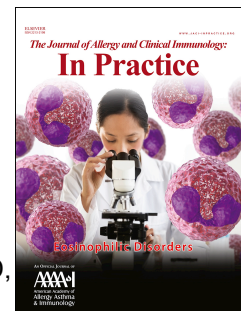


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Dupilumab treatment reduces hospitalizations in adults with moderate-to-severe atopic dermatitis

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Conflicts of interest

Dr Silverberg is a consultant and/or has received grants/honoraria from AbbVie, AnaptysBio, Asana Biosciences, Eli Lilly, Galderma, Glenmark, GlaxoSmithKline, Kiniksa, LEO Pharma, LLC, MedImmune, Menlo Therapeutics, Pfizer, PuriCore, Regeneron Pharmaceuticals, Inc., and

Sanofi. Dr Rubini is a consultant and/or has received grants/honoraria from AstraZeneca, GlaxoSmithKline, Novartis, and Sanofi. Dr Pires is a consultant and/or has received grants/honoraria from Eli Lilly, ISDIN, Mantecorp, and Sanofi. Drs Rossi and Zhang are employees, may hold stock and/or stock options in Sanofi Genzyme. Drs Chen, Levit, Chao, and Shumel are employees, may hold stock and/or stock options in Regeneron Pharmaceuticals, Inc. Ms Bégo-Le Bagousse is an employee, may hold stock and/or stock options in Sanofi.

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HIGHLIGHTS BOX

- **What is already known about this topic?**

Patients with atopic dermatitis (AD) may require hospitalization for refractory disease, flares, or infections.

- **What does this article add to our knowledge?**

Treatment with dupilumab significantly reduced the rate of all-cause and AD-related hospitalizations and reduced the duration of AD-related hospitalizations in a pooled analysis of 7 randomized controlled trials of dupilumab in adults with moderate-to-severe AD.

- **How does this study impact current management guidelines?**

These data demonstrate treatment impact on a novel dimension of AD-associated morbidity.

ABSTRACT (Word limit: 250 words; word count: 185 words)

BACKGROUND: Refractory disease, flares, or infections in atopic dermatitis (AD) can lead to hospitalizations.

OBJECTIVE: To compare hospitalization rates among adults with moderate-to-severe AD treated with dupilumab versus control.

METHODS: Data from 7 randomized, placebo-controlled trials of dupilumab (300 mg every 2 weeks [q2w] and/or weekly [qw]; with or without topical corticosteroids) were analyzed.

RESULTS: Patients in the dupilumab 300 mg q2w, qw, and combined dupilumab (q2w and qw, $n = 1841$) groups compared with patients in the control group ($n = 1091$) had lower rates of all-cause hospitalizations (5.8, 2.7, and 3.8 events, respectively, vs 9.0 events per 100 patient-years [PY]; all $P < .05$ [49%, 71%, and 62% risk reduction, respectively]); AD-related hospitalizations (2.0, 0.4, 1.0 events vs 4.1 events per 100 PY; $P < .05$ for qw and dupilumab combined [91% and 79% risk reduction, respectively]); as well as reduced overall duration of AD-related hospitalization (10.9, 7.3, and 8.6 days vs 38.9 days per 100 PY).

CONCLUSIONS: Among adults with moderate-to-severe AD, treatment with dupilumab versus control was associated with significant reductions in all-cause and AD-related hospitalization rates, and shorter duration of AD-related hospitalization.

Key words: atopic dermatitis; dupilumab; flares; hospitalization; resource utilization

69 Abbreviations used

70 AD: atopic dermatitis

71 EASI: Eczema Area and Severity Index

72 PY: patient-years

73 q2w: every 2 weeks

74 q4w: every 4 weeks

75 qw: weekly

76 RCT: randomized controlled trial

77 RR: rate ratio

78 SAE: serious adverse event

79 TCS: topical corticosteroids

80

INTRODUCTION

Patients with atopic dermatitis (AD), a chronic inflammatory skin disease, may require inpatient hospital treatment for refractory AD, severe AD flares (exacerbations), and infections,¹ particularly, but not limited to, cutaneous infections.²⁻⁴ In a US study, 18.9% of adults admitted to a hospital with a primary diagnosis of AD or eczema presented with a skin infection, compared with only 4.3% of adults without AD or eczema.¹ Cutaneous infections in patients with AD have been associated with significantly increased hospitalization rates and costs compared with patients with AD without skin infections.⁵ More severe AD was associated with higher inpatient costs.⁶ Moreover, about 1 in 5 patients (children and adults) who have had an AD-related hospitalization experience an all-cause hospital readmission within the next year.⁷

Treatment options for moderate-to-severe AD include various systemic immunosuppressants, some of which may increase the risk of infection⁸ and serious infection requiring hospitalization.⁹ However, dupilumab, a fully human monoclonal antibody that blocks the shared receptor component for interleukin-4 and interleukin-13, demonstrated efficacy and was well tolerated in adults, adolescents, and children aged ≥ 6 years with moderate-to-severe AD in various randomized controlled trials (RCTs).¹⁰⁻¹⁶

We compared the rates of hospitalizations among adult patients with moderate-to-severe AD treated with dupilumab versus control, by performing a post-hoc analysis of pooled data from 7 placebo-controlled RCTs including 2932 patients.

METHODS

Data sources and patients

Data were included from 7 placebo-controlled, phase 2 or 3 RCTs in adult patients with moderate-to-severe AD. Patients were treated with dupilumab 300 mg every 2 weeks (q2w) or weekly (qw) versus placebo for 12,¹⁰ 16,^{11-13,17} or 52 weeks.¹⁴ Five of these were monotherapy

studies,^{10,12,13,17} while concomitant topical corticosteroids (TCS) were required in 2 studies.^{11,14} In the latter 2 studies, patients received dupilumab 300 mg qw or q2w plus medium potency TCS, or placebo qw plus medium potency TCS.^{11,14} All studies were approved by local ethics committees, and were performed in accordance with the Declaration of Helsinki, with patients providing informed consent.

Full details of the individual studies (NCT01548404,¹⁰ NCT02210780,¹⁷ NCT02755649,¹¹ NCT02277743,¹² NCT02277769,¹² NCT01859988,¹³ and NCT02260986¹⁴) are provided in the respective primary manuscripts. Brief descriptions are as follows. In a monotherapy trial, 109 adult patients with moderate-to-severe AD were randomized (1:1) to dupilumab 300 mg qw (n = 55) or placebo qw (n = 54) for 12 weeks.¹⁰ In the LIBERTY AD EVALUATE study, 194 adult patients with moderate-to-severe AD were randomized (1:1) to receive dupilumab 300 mg qw (n = 97) or placebo (n = 97) for 16 weeks.¹⁷ In LIBERTY AD CAFÉ, 325 adult patients with moderate-to-severe AD were randomized (1:1:1) to receive dupilumab 300 mg + TCS qw (n = 110), dupilumab 300 mg + TCS q2w (n = 107), or placebo + TCS qw (n = 108) for 16 weeks.¹¹ In the 2 identically designed SOLO1/SOLO2 trials, 671/708 adult patients with moderate-to-severe AD, respectively, were randomized (1:1:1) to receive dupilumab 300 mg qw (n = 223/239), dupilumab 300 mg q2w (n = 224/233), or placebo (n = 224/236) for 16 weeks.¹² In a dose-ranging, phase 2b trial, 380 adult AD patients (379 of whom were included in the analysis) with an Eczema Area and Severity Index (EASI) score ≥ 12 were randomized (1:1:1:1:1:1) to receive dupilumab 300 mg qw (n = 63), 300 mg q2w (n = 64), 200 mg q2w (n = 61), 300 mg every 4 weeks (q4w) (n = 65), 100 mg q4w (n = 65), or placebo qw (n = 61) for 16 weeks.¹³ From this dose-ranging trial, only the patients who received dupilumab 300 mg qw or q2w or placebo were included in the current analysis. In LIBERTY AD CHRONOS, 740 adult patients with moderate-to-severe AD were randomized (3:1:3) to receive dupilumab 300 mg qw + TCS (n = 319), dupilumab 300 mg q2w + TCS (n = 106), or placebo + TCS qw (n = 315) for 52 weeks.¹⁴ Analyses were performed in the intent-to-treat population.

Outcomes

Study endpoints included hospitalization rates (“all-cause” and “AD-related”), length of AD-related hospitalizations, and time to first hospitalization.

Hospitalization events were identified through a review of serious adverse event (SAE) reports. Durations of hospitalization stay were manually extracted based on the admission and discharge dates recorded in the SAE reports. “All-cause” hospitalizations were defined as hospital admissions resulting from SAEs due to any reason. “AD-related” hospitalizations were defined as hospitalizations that were related to AD per the reviewing medical directors’ judgement of the written narratives in the SAE reports. Authors responsible for the review and adjudication of SAE reports were A. Rossi MD (Sanofi-Genzyme); A. Zhang MD, MPH (Sanofi-Genzyme); N. Levit MD, PhD (Regeneron); J. Chao PhD (Regeneron); B. Shumel MD (Regeneron); and G. Bego-Le Bagousse MSc (Sanofi Chilly Mazarin). A. Rossi and N. Levit are board-certified dermatologists.

Outcomes were compared for patients receiving dupilumab, as monotherapy or with concomitant TCS, in the dupilumab 300 mg q2w, dupilumab 300 mg qw, and “dupilumab combined” (all patients receiving dupilumab) groups versus control.

Statistical analyses

To account for patient difference in time under study per design or discontinuation, event rates were calculated as number of events per 100 patient-years [PY] for all-cause and adjudicated AD-related hospitalizations, along with the duration of AD-related hospitalizations (days per 100 PY). Nominal *P* values were calculated using negative binomial regression models with treatment and baseline Investigator’s Global Assessment score (≤ 3 vs 4) as covariates. A trial indicator variable was included in the statistical models to adjust for possible

heterogeneity between the different trials. Kaplan–Meier curves of times to first all-cause and AD-related hospitalizations were also presented.

Length of stay was measured as the number of days in hospital per 100 PY. The number of days in hospital was calculated using the equation:

Number of days in hospital = Discharge date – Admission date + 1 for each event

Statistical analyses were performed using SAS software (version 9.4, SAS Institute, Cary, NC).

RESULTS

Data for 2932 patients (1841 dupilumab and 1091 control patients) were included in the analysis. Patients were recruited in 28 different countries, with 29.4% of the patients from the USA, 14.9% from Germany, 13.3% from Poland, 10.3% from Canada, and 8.5% from Japan. The remaining 23.6% of patients were recruited in 23 other countries. Baseline demographics and characteristics (Table I) were similar between the dupilumab and control groups.

Among the included patients, 77 hospitalization events were identified (31 in the dupilumab group, 46 in the control group; Table II). For patients with hospitalizations, in each group the majority of patients had a single hospitalization event (Table II). In the placebo group, 5 patients had 2 events, and in each of the dupilumab 300 mg q2w and 300 mg qw groups, a single patient had 2 events. No patient in any group had ≥ 3 hospitalizations. The main causes/diagnoses of hospitalization are shown in Table II. “AD exacerbation” was the most common reason for hospitalization and was lower in the combined dupilumab versus control groups (0.7 vs 2.6 events per 100 PY; rate ratio [RR] 0.29; 95% confidence interval [CI] 0.11, 0.75; $P = .011$; 71% risk reduction [equals to $1 - \text{RR}$] by dupilumab). Other causes were also less frequent in the combined dupilumab group (3.1 vs 6.5 events per 100 PY; RR 0.47; 95% CI 0.26, 0.85; $P = .012$; 53% risk reduction), including “skin and soft-tissue infections” (0.5 vs 0.8 events per 100 PY; RR 0.62; 95% CI 0.16, 2.48; $P = .500$; 38% risk reduction).

Overall, patients with moderate-to-severe AD who received dupilumab (combined) versus control had lower rates of all-cause hospitalizations (3.8 vs 9.0 events per 100 PY; RR 0.38; 95% CI 0.23, 0.62; $P < .001$; 62% risk reduction) and AD-related hospitalizations (1.0 vs 4.1 events per 100 PY; RR 0.21; 95% CI 0.09, 0.51; $P < .001$; 79% risk reduction) (Figure 1, A). This also translated into reduced overall duration of AD-related hospitalizations for patients treated with dupilumab (combined) versus control (8.6 vs 38.9 days per 100 PY; RR 0.10; $P = .06$; 30.3-day reduction per 100 PY) (Figure 1, B).

The individual dupilumab dose regimens versus control also showed lower rates of all-cause hospitalizations (q2w: 5.8 vs 9.0 events per 100 PY; RR 0.51; 95% CI 0.27, 0.95; $P = .033$; 49% risk reduction; qw: 2.7 vs 9.0 events per 100 PY; RR 0.29; 95% CI 0.15, 0.55; $P < .001$; 71% risk reduction) and AD-related hospitalizations (q2w: 2.0 vs 4.1 events per 100 PY; RR 0.40; 95% CI 0.15, 1.08; $P = .07$; 60% risk reduction; qw: 0.4 vs 4.1 events per 100 PY; RR 0.09; 95% CI 0.02, 0.40; $P = .002$; 91% risk reduction) (Figure 1, A). The individual dupilumab dose regimens showed reduced duration of AD-related hospitalizations versus control (q2w: 10.9 vs 38.9 days per 100 PY; RR 0.45; 95% CI 0.07, 3.09; $P = .42$; qw: 7.3 vs 38.9 days per 100 PY; RR 0.02; 95% CI 0.00, 0.16; $P < .001$) (Figure 1, B).

Kaplan–Meier curves showing times to first all-cause hospitalization and first AD-related hospitalization are shown in Figure 2.

DISCUSSION

In this analysis of pooled data from 7 double-blind, placebo-controlled phase 2 and 3 RCTs, adults with moderate-to-severe AD who received dupilumab (either posology, as monotherapy or with concomitant TCS) had a lower rate of “all-cause” and “AD-related” hospitalizations than those who received placebo (with or without TCS). Dupilumab-treated patients also had a trend of fewer days of AD-related hospitalizations compared with control

patients. There was also a lower probability of hospitalization in patients treated with dupilumab than in control patients (Figure 2).

These analyses show that the efficacy of dupilumab translates into a benefit of reduced hospitalizations, overall and those related to AD. Although all-cause hospitalizations may include events that have no relationship to the drug or AD, a reduction of all-cause hospitalizations provides additional information relevant to the safety profile of dupilumab.

Overall, there was a 49% reduction in all-cause hospitalizations and a 60% reduction in AD-related hospitalizations with the approved dupilumab posology (300 mg q2w). An additional benefit was the reduction in hospitalization duration from 38.9 days per 100 PY for control to 10.9 days per 100 PY for dupilumab 300 mg q2w. This study found significant reductions in all-cause and AD-related hospitalization rates for the dupilumab pooled (300 mg q2w plus qw regimens) and for the 300 mg qw regimen alone, as well as significantly reduced overall duration of AD-related hospitalizations for the qw regimen. The reduction in all-cause hospitalizations for the approved dupilumab dosage of 300 mg q2w was statistically significant while a numerical but non-significant ($P = .07$) reduction was observed for AD-related hospitalization. This trend towards significance may be due to fewer patients being randomized to the 300 mg q2w regimen in the 52-week CHRONOS study, in which the randomization scheme was 3:1:3 for placebo, dupilumab 300 mg q2w, and dupilumab 300 mg qw, respectively.

The main differences in causes/diagnoses of hospitalization between dupilumab and control patients in the current study were AD exacerbations and skin and soft-tissue infections, which were 71% ($P = .011$) and 38% ($P = .5$) less frequent, respectively, in the dupilumab group. Bacterial colonization and infection (particularly *Staphylococcus aureus*) are well-known triggers of AD exacerbations;^{18,19} poor disease control and flaring (which is associated with impaired skin barrier function, increased skin pH, and down-regulated antimicrobial peptides) increase the risk of secondary skin infection.^{20,21} In addition, AD is associated with immune

dysregulation, which also favors greater susceptibility to other skin infections, including *Streptococcus pyogenes*, eczema herpeticum, eczema vaccinatum, and eczema coxsackium, with an increased risk of invasive infections, especially in patients with severe disease and atopy.²⁰ Unlike some systemic immunosuppressive AD treatments,^{8,9} dupilumab does not increase the overall risk of infection while also significantly reducing the risk of serious or severe infections.²² Dupilumab probably reduces infectious episodes through two mechanisms: local action with reduction of inflammation and improvement of the skin barrier, and systemic action by downregulation of T-helper type 2 driven inflammation.

Limitations of this study include the external generalization of the analyses, as the analyses are based on data from RCTs. Therefore, while the study has strong internal validity, the external generalization needs to be confirmed in a broader population and in a real-world setting. In addition to the approved dupilumab dosage of 300 mg q2w, the RCT data include results for a weekly dupilumab regimen, which has not been approved. Although hospitalizations are dependent on the local health care system, the included trials cover multiple countries, which mitigates the impact of local health care systems on the results.

CONCLUSIONS

Among adults with moderate-to-severe AD, treatment with dupilumab versus control was associated with significant reductions in all-cause and AD-related hospitalization rates, and shorter AD-related hospitalization duration.

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Note

For a video abstract of this article, see Video 1, available in this article's Online Repository at jaci-inpractice.org.

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331 **Figure legends:**

332 **FIGURE 1.** Atopic dermatitis. Rates of **A**, all-cause and AD-related hospitalizations and **B**, days
333 of AD-related hospitalization. *AD*, atopic dermatitis; *CI*, confidence interval; *PY*, patient-years;
334 *q2w*, every 2 weeks; *qw*, weekly; *RR*, rate ratio.

335

336 **FIGURE 2.** Atopic dermatitis. Kaplan–Meier estimates of times to first hospitalization. **A**, all-
337 cause hospitalizations and **B**, AD-related hospitalizations. *AD*, atopic dermatitis; *K–M*, Kaplan–
338 Meier; *q2w*, every 2 weeks; *qw*, weekly.

339 **TABLE I.** Baseline demographics and disease characteristics

	Control (n = 1091)	Dupilumab		
		300 mg q2w (n = 746)	300 mg qw (n = 1095)	Combined (N = 1841)
Baseline demographics and disease characteristics*				
Age, y, mean (SD)	38.0 (13.6)	38.5 (13.9)	37.6 (13.7)	38.0 (13.8)
Male, %	57.1	59.2	59.7	59.5
Race, n (%)				
White	774 (70.9)	546 (73.2)	781 (71.3)	1327 (72.1)
Black or African American	76 (7.0)	34 (4.6)	77 (7.0)	111 (6.0)
Asian	216 (19.8)	145 (19.4)	211 (19.3)	356 (19.3)
Native American/Alaskan	0	1 (0.1)	2 (0.2)	3 (0.2)
Native Hawaiian or Pacific Islander	1 (0.1)	1 (0.1)	2 (0.2)	3 (0.2)
Other	17 (1.6)	12 (1.6)	18 (1.6)	30 (1.6)
Not reported	7 (0.6)	7 (0.9)	4 (0.4)	11 (0.6)
Weight, kg, mean (SD)	76.5 (18.9)	76.4 (18.0)	76.7 (18.3)	76.6 (18.2)
BMI, kg/m ² , mean (SD)	26.4 (6.0)	26.1 (5.4)	26.1 (5.6)	26.1 (5.5)
AD disease duration, y, mean (SD)	28.2 (14.6)	28.6 (15.3)	28.2 (14.7)	28.4 (15.0)
EASI, mean (SD)	33.1 (13.5)	32.7 (13.0)	31.8 (12.8)	32.2 (12.9)
POEM score, mean (SD)	20.3 (5.9)	20.2 (6.0)	20.3 (6.1)	20.3 (6.1)
DLQI total score, mean (SD)	14.6 (7.4)	14.6 (7.3)	14.7 (7.5)	14.7 (7.4)
BSA, %, mean (SD)	55.0 (22.8)	54.6 (21.9)	52.9 (22.1)	53.6 (22.0)

AD, atopic dermatitis; BMI, body mass index; BSA, body surface area; DLQI, Dermatitis Life Quality Index; EASI, Eczema Area and Severity Index; POEM, patient-oriented eczema measure; PY, patient-years; q2w, every 2 weeks; qw, every week; SD, standard deviation.

*Values are given in mean (SD).

TABLE II. Causes/diagnoses* of hospitalization events, events per patient, and duration of hospitalizations

	Control (n = 1091)	Dupilumab		Combined (N = 1841)
		300 mg q2w (n = 746)	300 mg qw (n = 1095)	
Hospitalization causes/diagnoses[†]	46 (9.0)	17 (5.8)	14 (2.7)	31 (3.8)
Exacerbation of AD [§]	13 (2.6)	5 (1.7)	1 (0.2)	6 (0.7)
Other causes (non-exacerbation of AD)	33 (6.5)	12 (4.1)	13 (2.5)	25 (3.1)
Skin and soft-tissue infections	4 (0.8)	2 (0.7)	2 (0.4)	4 (0.5)
Acute myocardial infarction	0	0	2 (0.4)	2 (0.2)
Decompensation of mood disorder (anxiety/depression)	0	2 (0.7)	0	2 (0.2)
Suicidal ideation	2 (0.4)	0	0	0
Hospitalization events per patient				
Patients with 0 hospitalizations, n (%)	1050 (96.2)	730 (97.9)	1082 (98.8)	1812 (98.4)
Patients with 1 hospitalization, n (%)	36 (3.3)	15 (2.0)	12 (1.1)	27 (1.5)
Patients with 2 hospitalizations, n (%)	5 (0.5)	1 (0.1)	1 (0.1)	2 (0.1)
Patients with ≥3 hospitalizations, n	0	0	0	0
Duration of hospitalization for patients with ≥1 hospitalization event				
Days, mean (SD)	10.4 (7.8)	5.3 (1.0)	19.0 (18.4)	8.8 (9.4)
Days, median (min, max)	8.0 (4, 38)	5.0 (4, 7)	19.0 (6, 32)	5.5 (4, 32)

AD, atopic dermatitis; SD, standard deviation.

*Diagnoses were extracted from serious adverse event reports. Only diagnoses with >1 event are shown.

[†]Values are given as events (events per 100 PY).

[§]Exacerbation of AD includes both “exacerbation of AD” and “exacerbation of AD (erythrodermic AD)”.

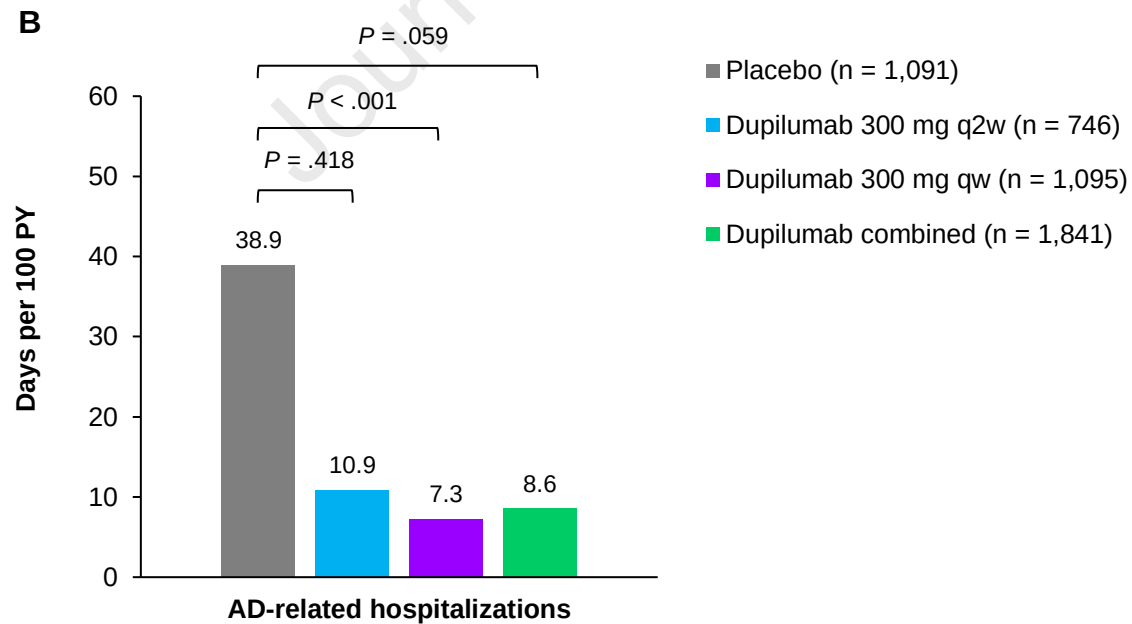
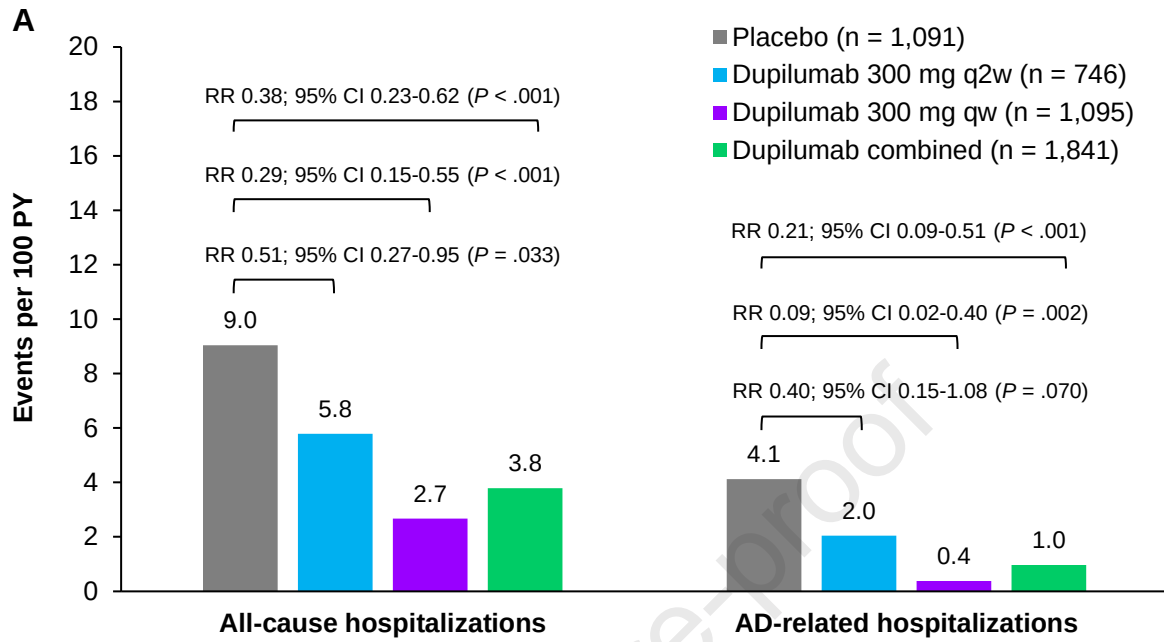
JACI: In Practice

Dupilumab treatment reduces hospitalizations in adults with moderate-to-severe atopic dermatitis: a pooled analysis of data from seven randomized, placebo-controlled studies

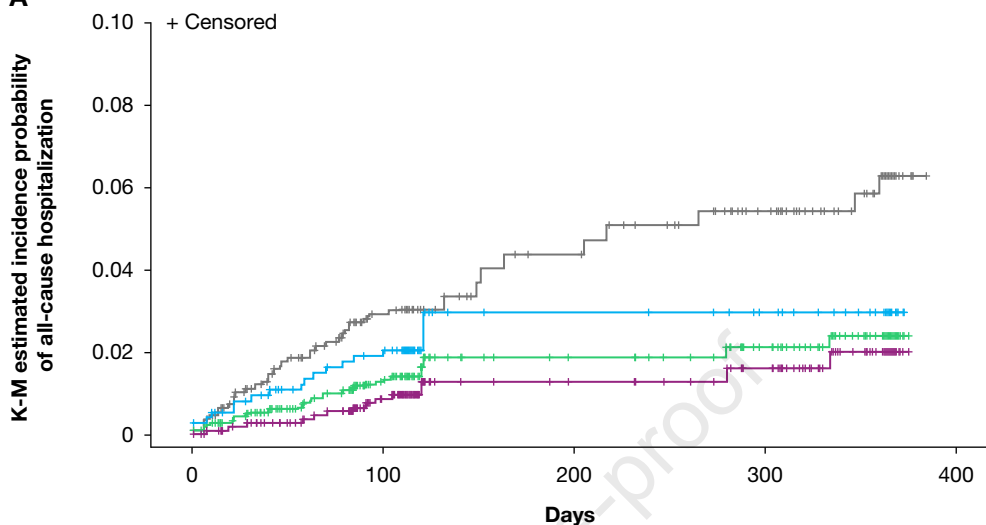
VIDEO SCRIPT

TIME	SCRIPT	VISUAL ELEMENTS Description of scenes only serve as a reference to what data will be depicted in the animations.
1	Does dupilumab reduce the rate of hospitalizations in adults with moderate-to-severe atopic dermatitis?	
2	Hi, I'm Dr. Jonathan Silverberg, and on behalf of my co-authors I will present our analysis of the effect of dupilumab on all-cause and AD-related hospitalizations in atopic dermatitis patients.	Jonathan I. Silverberg Department of Dermatology George Washington University School of Medicine and Health Sciences Washington, DC, USA
3	Patients with atopic dermatitis may require inpatient hospital treatment for refractory atopic dermatitis, severe atopic dermatitis flares or infections. In particular, cutaneous infections are associated with increased risk of hospitalizations.	
4	Dupilumab is effective and well tolerated in patients with moderate-to-severe atopic dermatitis. However, the impact of dupilumab on hospitalizations is unknown.	
5	We conducted a post-hoc analysis of seven randomized placebo-controlled trials to analyze all-cause hospitalizations, atopic dermatitis-related hospitalizations and duration of atopic dermatitis-related hospital stay in dupilumab versus control. The analysis included 2,932 patients from 28 countries.	2,932 patients 1,841 dupilumab and 1,091 control

6	Patients who received dupilumab had a 62% lower risk of all-cause hospitalizations and 79% lower risk of atopic dermatitis-related hospitalizations compared with controls.	
7	Dupilumab also reduced overall duration of atopic dermatitis-related hospitalization, which was 8.6 days per 100 patient years for dupilumab-treated patients compared with 38.9 days in the control group.	
8	In conclusion, dupilumab significantly reduced hospitalizations and shortened the duration of atopic dermatitis-related hospital stays compared with control in adults with moderate-to-severe AD. These data suggest that dupilumab leads to improvement of health-resource utilization and has previously unrecognized cost-effectiveness in reducing hospitalizations.	

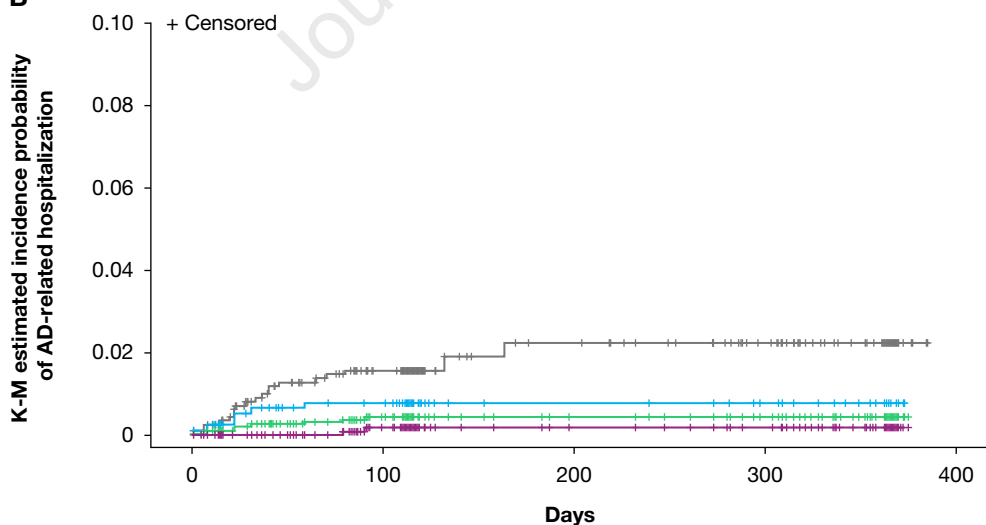


A



Patients at risk:	746	722	712	101	100	99	95	86	0
	1,095	1,066	988	298	295	293	281	246	0
	1,841	1,788	1,700	399	395	392	376	332	0
	1,091	1,040	961	284	278	268	253	223	0

B



Patients at risk:	746	724	719	101	100	99	95	86	0
	1,095	1,069	994	299	295	293	282	248	0
	1,841	1,793	1,713	400	395	392	377	334	0
	1,091	1,045	972	286	281	273	257	228	0