in 58 patients (27.5%), dupilumab was discontinued in only 5 (2.4%). The other patients were able to continue dupilumab treatment, but remained dependent on ocular anti-inflammatory treatment. The pathogenesis of dupilumab-related conjunctivitis is still unknown. In asthma and nasal polyp patients, dupilumab treatment was not associated with higher conjunctivitis rates compared with that of placebo-treated patients.<sup>22</sup> It is therefore likely that atopic dermatitis-specific factors contribute to the higher prevalence of conjunctivitis in atopic dermatitis during dupilumab treatment. Because ocular comorbidities are prevalent in patients with atopic dermatitis compared with the general population, it is possible that preexisting ocular comorbidities predispose to higher conjunctivitis rates in atopic dermatitis patients during dupilumab treatment.<sup>23</sup> Previously, we described a remarkable scarcity of conjunctival goblet cells and an extensive cellular infiltrate, mainly consisting of CD4<sup>+</sup> T cells in the conjunctival stroma, in 6 patients with conjunctivitis during dupilumab treatment.<sup>24</sup>

Comparable with that in clinical trials, we observed an asymptomatic and transient eosinophilia during dupilumab treatment, which was independent of concomitant treatment with systemic corticosteroids.<sup>1-3,25-27</sup> The increase of eosinophil levels in the peripheral blood is consistent with the hypothesis that blockage of IL-4 and IL-13 inhibits the production of eotaxins and migration of eosinophils into tissue, but does not inhibit the production and migration from the bone marrow. This mechanism results in a transient increase in circulating eosinophils. Recently, we demonstrated that serum concentrations of eotaxin-1 and -3 chemokines significantly decreased during dupilumab treatment.<sup>8</sup> In addition, previous studies in patients with chronic rhinosinusitis showed that dupilumab decreased eotaxin-2 and -3 levels locally in nasal polyp tissue, nasal secretion, and serum.<sup>25,28</sup>

Several limitations resulted from the daily practice setting of this study. Because of the lack of a control group and observational design, factors of bias may have been induced. Additionally, owing to the lack of an ophthalmologic examination before the start of dupilumab treatment, preexisting specific signs and symptoms of conjunctivitis could not be determined.

In conclusion, this observational 52-week daily practice study showed long-term effectiveness in a large cohort of treatment-refractory atopic dermatitis patients. Treatment with dupilumab resulted in a rapid improvement of all clinical outcome measures in the first 16 weeks of treatment, and clinical effectiveness was sustained or even improved during the total 52-week follow-up period. A limited number of patients (17; 8.1%) discontinued dupilumab treatment, with only 8 (3.8%) discontinuing because of adverse effects and 9 (4.3%) because of ineffectiveness. In this study, conjunctivitis was the most common adverse effect, but this rarely resulted in discontinuation of dupilumab treatment. Future daily practice data derived from the BioDay registry will provide further important information on the long-term effectiveness and safety of dupilumab treatment.

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