Dupilumab significantly improves sleep in adults with atopic dermatitis: results from the 12-week placebo-controlled period of the 24-week phase 4 randomized double-blinded placebo-controlled DUPISTAD study

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Running head: Dupilumab improves sleep in atopic dermatitis

Joseph F. Merola,[1,2] Albert S. Chiou,[3] Emmanuel During,[4,5] Antonio Costanzo,[6] Peter Foley,[7,8,9] Amani Alfalasi,[10] Shaila Gogate,[11] Andreas Pinter,[12] Roni Dodiuk-Gad,[13,14,15] Dagmar Simon,[16] Marie Tauber,[17] Richard Weller,[18] Jose-Juan Pereyra-Rodriguez,[19] Marius Ardeleanu,[20] Jiangming Wu[21] and Zafer E. Ozturk[22]

[1]Department of Dermatology, Brigham and Women's Hospital, Boston, MA, USA
[2]Harvard Medical School, Boston, MA, USA
[3]Department of Dermatology, Stanford University, Palo Alto, CA, USA
[4]Department of Neurology & Neurological Sciences, Stanford University, Palo Alto, CA, USA
[5]Department of Psychiatry and Behavioral Sciences, Division of Sleep Medicine, Stanford University, Palo Alto, CA, USA
[6]Dermatology Unit, IRCCS Humanitas Research Hospital, Rozzano, Milan, Italy
[7]Skin Health Institute, Carlton, Victoria, Australia
[8]Department of Dermatology, St Vincent's Hospital Melbourne, Fitzroy, Victoria, Australia
[9]Department of Medicine, The University of Melbourne, Melbourne, Victoria, Australia
[10]Al Safa Dermatology Clinic, Dubai, United Arab Emirates
[11]Colorado Allergy & Asthma Centers, Denver, CO, USA
[12]Department of Dermatology, University Hospital Frankfurt am Main, Frankfurt am Main, Germany
[13]Bruce Rappaport Faculty of Medicine, Technion Institute of Technology, Haifa, Israel
[14]Division of Dermatology, Department of Medicine, University of Toronto, Toronto, Ontario, Canada
[15]Dermatology Department, Emek Medical Center, Afula, Israel
[16]Department of Dermatology, Universitätsspital Bern, Bern, Switzerland

[17]Department of Allergology and Clinical Immunology, CIRI Inserm U1111, Lyon Sud Hospital, Lyon, France
[18]Centre for Inflammation Research, University of Edinburgh, Edinburgh, UK
[19]Dermatology Unit, Hospital Universitario Virgen del Rocio, Sevilla, Spain
[20]Regeneron Pharmaceuticals Inc., Tarrytown, NY, USA
[21]Sanofi, Bridgewater, NJ, USA
[22]Sanofi, Cambridge, MA, USA

Corresponding author: Zafer E. Ozturk

Email: Zafer.Ozturk@sanofi.com

ORCiD: JFM - 0000-0001-6514-4353
ASC - 0000-0002-8436-0008
ED - 0000-0002-0539-5115
AC - 0000-0001-9697-2557
PF - 0000-0001-5891-5607
AP - 0000-0002-1330-1502
RD-G - 0000-0003-2168-3798
DS - 0000-0001-8965-9407
MT - 0000-0001-6245-7442
RW - 0000-0003-2550-9586
J-JP-R - 0000-0001-6843-5877
MA - 0000-0002-7712-6862

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Data availability: Qualified researchers may request access to patient-level data and related study documents including the clinical study report, study protocol, blank case report form, statistical analysis plan, and dataset specifications. Amendments to the study protocol are summarized in Table S1. Patient-level data will be anonymized, and study documents will be redacted to protect the privacy of our trial participants. Further details on Sanofi's data sharing criteria, eligible studies, and process for requesting access can be found at: https://www.vivli.org/.

Ethics statement: DUPISTAD 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 participating site oversaw trial conduct and documentation. All patients provided written informed consent before participating in the trial.

What's already known about this topic?

- Sleep disturbance is common in patients with atopic dermatitis (AD) and has a significant impact on quality of life (QoL)
- Sleep was previously shown to improve with dupilumab treatment in adult patients with AD

What does this study add?

- The prospective double-blind DUPISTAD study provides further insight into the effect of dupilumab on sleep in patients with moderate-to-severe AD
- Dupilumab significantly improved overall sleep, itch, and other AD-related signs, symptoms, and QoL in adults with moderate-to-severe AD, versus placebo

Abstract

Background Sleep disturbance is a prominent symptom of atopic dermatitis (AD) and can result in insomnia, daytime fatigue, drowsiness, reduced productivity, and impaired quality of life (QoL).

Objectives The DUPISTAD (Dupilumab Effect on Sleep in AD Patients) phase 4 randomized double-blinded placebo-controlled study evaluated the impact of dupilumab treatment on sleep and other patient- and physician-reported outcomes.

Methods Adults with moderate-to-severe AD were randomized 2:1 to dupilumab 300 mg once every 2 weeks (q2w) or placebo for 12 weeks; concomitant topical corticosteroids were permitted. Patients subsequently entered an open-label phase and received dupilumab 300 mg q2w for a further 12 weeks. The primary endpoint was percentage change from baseline to Week 12 in sleep quality, assessed using a novel numeric rating scale (NRS). Secondary and exploratory endpoints included percent change in peak pruritus NRS (PP NRS), change in SCORing Atopic Dermatitis (SCORAD), SCORAD sleep visual analog scale (VAS), Eczema Area and Severity Index, Patient Reported Outcomes Measurement Information System (PROMIS) sleep-related impairment T-score, and the Epworth Sleepiness Scale (ESS). Sleep diary and wrist actigraphy measurements were recorded throughout the study.

Results In total, 127 patients received dupilumab and 61 placebo. Demographic and baseline disease characteristics were balanced between groups. Sleep quality NRS significantly improved in dupilumab-treated patients by Week 12 versus placebo (LSMD-15.5%, P<0.001). PP NRS (LSMD -27.9%, P<0.001), SCORAD (LSMD -15.1, P<0.001), SCORAD sleep VAS (LSMD -2.1, P<0.001), and PROMIS T-score (LSMD -3.6, P<0.001) were also significantly improved at Week 12 with dupilumab versus placebo. The overall percentage of patients reporting treatment-emergent adverse events was lower in the dupilumab group (56.7%) than in the placebo group (67.2%).

Conclusions Dupilumab significantly improved sleep quality and perception of sleep continuity, itch, metrics of AD severity, and QoL in adults with moderate-to-severe AD, with an acceptable safety profile versus placebo.

Trial registration number ClinicalTrials.gov: NCT04033367

Introduction

Atopic dermatitis (AD) is a chronic inflammatory skin disease characterized by eczematous lesions and pruritus (itch).[1,2] AD affects approximately 2 to 7% of adults worldwide.[3,4] In moderate-to-severe AD, lesions can be extensive, with intense pruritus.[5] Sleep disturbance represents one of the prominent symptoms of AD, primarily related to nighttime itching and scratching, affecting the ability to fall and stay asleep, and leading to daytime drowsiness, a high burden of fatigue, and reduced productivity and quality of life (QoL).[6-14] Accumulating evidence suggests that type 2 inflammation underlies the chronic itch in AD.[15]

Dupilumab is a fully human VelocImmune®-derived[16,17] monoclonal antibody that blocks the shared receptor component for interleukin (IL)-4 and IL-13, inhibiting signaling of both IL-4 and IL-13, which are key and central drivers of type 2-mediated inflammation in AD.[18] Sleep disturbance was previously shown to improve with dupilumab treatment in adult patients with AD.[19] The prospective double-blind DUPISTAD (Dupilumab Effect on Sleep in AD Patients) study was designed to provide further insight into the effect of dupilumab on sleep in patients with moderate-to-severe AD using dedicated sleep outcome measures, while also assessing the clinical and patient-reported outcomes of AD.

The objective of this analysis was to assess the effect of dupilumab on sleep quality and duration in adult patients with moderate-to-severe AD following 12 weeks of treatment with the approved adult dose of dupilumab (300 mg once every 2 weeks [q2w])[20,21] compared with placebo.

Patients and methods

DUPISTAD (NCT04033367) was a phase 4 randomized double-blinded placebo-controlled study which evaluated the impact of dupilumab treatment on sleep and other patient- and physician-reported outcomes in patients with AD. Patients were enrolled at 42 sites across 10 countries (Australia, France, Germany, Israel, Italy, Spain, Switzerland, the United Arab Emirates, the UK, and

the USA). Eligible patients were aged ≥18 years, had moderate-to-severe AD, as defined by an Eczema Area and Severity Index [EASI] score of ≥12, peak pruritus NRS (PP NRS) score of ≥3, and sleep disturbance NRS score ≥5, and had an inadequate response to topical AD treatments. Exclusion criteria included concomitant treatment with sedative anxiolytic or hypnotic treatments (other than melatonin) on a regular basis, systemic sedative antihistamines >5 days per week, or treatment with antidepressants, beta blockers, clonidine, opioids, theophylline, or other medications known to interfere with sleep. Full inclusion and exclusion criteria are provided in Appendix S1. All patients were required to apply moisturizers (emollients) twice daily for at least seven consecutive days before randomization and throughout the study. Patients were randomized to receive dupilumab 300 mg administered as subcutaneous injection q2w (following a loading dose of 600 mg on Day 1), or a matching placebo, for a period of 12 weeks. Patients were randomized using an interactive voice response/interactive web response system; patients and investigators were blinded to treatment. All patients subsequently entered a 12-week open-label treatment phase and received 300 mg q2w for a further 12 weeks. All patients were required to apply medium potency topical corticosteroids (TCS) daily on active lesions. When the lesions were under control, TCS frequency was reduced to twice weekly.

DUPISTAD 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 participating site oversaw trial conduct and documentation. All patients provided written informed consent before participating in the trial.

Study outcomes

The primary endpoint of the study was percentage change from baseline to Week 12 in sleep quality, assessed on a 0 to 10 NRS,[22] where 0 was “worst possible sleep” (i.e. lowest quality) and 10 was

"best possible sleep" (i.e. highest quality).However, this scale was reversed for the analysis (Table S2), to ensure accurate, in-proportion representation of the primary endpoint results. Since the primary endpoint was percent change from baseline, using the unmodified scale would have led to disproportionately large changes in patients with very low sleep quality scores at baseline, compared with those with higher scores, or even result in no data (i.e. not possible to calculate percent change) for patients with a sleep NRS score = 0 at baseline. Furthermore, as other AD outcome measures (e.g. PP NRS, Patient-Oriented SCORing Atopic Dermatitis [SCORAD] sleep visual analog scale [VAS], etc.)[23,24] use scales with opposite directionality (0 or left end = best, 10 or right end = worst), reversing the sleep NRS made it compatible with other outcome measures, better suited for correlation analyses, and confirmed that it would not affect the magnitude of change or interpretation of the results.

Secondary and exploratory study endpoints included percent change from baseline to Week 12 in PP NRS; change from baseline to Week 12 in: SCORAD, SCORAD sleep VAS, Patient-Oriented Eczema Measure (POEM), Dermatology Life Quality Index (DLQI), Patient-Reported Outcomes Measurement Information System (PROMIS) sleep-related impairment T-score, and the Epworth Sleepiness Scale (ESS); percent change from baseline to Week 12 in sleep efficiency, total sleep time, wake after sleep onset, and sleep onset latency based on actigraphy data; and proportion of patients achieving EASI-50, EASI-75, and EASI-90 (i.e. a 50%, 75%, or 90% reduction in EASI score) at Week 12 versus baseline EASI score.

Assessments

The treating clinician assessed the AD disease status severity utilizing the EASI (range 0 to 72)[25] and SCORAD (range 0 to 103).[243] Patient-reported data included the sleep disturbance NRS score (range 0 to 10); PP NRS (range 0 to 10)[21]; DLQI (range 0 to 30)[24]; POEM (range 0 to 28)[25,26]; SCORAD sleep VAS (0 to 100 mm [0 to <40 mm indicating none or mild impairment, 40 to <70 mm moderate impairment, 70 to <90 mm severe impairment, and ≥90 mm very severe impairment]); PROMIS-T

score (a standardized score with a mean of 50 and a standard deviation (SD) of 10 that is measured on a scale of 30 to 80, with 30 being worst and 80 best sleep); and ESS (range 0 to 24).[27] For each of these metrics, higher scores represent greater severity. Wrist actigraphy using the Actiwatch Spectrum® (Philips Respironics, Inc. Murrysville, PA, USA) was used to provide estimates of the duration, timing, and patterns of sleep. A sleep diary was also used for patient-reported measures of sleep metrics. With regards to safety, all adverse events were recorded, and were coded using MedDRA, version 24.0.

Statistical analysis

Efficacy analyses were conducted using the modified intention-to-treat (mITT) population, which included all randomized patients who had baseline and at least one post-baseline assessment. The percent change from baseline to Week 12 in sleep quality NRS was analyzed using a mixed effect model with repeated measures (MMRM) with treatment, baseline value, randomization stratum, visit, treatment by visit interaction, and baseline value by visit interaction terms (all as fixed effects) in the model. A similar approach was used for analysis of secondary continuous endpoints. Endpoints comparing proportion of patients meeting certain criteria at a specific visit were analyzed via the Cochran-Mantel-Haenszel test adjusted by the randomization stratum. Least squares mean of the difference (LSMD) between the dupilumab group and placebo, the corresponding 95% confidence interval (CI) of the differences and p-values were provided. Safety analyses were performed on the safety set (all patients who received at least one dose of the study drug); analyses were descriptive. All statistical analyses were performed using SAS version 9.2 or higher (SAS Institute, Cary, NC, USA).

Results

Patient disposition

In total, 127 patients received dupilumab 300 mg q2w and 61 received placebo between August 22, 2019 and October 6, 2021 (Table S3). Mean baseline demographics and disease characteristics were well balanced between groups (Table 1). Mean SCORAD total score was 64.7 in the dupilumab group, and 62.8 in the placebo group. Mean EASI score was 26.2 versus 26.0 in the dupilumab and placebo groups, respectively. The QoL burden, as measured by DLQI and POEM, was relatively high in both groups.

Primary efficacy endpoint

Overall, the improvement in sleep NRS was significantly greater with dupilumab than with placebo, with a LSMD (95% CI) of -15.5% (-24.1, -6.9) by Week 12, representing a 47.7% improvement in sleep with dupilumab versus 33.0% in the placebo group, P<0.001 (Figure 1). Dupilumab treatment was associated with significant improvement in sleep compared with placebo across most subgroups, including patients with PP NRS ≥7 at baseline (mean (SD) percent change from baseline in the dupilumab and placebo groups of -51.1 (27.5) and -31.8 (29.3), respectively, LSMD (95% CI) -19.6 (-30.2, -8.9), P<0.001) (Table 2).

Secondary endpoints measuring disease severity and QoL

Itch, as measured by weekly patient-reported PP NRS, was significantly reduced with dupilumab versus placebo, LSMD (95% CI) 27.9% (-38.0, -17.8), P<0.001 (Figure 2). Mean PP NRS scores reported at baseline were 7.5 and 7.6 in the dupilumab and placebo groups, respectively, which decreased to 3.5 and 5.9, respectively, at Week 12, representing a mean (SD) percent change from baseline in the dupilumab and placebo groups of -52.5 (30.6) and -23.3 (30.1), respectively. A ≥4-point improvement in PP NRS was achieved by 74.0% of patients in the dupilumab group compared with 49.2% of patients in the placebo group.

Clinical signs and symptoms, as measured by total SCORAD score, also significantly improved with dupilumab. Mean (SD) change from baseline in the dupilumab group was -37.8 (17.7) compared

with -20.6 (17.9) in the placebo group; LSMD (95% CI) -15.1 (-20.6, -9.6), P<0.001 (Figure 3a), with dupilumab-treated patients moving from a mean (SD) SCORAD score considered to be severe at baseline (64.7 [12.5]) to one considered mild (26.8 [16.8]) at Week 12. QoL metrics of POEM and DLQI both improved significantly more with dupilumab than with placebo. Mean (SD) change from baseline in POEM was -13.6 (7.5) and -4.4 (6.8) in the dupilumab and placebo groups, respectively; LSMD (95% CI) -8.3 (-10.9, -5.8), P<0.001. Mean (SD) change from baseline in DLQI was -11.8 (6.5) and -7.5 (6.8) in the dupilumab and placebo groups, respectively; LSMD (95% CI) -4.5 (-6.4, -2.6, P<0.001 (Table 3). Lastly, significantly more patients treated with dupilumab achieved the clinically meaningful endpoints of EASI-50, EASI-75 (both P<0.001), and EASI-90 (P=0.002) than those receiving placebo (Figure 4).

Sleep secondary and exploratory endpoints

SCORAD sleep VAS was significantly decreased at Week 12 with dupilumab versus placebo. Mean (SD) change from baseline in the dupilumab group was -4.9 (3.0) compared with -2.3 (3.0) in the placebo group (LSMD [95% CI] -2.1 [-3.0, -1.2], P<0.001; Figure 3b). The PROMIS sleep-related impairment T-score was also reduced significantly more with dupilumab than with placebo at Week 12 (mean [SD] change from baseline -11.4 [6.7] with dupilumab versus -7.8 [7.2], LSMD [95% CI] -3.6 [-5.7, -1.5], P<0.001; Table 3). Sleep diary data at Week 12 showed a significantly larger reduction in awakenings (mean [SD] change from baseline -1.5 [1.7] vs -0.9 [1.3] for dupilumab vs placebo, LSMD [95% CI] -0.5 [-0.8, -0.1], P=0.010) and improved sleep efficiency (mean [SD] change from baseline 12.2 [16.4] vs 7.7 [13.9] for dupilumab vs placebo, LSMD [95% CI] 4.3 [0.4, 8.3], P=0.033) with dupilumab versus placebo. Sleepiness, as measured by the ESS, was significantly reduced at Week 12 with dupilumab versus placebo (mean [SD] change from baseline -4.1 [4.9] vs -1.3 [4.8] for dupilumab vs placebo, LSMD [95% CI] -2.6 [-4.1, -1.2] points, P<0.001. Mean sleepiness reduction on ESS was 4.1 points, which exceeds the 3-point threshold of clinical significance. Actigraphy did not

discern any significant differences between dupilumab and placebo with respect to sleep onset latency, wake after sleep onset, total sleep time, or sleep efficiency (Table 3).

Safety

The overall percentage of patients reporting treatment-emergent adverse events (TEAEs) was lower in the dupilumab group (56.7%) than in the placebo group (67.2%; Table 4). The most frequently reported TEAEs (preferred term with an incidence ≥5% in any treatment group) were in "Infections and infestations," "Nervous system disorders," and "Skin and subcutaneous tissue disorders" (Table S4). Most infections were mild or moderate in severity. Conjunctivitis was reported in a higher proportion of patients receiving dupilumab than in those receiving placebo (9.4% versus 4.9%, respectively), while headache and AD were reported in a higher proportion of patients receiving placebo than in those receiving dupilumab (8.2% and 13.1% in the placebo group and 7.1% and 3.1% in the dupilumab group, respectively).

Discussion

The primary endpoint of improvement in sleep NRS was significantly improved in dupilumab-treated patients at Week 12 compared with those receiving placebo. The results from DUPISTAD support previous reports of improved sleep quality in adult patients with AD who received dupilumab.[19] Furthermore, while a high placebo response was observed, the threshold for meaningful change (i.e. a 2- to 5-point reduction)[22] was met, with sleep NRS scores in dupilumab-treated patients improving by a mean of 3.2 points. Secondary endpoints, including PP NRS, EASI-50, EASI-75, DLQI, POEM, SCORAD, sleep efficiency, SCORAD sleep VAS, and PROMIS sleep-related impairment T-score, were also significantly improved with dupilumab versus placebo, with improvements reaching significance as early as Week 2 and continuing through Week 12. Of importance to note is that all patients in this study were provided with TCS to be used as needed, and patients were required to moisturize all

eczematous lesions, which may have contributed to the improvements in all AD metrics and sleep achieved in the placebo arm.

The reductions in itch observed with 12 weeks of dupilumab treatment were clinically meaningful, with an approximate 4-point mean improvement in PP NRS being achieved in the dupilumab-treated group.[23] This is an important result which may be reflected in the reported improvements in sleep, as it has been reported extensively that nighttime itching and scratching affects sleep in patients with AD.[6-14] However, reduction in inflammation has also been linked to better sleep, and as dupilumab inhibits signaling of both IL-4 and IL-13, key drivers of type 2-mediated inflammation, the improvements in sleep observed in this study may also stem from reduced inflammation.[18,31-33]

Furthermore, the minimally clinically important difference threshold of 8.7 points[27] was met for SCORAD total score, with the dupilumab group improving by an average of 37.8 points. Likewise, the clinically significant EASI-50[34] was also achieved in the vast majority of dupilumab-treated patients. With regards to the impact of AD on QoL, DLQI scores improved from a severe impact to a mild impact with dupilumab and optional TCS, whereas in the placebo and optional TCS group, DLQI scores only improved from a severe impact to a moderate impact, according to established severity strata for DLQI.[35]

Patient-reported awakening and sleep efficiency (captured by sleep diary) were also significantly improved with dupilumab versus placebo. However, dupilumab showed no statistically significant benefit over placebo on sleep onset latency and total sleep time, based on sleep diary data. Conceivably, as sleep becomes more restorative, sleep duration may not increase. Improvement of sleep efficiency and wake after sleep onset time was not noted with actigraphy. This may be related to differences between the AD patient population and usually healthy populations studied to validate actigraphy estimates of sleep parameters.[36,37] In addition, wrist-worn actigraphy may have caused discomfort in patients with local lesions, resulting in additional pruritus and scratching. The assessment of patient-reported sleep quality is important in this population and

it may be a limitation of wrist actigraphy that it is not as sensitive to sleep disturbance in patients with AD. More specific wearables may be required to measure nighttime scratch activity.

The primary endpoint of this study was a novel numeric rating scale (sleep NRS) developed to assess sleep quality. As such, it was directionally different (higher score = better) from all other numeric scales like itch, SCORAD sleep VAS, etc., which are designed to measure discomfort and inconvenience (i.e. higher score = worse). A limitation of these findings is that no validation data or psychometric properties are currently available for this novel numeric rating scale. While various actigraphy devices have been used for collecting objective wrist movement data that might correlate with sleep, data assessed by actigraphy remains open to issues of validity and reliability, particularly in patients with poor sleep quality.[36,37] Dupilumab significantly improved overall sleep continuity and quality and reduced daytime sleepiness, itch, and other AD-related signs, symptoms, and QoL in adults with moderate-to-severe AD, versus placebo. These improvements with dupilumab started as early as Week 2 and continued throughout the study. Dupilumab demonstrated a similar safety profile to that observed in earlier trials, with no new safety concerns identified. Future analyses will assess the persistence of dupilumab's effect on sleep disturbance through 24 weeks.

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Figure legends

Figure 1 Sleep quality NRS percent change from baseline over time; mITT population, mean (SE).

**P<0.001.

mITT, modified intention to treat; NRS, numeric rating scale; q2w, once every 2 weeks; SE, standard error.

Figure 2 Percent change in peak pruritus NRS over time mITT population; mean (SE).

**P<0.001.

mITT, modified intention to treat; NRS, numeric rating scale; q2w, once every 2 weeks; SE, standard error.

Figure 3 Change in (**a**) SCORAD total score and (**b**) SCORAD sleep VAS over time; mITT population, mean (SE).

**P<0.001.

mITT, modified intention to treat; q2w, once every 2 weeks; SCORAD, SCORing Atopic Dermatitis; SE, standard error; VAS, visual analog scale.

Figure 4 Percentage of patients with (**a**) EASI-50, (**b**) EASI-75, and (**c**) EASI-90 over time; mITT population, mean.

*P<0.05. **P<0.001.

EASI-50, 50% decrease in Eczema Area and Severity Index; EASI-75, 75% decrease in Eczema Area and Severity Index; EASI-90, 90% decrease in Eczema Area and Severity Index; mITT, modified intention to treat; q2w, once every 2 weeks.

Table 1 Baseline demographics and disease characteristics

Parameter[a]	Dupilumab 300 mg q2w (N=127)	Placebo (N=61)
Age, years	36.2 (14.7)	34.5 (15.4)
Male, n (%)	61 (48.0)	30 (49.2)
Race, n (%)		
White	103 (81.1)	46 (75.4)
Black or African American	6 (4.7)	1 (1.6)
Asian	13 (10.2)	11 (18.0)
Multiple	2 (1.6)	0
Not reported/unknown	3 (2.4)	3 (4.9)
Sleep quality NRS	6.7 (1.1)	7.0 (1.1)
SCORAD total score	64.7 (12.5)	62.8 (12.5)
SCORAD sleep VAS	7.1 (1.8)	7.0 (2.0)
PROMIS sleep-related impairment T-score	60.9 (5.7)	61.5 (5.8)
IGA, n (%)		
3	79 (62.2)	44 (72.1)
4	48 (37.8)	17 (27.9)
EASI	26.2 (11.9)	26.0 (9.9)
PP NRS	7.5 (1.4)	7.6 (1.5)
POEM	23.2 (3.9)	22.6 (4.6)
DLQI	16.2 (6.4)	16.8 (6.3)

[a]Values are presented as mean (SD) unless otherwise stated.

DLQI, Dermatology Life Quality Index; EASI, Eczema Area and Severity Index; IGA, Investigator's Global Assessment; NRS, numeric rating scale; POEM, Patient-Oriented Eczema Measure; PP, peak pruritus; PROMIS, Patient-Reported Outcomes Measurement Information System; q2w, every 2 weeks; SCORAD, SCORing Atopic Dermatitis; SD, standard deviation; VAS, visual analog scale.

Table 2 Overview of mean and change from baseline to Week 12 in sleep quality NRS, by subgroup

	Dupilumab 300 mg q2w (N=127)			Placebo (N=61)			LSMD (95% CI) between the dupilumab and placebo groups	P-value[a]
	Baseline	Week 12	% change from baseline	Baseline	Week 12	% change from baseline		
Sleep quality NRS[b]	n=126 6.7 (1.1)	n=122 3.4 (1.8)	-47.7 (27.2)	n=61 7.0 (1.1)	n=60 4.6 (2.0)	-33.0 (29.5)	-15.5 (-24.1, -6.9)	<0.001
Age, years								
≥18 to <40	n=78 6.7 (1.2)	n=75 3.4 (1.7)	-48.2 (24.9)	n=41 7.0 (1.2)	n=41 4.6 (2.1)	-33.3 (31.7)	-15.9 (-26.1, -5.7)	0.002
≥40 to <65	n=39 6.6 (1.0)	n=39 3.65 (2.2)	-44.8 (31.2)	n=15 6.8 (0.7)	n=14 4.5 (1.9)	-34.6 (26.7)	-10.7 (-29.8, 8.4)	0.267
≥65	n=9 6.6 (1.2)	n=8 2.6 (1.6)	-57.6 (28.9)	n=5 7.3 (0.9)	n=5 5.4 (1.7)	-25.5 (21.1)	-27.9 (-68.7, 12.9)	0.157
Gender								
Male	n=60 6.7 (1.0)	n=59 3.2 (1.8)	-51.3 (27.5)	n=30 7.0 (1.1)	n=29 4.6 (2.3)	-34.3 (30.8)	-17.8 (-30.7, -5.0)	0.007
Female	n=66 6.7 (1.3)	n=63 3.7 (1.8)	-44.4 (26.8)	n=31 7.0 (1.1)	n=31 4.7 (1.7)	-31.7 (28.8)	-13.5 (-25.2, -1.7)	0.025
Bodyweight, kg								
<70	n=58 6.7 (1.2)	n=55 3.4 (1.8)	-48.2 (26.4)	n=31 6.9 (0.9)	n=30 4.5 (2.0)	-34.0 (31.2)	-13.7 (-26.2, -1.2)	0.033
≥70 to <100	n=53 6.6 (1.0)	n=52 3.5 (1.8)	-45.4 (28.5)	n=24 7.1 (1.3)	n=24 4.6 (2.1)	-34.2 (27.6)	-14.5 (-28.3, -0.6)	0.041
≥100	n=14 6.9 (1.5)	n=14 3.3 (2.1)	-52.4 (26.9)	n=6 6.9 (1.1)	n=6 5.3 (2.4)	-23.5 (32.0)	-26.6 (-56.0, 2.7)	0.073
Baseline PP NRS								
<7	n=38 6.0 (0.8)	n=36 3.5 (1.6)	-40.6 (26.6)	n=18 6.6 (0.6)	n=18 4.0 (2.2)	-39.3 (30.9)	-2.1 (-20.2, 16.0)	0.816
≥7	n=86 7.0 (1.1)	n=82 3.4 (2.0)	-51.1 (27.5)	n=39 7.2 (1.1)	n=38 4.8 (1.9)	-31.8 (29.3)	-19.6 (-30.2, -8.9)	<0.001

Values are presented as mean (SD).

[a]The overall family-wise type-I error rate was controlled at the 0.05 level (two-sided) using a sequential testing procedure (in the order shown in the table).

To proceed to the secondary endpoints, the primary endpoint must be significant at the 0.05 significance level. Each endpoint was tested at the 0.05 (two-

sided) level of significance. If at any step the null statistical hypothesis of no treatment difference is not rejected (i.e. P>0.05), the endpoints listed after that step were reported at the nominal level.

[b]Primary endpoint.

CI, confidence interval; LSMD, least squares mean of the difference; NRS, numerical rating scale; PP, Peak Pruritus; q2w, every 2 weeks; SD, standard deviation.

Table 3 Overview of mean and change from baseline to Week 12 in secondary and selected exploratory endpoints

	Dupilumab 300 mg q2w (N=127)			Placebo (N=61)			LSMD (95% CI) between the dupilumab and placebo groups	P-value[a]
	Baseline	Week 12	% change/change	Baseline	Week 12	% change/change		
EASI score	n=127 26.2 (11.9)	n=109 6.1 (7.4)	-74.1 (38.0)	n=61 26.0 (9.9)	n=48 12.8 (10.3)	-50.3 (38.3)	-25.1 (-37.7, -12.5)	<0.001
DLQI score	n=115 16.2 (6.4)	n=90 4.5 (5.2)	-11.8 (6.5)	n=52 16.8 (6.3)	n=39 9.3 (5.4)	-7.5 (6.8)	-4.5 (-6.4, -2.6)	<0.001
POEM score	n=115 23.2 (3.9)	n=90 9.5 (7.1)	-13.6 (7.5)	n=52 22.6 (4.6)	n=39 17.9 (7.4)	-4.4 (6.8)	-8.3 (-10.9, -5.8)	<0.001
PROMIS sleep-related impairment T- score	n=117 60.9 (5.7)	n=103 49.8 (6.8)	-11.4 (6.7)	n=56 61.6 (5.7)	n=54 54.0 (7.00)	-7.8 (7.2)	-3.6 (-5.7, -1.5)	<0.001
Weekly average awakenings (sleep diary)	n=122 2.8 (1.8)	n=117 1.3 (1.1)	-1.5 (1.7)	n=61 2.6 (1.2)	n=57 1.6 (1.4)	-0.9 (1.3)	-0.5 (-0.8, -0.1)	0.010
Rested NRS at awakening (sleep diary)	n=122 3.5 (1.3)	n=117 6.3 (1.8)	2.8 (1.9)	n=61 3.4 (1.4)	n=57 5.1 (1.9)	1.9 (1.9)	1.0 (0.5, 1.5)	<0.001
Weekly average sleep efficiency (sleep diary)	n=122 75.4 (17.1)	n=117 87.8 (15.1)	12.2 (16.3)	n=61 76.4 (13.7)	n=57 83.8 (12.0)	7.7 (13.9)	4.3 (0.4, 8.3)	0.033
Weekly average sleep onset latency (sleep diary), min	n=122 75.0 (68.8)	n=117 44.3 (76.0)	-28.7 (97.7)	n=61 72.9 (63.6)	n=57 56.1 (55.0)	-19.6 (79.2)	-11.3 (-33.5, 11.0)	0.320
Weekly average total sleep time (sleep diary), min	n=122 408.7 (143.6)	n=117 453.4 (121.0)	47.0 (151.8)	n=61 411.7 (103.5)	n=57 437.4 (82.2)	33.5 (87.1)	18.9 (-13.8, 51.7)	0.255
Weekly average wake after sleep onset (sleep diary), min	n=122 61.9 (68.9)	n=117 24.7 (56.3)	-36.0 (48.4)	n=61 57.8 (45.8)	n=57 32.3 (43.4)	-24.4 (35.9)	-9.8 (-21.7, -2.0)	0.104
ESS score	n=114 10.9 (4.5)	n=99 6.8 (4.9)	-4.1 (4.9)	n=52 10.5 (4.9)	n=50 9.3 (5.0)	-1.3 (4.8)	-2.6 (-4.0, -1.2)	<0.001
Sleep efficiency (actigraphy), %	n=118 75.7 (9.0)	n=108 77.3 (7.6)	1.8 (6.6)	n=56 76.5 (6.6)	n=47 78.0 (7.0)	1.5 (6.0)	0.2 (-1.6, 2.0)	0.824
Total sleep time (actigraphy), min	n=118 369.1 (85.0)	n=108 375.5 (70.6)	9.0 (71.0)	n=56 370.8 (60.4)	n=47 372.4 (66.4)	-6.4 (55.6)	10.6 (-8.2, 29.5)	0.268
Wake after sleep onset (actigraphy), min	n=118 72.3 (26.5)	n=108 65.8 (28.3)	-6.8 (22.8)	n=56 74.3 (29.9)	n=47 66.7 (27.4)	-9.2 (24.7)	0.7 (-6.5, 7.9)	0.842
Sleep onset latency (actigraphy), min	n=118 24.7 (17.6)	n=108 23.4 (15.4)	-1.4 (20.0)	n=56 24.0 (18.0)	n=47 21.6 (17.2)	-3.4 (21.5)	2.1 (-3.1, 7.3)	0.427

Values are presented as mean (SD) unless otherwise stated.

[a]The overall family-wise type-I error rate was controlled at the 0.05 level (two-sided) using a sequential testing procedure (in the order shown in the table). To proceed to the secondary endpoints, the primary endpoint must be significant at the 0.05 significance level. Each endpoint was tested at the 0.05 (two-sided) level of significance. If at any step the null statistical hypothesis of no treatment difference is not rejected (i.e. P>0.05), the endpoints listed after that step were reported at the nominal level.

CI, confidence interval; DLQI, Dermatology Life Quality Index; EASI, Eczema Area and Severity Index; ESS, Epworth Sleepiness Scale; LSMD, least squares mean of the difference; POEM, Patient-Oriented Eczema Measure; PROMIS, Patient-Reported Outcomes Measurement Information System; NRS, numeric rating scale; q2w, every 2 weeks; SD, standard deviation.

Table 4 Summary of treatment-emergent adverse events during the double-blind treatment period

n (%)	Dupilumab 300 mg q2w (N=127)	Placebo (N=61)
TEAE	72 (56.7)	41 (67.2)
Serious TEAE	2 (1.6)	1 (1.6)
TEAE leading to permanent treatment discontinuation	3 (2.4)	1 (1.6)
TEAE of special interest	4 (3.1)	1 (1.6)
Serious TEAE of special interest[a]	1 (0.8)	1 (1.6)
TEAE leading to death	0	0

[a]Pre-specified TEAEs of special interest included: anaphylaxis, systemic or severe hypersensitivity reactions, malignancy (except *in situ* carcinoma of the cervix and non-basal cell carcinoma of the skin), helminth infections, suicide-related events, any type of conjunctivitis or blepharitis (severe or serious), keratitis, pregnancy occurring in a female patient or female partner of a male patient administered IMP/NIMP, or symptomatic overdose of IMP/NIMP.

IMP, investigational medicinal product; NIMP, non-investigational medicinal product; q2w, once every 2 weeks; TEAE, treatment-emergent adverse event.

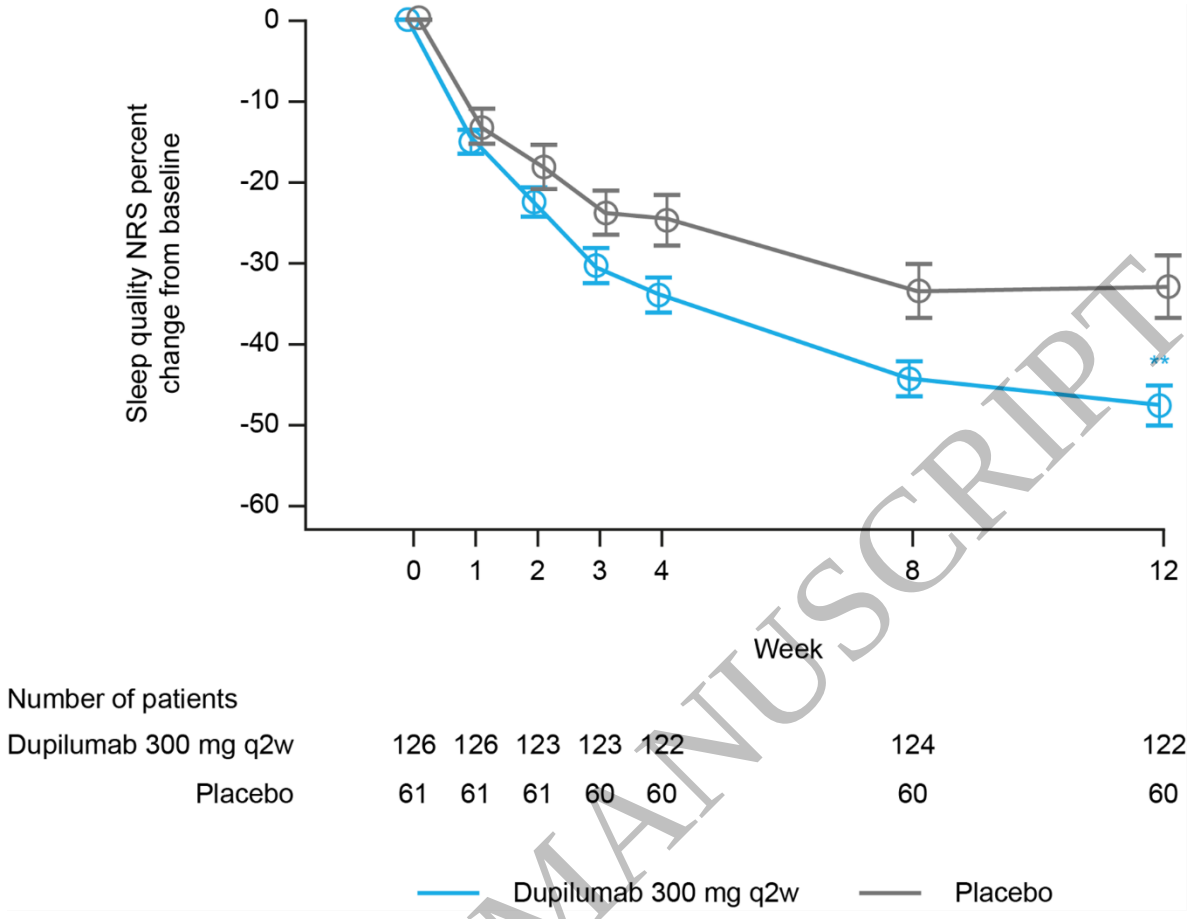

Figure 1
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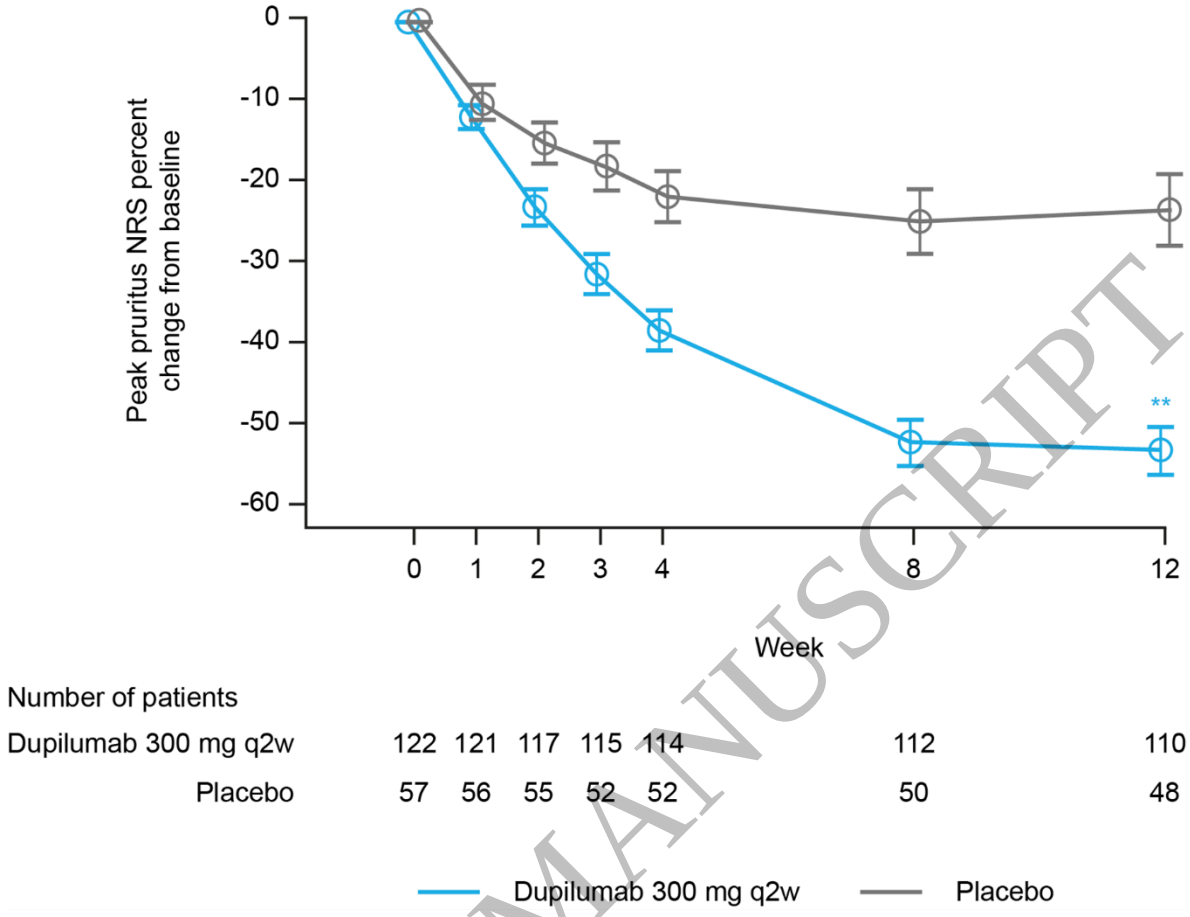

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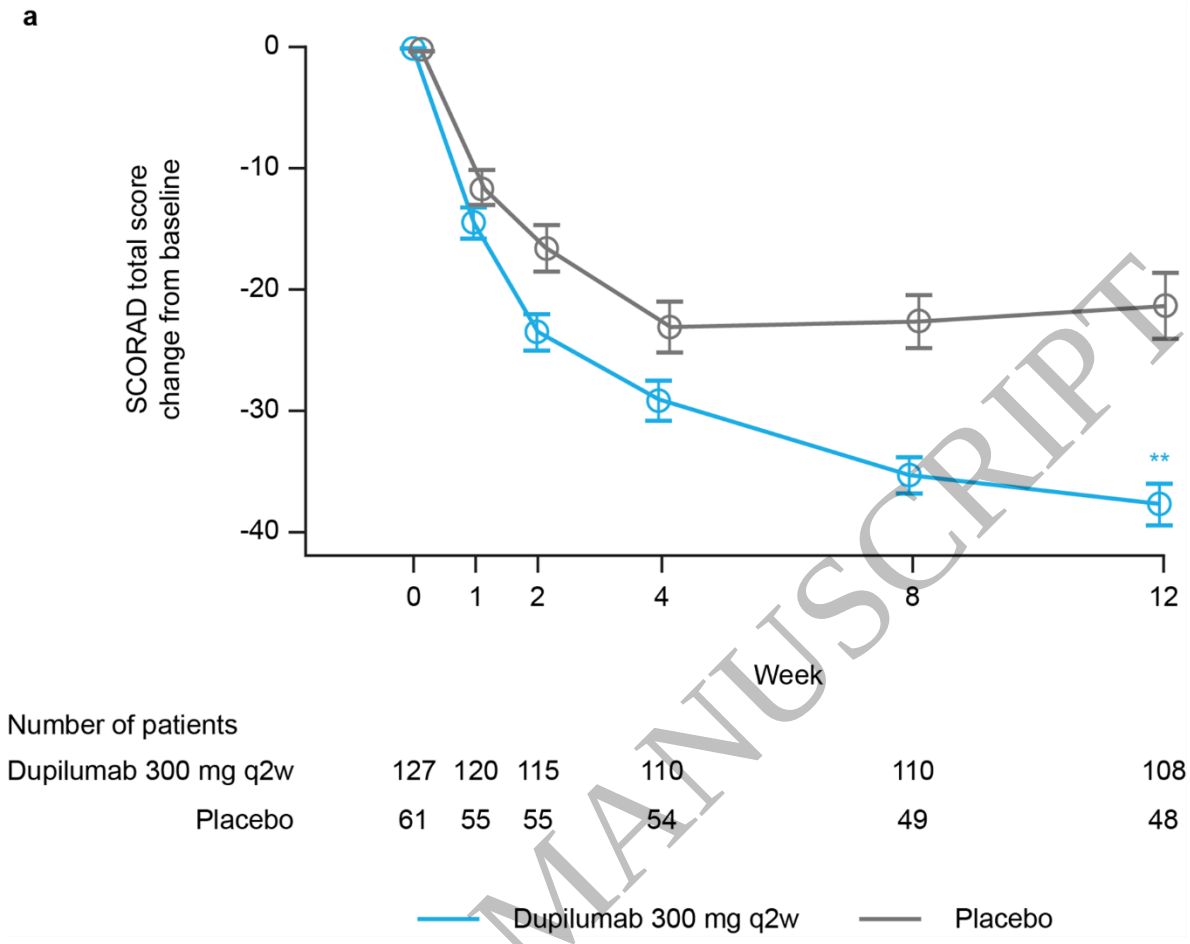

Figure 3a
156x124 mm (x DPI)

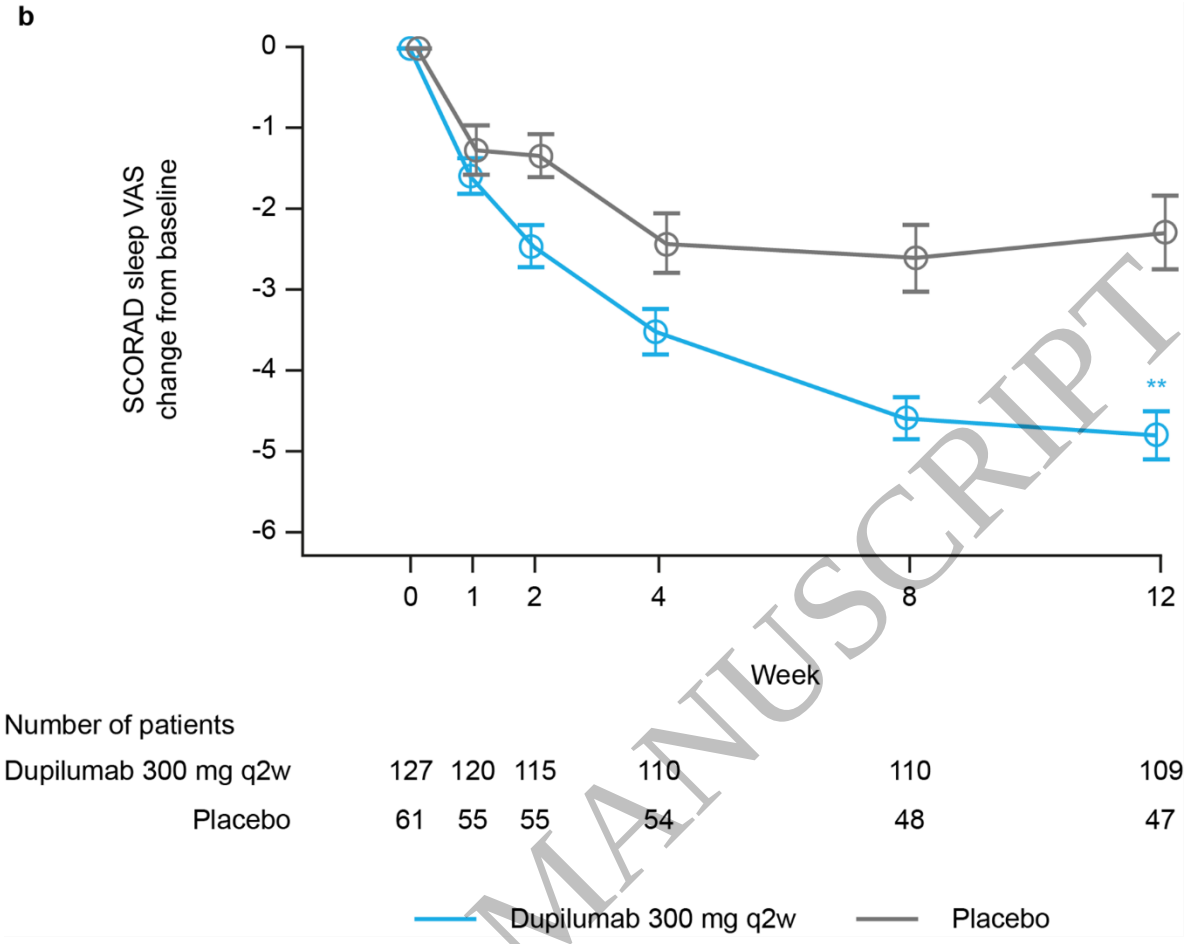

Figure 3b
156x124 mm (x DPI)

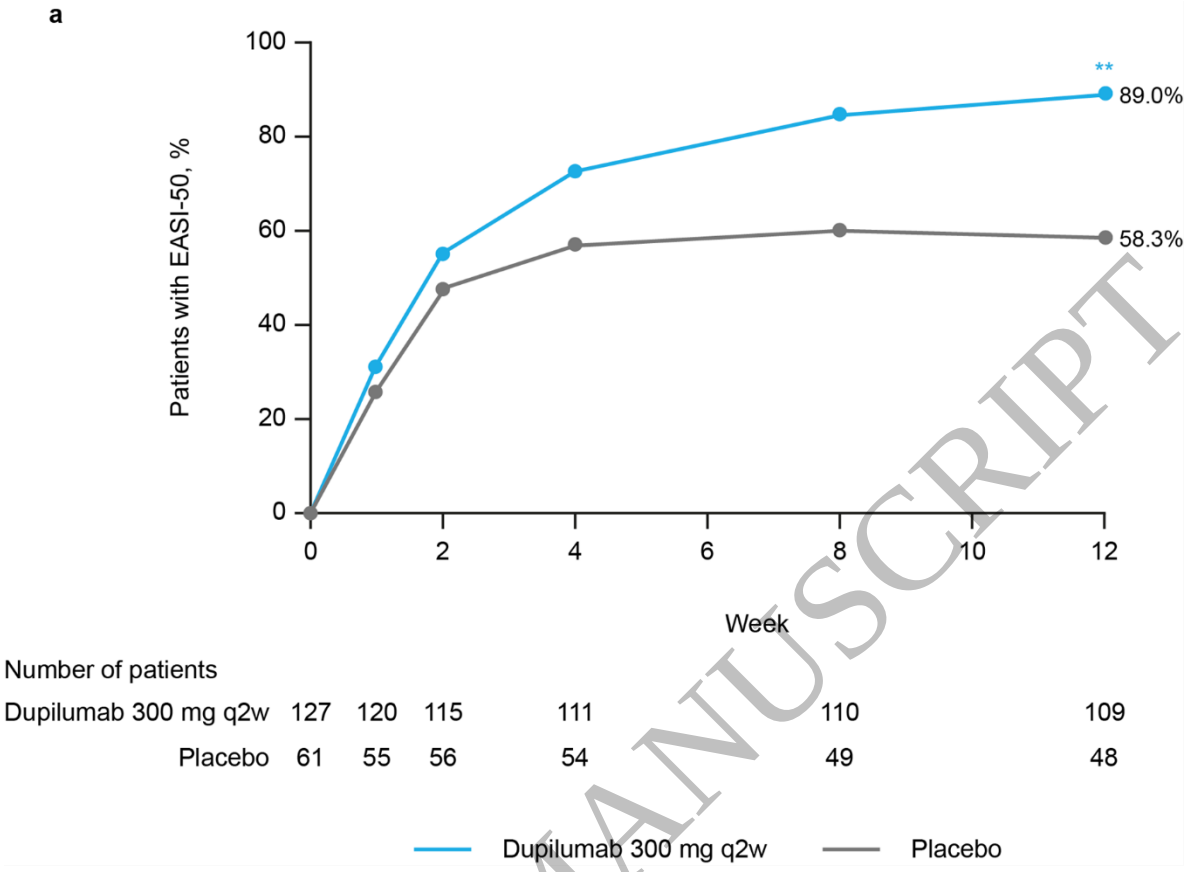

Figure 4a
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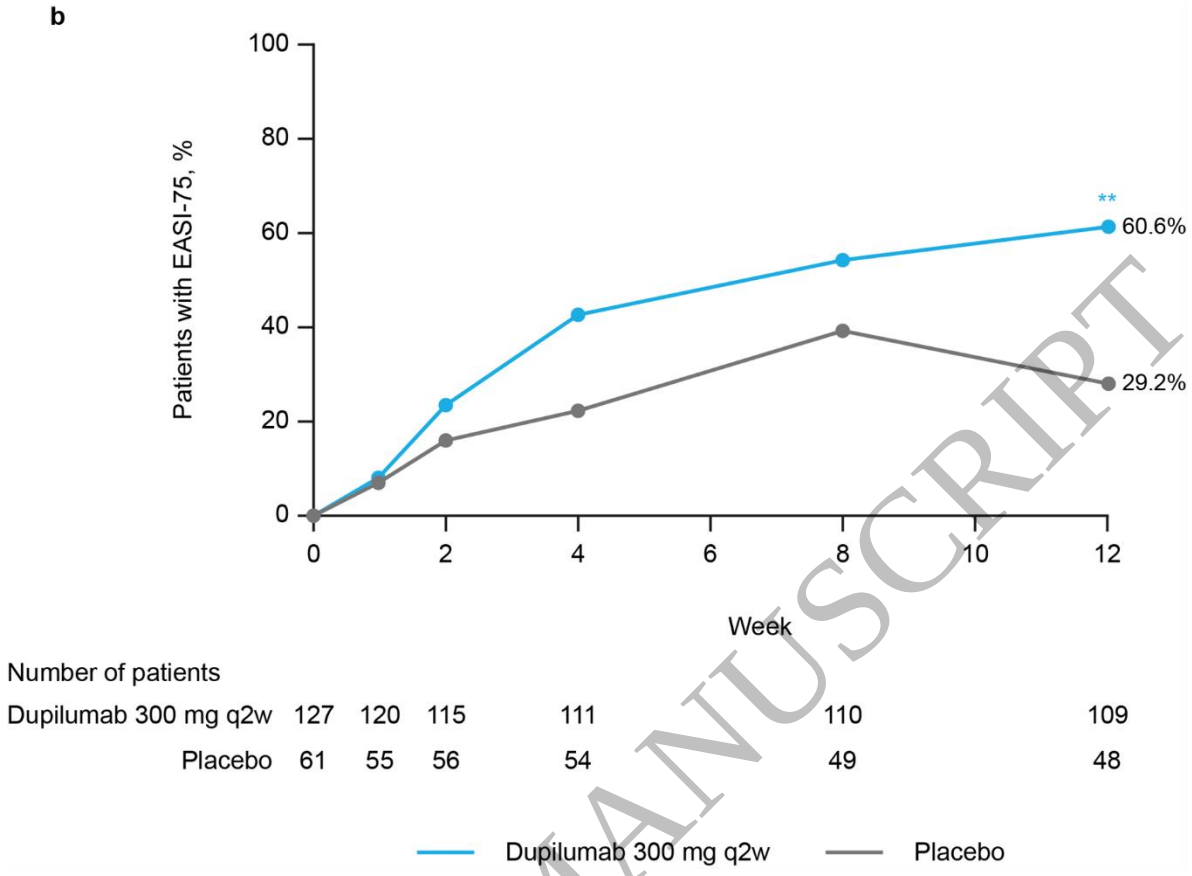

Figure 4b
156x114 mm (x DPI)

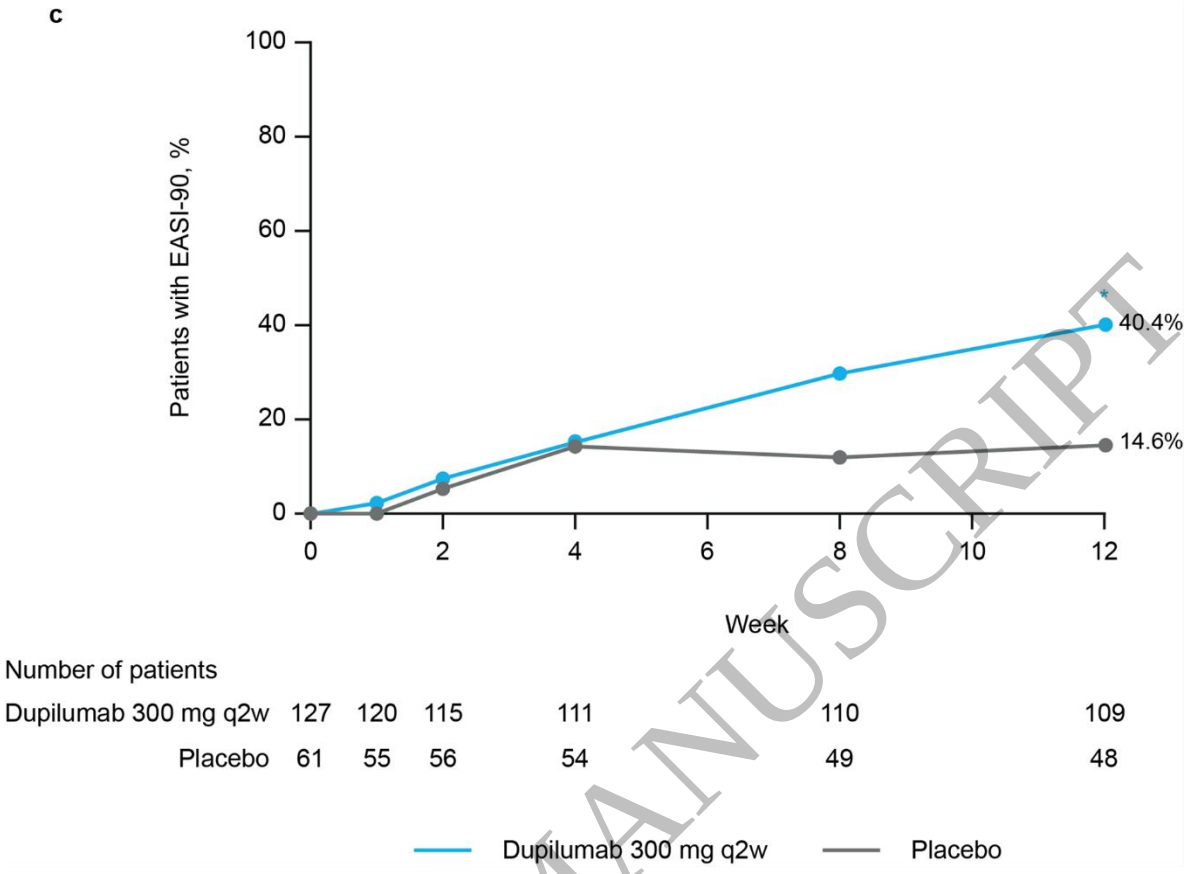

Figure 4c
156x114 mm (x DPI)