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ORIGINAL RESEARCH

# Onset and Long-Term Maintenance of Optimal Itch Response in Adult Patients with Moderate-to-Severe Atopic Dermatitis Treated with Dupilumab: Post Hoc Analysis from Two Phase 3 Trials

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## ABSTRACT

***Introduction***: The treat-to-target concept established goals to guide treatment with systemic therapies in atopic dermatitis (AD), including goals for itch improvement, reported as the most burdensome symptom. The aim of this study is to assess optimal itch response onset and long-term maintenance using treat-to-target criteria in dupilumab-treated patients.

***Methods***: This post hoc analysis assessed patients ≥ 18 years with moderate-to-severe AD in two phase 3, randomized, double-blind, placebo-controlled studies. Patients received dupilumab 300 mg every 2 weeks or placebo with concomitant topical corticosteroids (TCS) for 52 weeks (CHRONOS); or dupilumab monotherapy 300 mg every week/every 2 weeks/every 4 weeks/every 8 weeks or placebo for 36 weeks after achieving Eczema Area and Severity Index improvement of 75% or Investigator's Global Assessment 0/1 with dupilumab in SOLO1/2 (SOLO-CONTINUE). Optimal itch response was defined as Peak Pruritus Numeric Rating Scale ≤ 4.

***Results***: Patients receiving dupilumab + TCS achieved optimal itch response faster and in higher proportion than those receiving placebo + TCS ($P < 0.0001$) and maintained optimal response longer (median [Q1–Q3] 40 [11–50] vs 3 [0–23] weeks; $P < 0.0001$). Patients achieving

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optimal itch response with dupilumab monotherapy who continued treatment maintained response longer compared with those transitioned to placebo, although duration decreased with less frequent dosing ($P < 0.0001$ for all dupilumab regimens vs placebo).

***Conclusion***: Optimal itch response was achieved rapidly and maintained long term in adult patients treated with dupilumab with or without concomitant TCS therapy.

***Trial Registration***: NCT02395133 and NCT02260986.

## PLAIN LANGUAGE SUMMARY

Atopic dermatitis (AD), the most common skin disorder, presents mainly with skin lesions that can be intensely itchy. Itch deeply impacts patients with AD and their quality of life; scratching due to itching can also worsen the lesions. An increasing number of "systemic therapies" (working through the whole body as opposed to, for example, treatments applied on the skin) have recently been approved for the treatment of AD. To help physicians decide between systemic treatment options, a guidance called "treat-to-target concept" defines specific treatment goals to be reached within a certain time, including specific improvements in itch. In this work, we analyzed itch improvement in patients with moderate-to-severe AD treated with the systemic therapy dupilumab. Patients treated with dupilumab achieved the intended itch improvement significantly faster compared to those receiving placebo (a saline solution without active treatment). Most importantly, patients treated with dupilumab maintained this improvement significantly longer than those receiving placebo. When patients who had achieved improvement in AD signs and symptoms (including itch) were assigned to continue dupilumab (in the same dose or less frequently) or placebo, those patients continuing dupilumab maintained itch improvement significantly longer than those switched to placebo, although the duration of improvement decreased in those receiving dupilumab less frequently. It should be noted that these analyses were decided upon and performed only after the data became available ("post hoc analyses"), which is a limitation. In conclusion, patients with AD treated with dupilumab achieved improvement of their itch rapidly, and this improvement was maintained long term.

**Keywords:** Atopic dermatitis; Pruritus; Clinical studies; Efficacy; Treat-to-target; Adults; Dupilumab

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**Key Summary Points**

*Why carry out this study?*

Treatment of patients with moderate-to-severe atopic dermatitis is becoming increasingly complex as a result of approval of an increasing number of advanced systemic therapies.

A treat-to-target (T2T) concept has been developed, defining specific treatment goals to be reached within a set timeframe to guide treatment decisions.

This analysis assessed onset and long-term maintenance of optimal itch response as defined per T2T concept for treatment with dupilumab.

*What was learned from the study?*

Long-term maintenance of optimal itch response was achieved in most patients treated with dupilumab, but was gradually lower for patients who switched to less frequent dosing.

## INTRODUCTION

Atopic dermatitis (AD) is the most common inflammatory skin disorder, affecting up to 10% of adults and 20% of children in high-income countries [1, 2]. It is a chronic, relapsing disease characterized by eczematous skin lesions, intense itch, and increased risk of skin infections, which can be accompanied by additional manifestations and conditions such as xerosis and other diseases with type 2 inflammation [2–4]. AD imposes a substantial disease burden on patients, underlining the need for efficacious treatments [1].

With the approval of an increasing number of advanced systemic therapies, treatment of patients with moderate-to-severe AD is becoming increasingly complex. To guide treatment decisions, a treat-to-target (T2T) concept has been developed that defines specific treatment goals, to be reached within a set timeframe [5–7]. It proposes both initial relative 3-month and optimal absolute 6-month treatment targets. These time points reflect the usual clinical practice check-ins.

A key feature of disease control as perceived by patients is itch [8, 9]. Excessive and prolonged itching can lead to sleep disturbances: patients with AD report an average of 4.4 nights per week of impacted sleep [10, 11]. Itch not only impacts the patients' quality of life but also contributes to furthering AD pathogenesis through the itch–scratch cycle and additional breakdown of the epidermal barrier [4, 12].

For pruritus, the optimal 6-month treatment target based on the T2T concept is a patient-reported Peak Pruritus Numeric Rating Scale (PP-NRS) score of ≤ 4 points. This target stems from a consensus agreement from an expert panel consisting of physicians, nurses, and patients/patient organizations. Adaptations of this algorithm to local clinical practice have been published [5, 13].

Dupilumab was the first advanced systemic treatment approved for the treatment of moderate-to-severe AD in patients uncontrolled with topical prescription therapies and has shown a significant itch improvement in multiple clinical studies with adult patients [14, 15]. Here, we aim to assess the onset and long-term maintenance of optimal itch response (PP-NRS ≤ 4) according to the T2T concept in adult patients with moderate-to-severe AD treated with dupilumab. We conducted post hoc analyses of the two long-term, randomized, placebo-controlled phase 3 studies: the 52-week study CHRONOS was used to determine onset and long-term maintenance of optimal itch response of dupilumab in combination with topical corticosteroids (TCS), and the 36-week study SOLO-CONTINUE (in patients who achieved 75% improvement from baseline in Eczema Area and Severity Index [EASI-75] and/or Investigator's Global Assessment [IGA] 0/1 after 16 weeks of dupilumab monotherapy in parent studies SOLO1 and SOLO2) was used to determine long-term maintenance of optimal itch response with different dosing regimens of dupilumab monotherapy in those with PP-NRS ≤ 4 at SOLO-CONTINUE baseline.

# METHODS

## Study Design

This analysis included patients enrolled in two different phase 3, randomized, double-blind, placebo-controlled studies: LIBERTY AD CHRONOS and LIBERTY AD SOLO-CONTINUE.

CHRONOS enrolled adult patients with moderate-to-severe AD that were not adequately controlled with medium-to-high-potency TCS. Patients were treated with dupilumab 300 mg every 2 weeks (q2w) or every week (qw) in combination with TCS or placebo + TCS for 52 weeks. Details on the required TCS application, tapering, and protocols for rescue medication were reported previously [14]. This post hoc analysis included only patients randomized to receive either the approved dupilumab 300 mg q2w dosing + TCS or placebo + TCS.

SOLO-CONTINUE enrolled adult patients from SOLO1 and SOLO2, who, after treatment with dupilumab 300 mg q2w or qw, had achieved either IGA 0/1 or EASI-75 at the end of the 16-week treatment period. Patients were then re-randomized to dupilumab 300 mg qw, q2w, every 4 weeks (q4w), every 8 weeks (q8w), or placebo for 36 weeks. For this post hoc analysis, only patients with a PP-NRS score ≤ 4 at SOLO-CONTINUE baseline after 16 weeks of treatment with dupilumab qw/q2w were included.

## Endpoints

In CHRONOS, time to optimal itch response, percentage of patients achieving optimal response over time, and duration of optimal itch response (number, percentage, and maximum weeks with itch response) were assessed. To measure long-term maintenance of optimal itch response, the number and percentage of weeks with PP-NRS ≤ 4 were calculated for each patient, and the maximum duration of weeks was defined as the longest period of consecutive weeks with PP-NRS ≤ 4 for each patient. Patients reported PP-NRS daily (weeks 0–16) or weekly (weeks 17–52); therefore, weekly average of daily PP-NRS was used on weeks 0–16.

In SOLO-CONTINUE, maintenance of optimal itch response, both as percentage of patients maintaining itch response over time and number of weeks with maintenance of itch response, was assessed. Patient assessment of PP-NRS was recorded weekly during SOLO-CONTINUE; therefore, we report weekly PP-NRS.

## Statistical Analysis

For median time to optimal itch response in CHRONOS, Kaplan–Meier analyses were conducted to estimate time to event. Patients were considered non-responders after rescue treatment use and were censored at the date when rescue treatment was used; non-responders without rescue treatment were censored at last assessment date within the treatment period, and patients without assessments post baseline were considered to be non-responders after rescue and were censored at randomization date. Time to event was calculated as date of first event − date of first dose + 1. Patients without an event were censored at the end of the 52-week treatment period or at last study date if the patient discontinued early from study. Hazard ratios were calculated using a Cox model, including factors of treatment group and randomization strata (disease severity [IGA = 3 vs IGA = 4]).

For the percentage of patients achieving and maintaining optimal itch response in CHRONOS, last observation carried forward (LOCF) was used to impute missing data. Data recorded on or after rescue medication use were considered to be loss of itch response. *P* values were derived from a Cochran–Mantel–Haenszel test stratified by region and baseline disease severity (IGA = 3 vs IGA = 4).

For analysis of duration of optimal itch response in CHRONOS, estimate rate, rate ratio, and *P* values were calculated from a Poisson regression model, with treatment as a fixed factor and LOCF was used to impute missing data. If a patient received rescue medication, any subsequent days (including day of rescue) were considered to be days with loss of itch response.

For percentage of patients maintaining optimal itch response in SOLO-CONTINUE, LOCF was used for missing data, and patients who received or after receiving rescue treatment were considered non-responders. No *P* values were calculated; the data were descriptive.

For number of weeks with maintenance of optimal itch response in SOLO-CONTINUE, LOCF was used for missing data, and data on or after rescue treatment use were considered loss of itch response. *P* values are from a Poisson regression model, with number of weeks with maintenance of itch response as response variable, treatment as the only covariate, and log-transformed standardized number of weeks during treatment period as an offset variable.

### Ethics

The study was conducted in accordance with the Declaration of Helsinki, the International Conference on Harmonisation Good Clinical Practice guideline, and applicable regulatory requirements. An independent data and safety monitoring committee conducted blinded monitoring of patient safety data. The local institutional review board or ethics committee at each study center oversaw trial conduct and documentation. Signed written informed consent was obtained from all patients participating in both trials.

## RESULTS

Baseline demographics and disease characteristics were comparable between treatment arms in both studies (CHRONOS [14]; Table S1 in the electronic supplementary material [SOLO-CONTINUE]).

### Onset and Long-Term Maintenance of Optimal Itch Response in CHRONOS

In CHRONOS, 106 patients were randomized to receive dupilumab 300 mg q2w with concomitant TCS and 315 to placebo with concomitant TCS. Median time to optimal itch response (PP-NRS ≤ 4) was significantly faster in patients treated with dupilumab 300 mg q2w + TCS than those treated with placebo + TCS (median days [95% confidence interval (CI)] = 29.0 [22.0–43.0] for dupilumab + TCS vs 64.0 [43.0–105.0] for placebo + TCS; hazard ratio [95% CI] = 1.7 [1.3–2.2], $P < 0.0001$).

A significantly higher proportion of patients treated with dupilumab + TCS compared with those treated with placebo + TCS achieved optimal itch response at both 6 months (61.3% vs 26.7%, $P < 0.0001$) and 52 weeks (64.2% vs 21.9%, $P < 0.0001$) (Fig. 1).

Optimal itch response was achieved in most of the treatment period for patients treated with dupilumab + TCS, the median (quartile [Q]1–Q3) number of weeks with optimal itch response was 40.0 (11.0–50.0) weeks; in the placebo + TCS group, it was 3.0 (0.0–23.0) weeks ($P < 0.0001$) (Fig. 2). This corresponds to a median (Q1–Q3) of 77.1 (24.5–94.3) percent of the total study duration (52 weeks) with optimal itch response in the dupilumab + TCS group and 5.7 (0.0–49.1) percent in the placebo + TCS group (Fig. 2). The median (Q1–Q3) maximum duration of consecutive weeks with optimal itch response was 29.5 (4.0–50.0) weeks in patients treated with dupilumab + TCS. In patients treated with placebo + TCS, this duration was 2.0 (0.0–13.0) weeks ($P < 0.0001$) (Fig. 2).

### Long-Term Maintenance of Optimal Itch Response in SOLO-CONTINUE

In this post hoc analysis of SOLO-CONTINUE, a total of 324 patients were analyzed after achieving EASI-75 or IGA 0/1 and PP-NRS ≤ 4 following 16 weeks of treatment with dupilumab 300 mg qw/q2w in parent studies SOLO1 and SOLO2: 69 patients were re-randomized to dupilumab 300 mg qw, 58 to q2w, 61 to q4w, 68 to q8w, and 68 to placebo. The percentage of patients who maintained optimal itch response (PP-NRS ≤ 4) was highest for patients who continued treatment with dupilumab 300 mg qw or q2w (75.8% and 77.6% patients at week 36, respectively), and it decreased with less frequent dosage

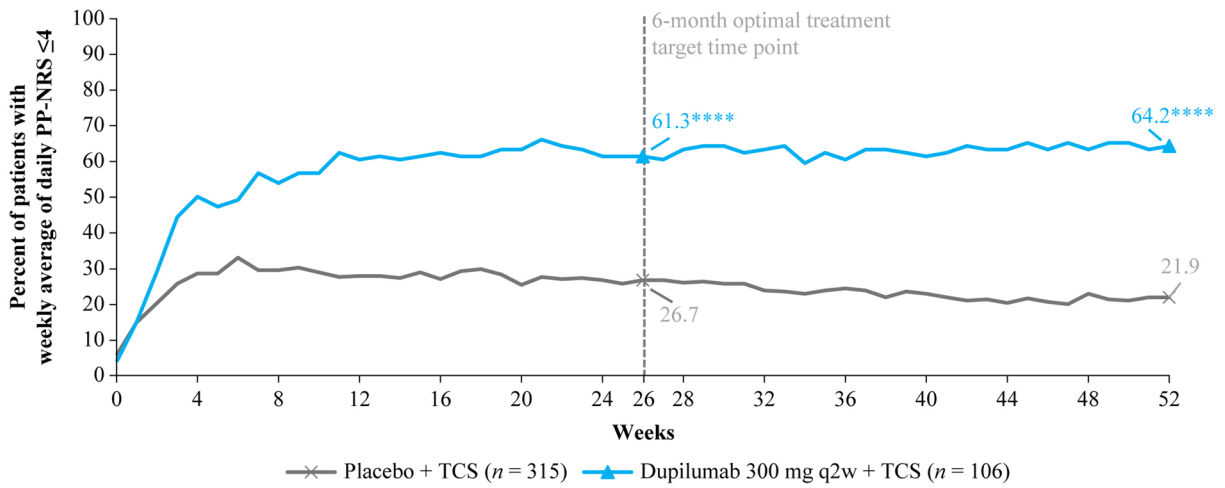
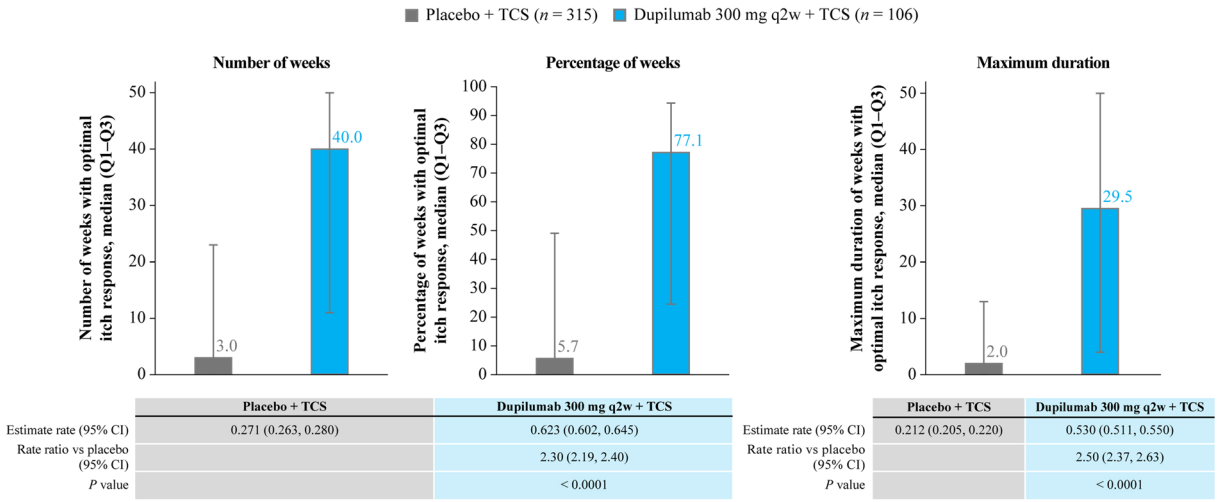



**Fig. 1** CHRONOS: proportion of patients achieving optimal itch response (PP-NRS ≤ 4) through 52 weeks. *PP-NRS* Peak Pruritus Numeric Rating Scale, *q2w* every 2 weeks, *TCS* topical corticosteroids. ****$P < 0.0001$




| | Placebo + TCS | Dupilumab 300 mg q2w + TCS |
|---|---|---|
| Estimate rate (95% CI) | 0.271 (0.263, 0.280) | 0.623 (0.602, 0.645) |
| Rate ratio vs placebo (95% CI) | | 2.30 (2.19, 2.40) |
| *P* value | | < 0.0001 |

| | Placebo + TCS | Dupilumab 300 mg q2w + TCS |
|---|---|---|
| Estimate rate (95% CI) | 0.212 (0.205, 0.220) | 0.530 (0.511, 0.550) |
| Rate ratio vs placebo (95% CI) | | 2.50 (2.37, 2.63) |
| *P* value | | < 0.0001 |

**Fig. 2** CHRONOS: number, percentage, and maximum duration of weeks with optimal itch response (PP-NRS ≤ 4) through 52 weeks. *CI* confidence interval, *PP-NRS* Peak Pruritus Numeric Rating Scale, *Q* quartile, *q2w* every 2 weeks, *TCS* topical corticosteroids

(60.4% and 47.3% for the dupilumab q4w and q8w arms, respectively), being the lowest for patients who transitioned to placebo (30.4% patients; Fig. 3). Patients continuing dupilumab treatment maintained optimal itch response for most of the treatment period: median (Q1–Q3) number of weeks with optimal itch response was 34.0 (23.0–37.0) for dupilumab qw, 35.5 (19.0–37.0) for q2w, 31.0 (10.0–35.0) for q4w, and 27.0 (12.5–36.0) for q8w. Patients who transitioned to placebo maintained optimal itch response for 14.5 (6.0–30.0) weeks (Fig. 4).

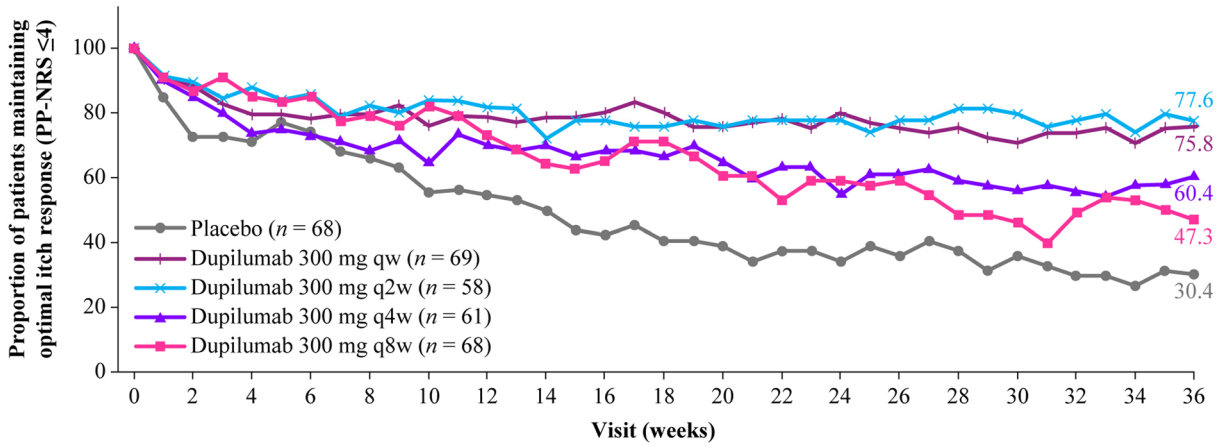



**Fig. 3** SOLO-CONTINUE: percent of patients who achieved EASI-75 and/or IGA 0/1 at the end of parent study with maintenance of optimal itch response (PP-NRS ≤ 4) through 36 weeks. *EASI-75* 75% improvement from baseline in Eczema Area and Severity Index, *IGA* Investigator's Global Assessment, *PP-NRS* Peak Pruritus Numeric Rating Scale, *qw* weekly, *q2w* every 2 weeks, *q4w* every 4 weeks, *q8w* every 8 weeks

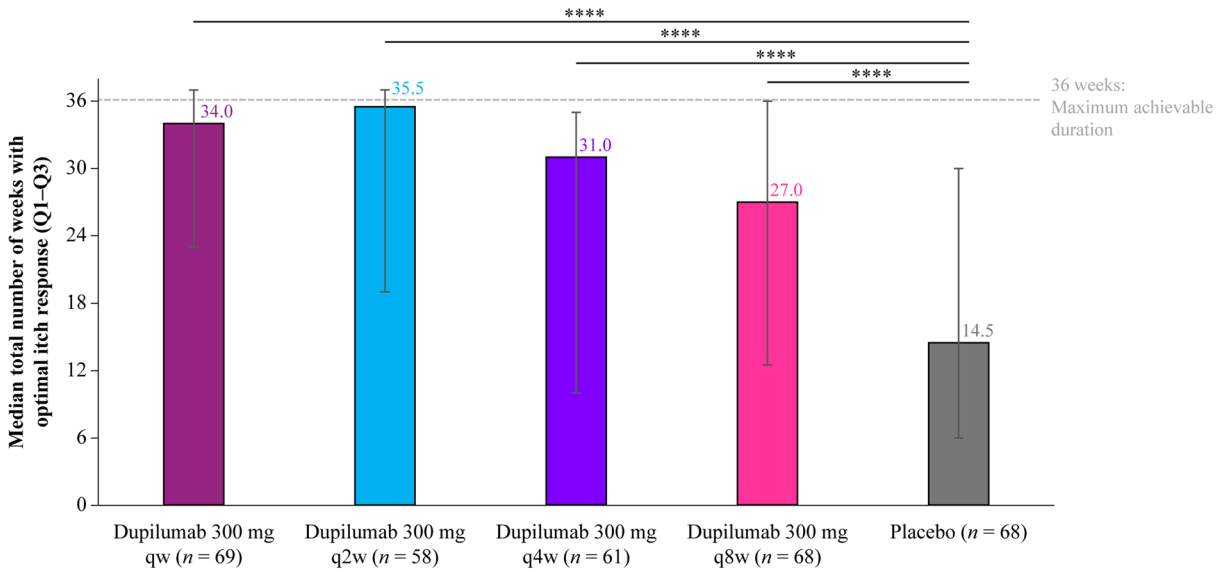



**Fig. 4** SOLO-CONTINUE: number of weeks with optimal itch response (PP-NRS ≤ 4) at week 36 after achieving EASI-75 and/or IGA 0/1 and PP-NRS ≤ 4 at the end of parent study. *EASI-75* 75% improvement from baseline in Eczema Area and Severity Index, *IGA* Investigator's Global Assessment, *PP-NRS* Peak Pruritus Numeric Rating Scale, *Q* quartile, *qw* weekly, *q2w* every 2 weeks, *q4w* every 4 weeks, *q8w* every 8 weeks. ****$P < 0.0001$

## DISCUSSION

Patients treated with dupilumab + TCS in the CHRONOS trial achieved optimal itch response rapidly, with a median of 29 days, and a significantly higher proportion of patients treated with dupilumab + TCS achieved optimal itch response until week 52 compared with patients treated with placebo + TCS. Optimal itch response was reported by patients treated

with dupilumab + TCS for most of the treatment period (77.1% of the time [40/52 weeks]).

In patients from SOLO-CONTINUE who had a PP-NRS ≤ 4 at baseline, the proportion of patients maintaining that itch response was highest in the dupilumab qw and q2w treatment arms. There was no added benefit with dupilumab qw compared with q2w. Maintenance of itch response was gradually lower for patients who switched to less frequent dosing of dupilumab, although a majority switching to q4w still maintained optimal itch response. These results are consistent with real-world data from the Dutch BioDay registry, in which some patients were able to taper dupilumab treatment to less frequent dosage while maintaining optimal itch response (PP-NRS ≤ 4) [16]. Most patients in the placebo arm in SOLO-CONTINUE (after dupilumab withdrawal) lost optimal itch response within 36 weeks. The number of weeks with maintenance of itch response was highest with dupilumab monotherapy in the qw and q2w arms (34.0 and 35.5 weeks out of 36.0, respectively). Also, dupilumab q4w demonstrated high maintenance of optimal itch response (31.0 out of 36.0 weeks). In general, the number of weeks with maintenance of optimal itch response was significantly higher in all patients who continued dupilumab treatment regardless of dosage compared with those who transitioned to placebo (14.5 weeks out of 36 of the treatment period).

Itch is the cardinal symptom in AD [8]; therefore, the timing of onset and, especially, the maintenance of optimal itch response are clinically most relevant in this chronic disease. Dupilumab has previously shown improvement of itch as assessed by PP-NRS reductions of 3 or 4 points in adults with moderate-to-severe AD; these improvements were gradually reduced when transitioned to less frequent dosing or placebo [15, 17]. Here, we show that itch response is stable without tachyphylaxis for up to 52 weeks. This is of critical relevance to patients, not only for improvements in quality of life but also because itching leads to scratching, which perpetuates the eczema through the itch–scratch cycle and adds damage to the epidermal barrier [4].

Dose spacing is used in the real world in some patients [18–20]. It is important to assess maintenance of itch response if patients move to less frequent dosing or even undergo temporary discontinuation. Our results indicate that dose spacing with dupilumab monotherapy can lead to loss of itch response in some patients, which was most prevalent in the dupilumab q8w arm. This is similar to results observed in a sub-study from the BioDay registry [19]. There seems to be a tipping point between dupilumab q4w and q6w dosing, at which disease activity may return in some patients [21].

Looking at the kinetics of itch response, we observed that the proportion of patients who maintained itch response after transitioning from dupilumab monotherapy to placebo at SOLO-CONTINUE baseline showed a gradual decline over time. These kinetics might be different with JAK inhibitors. A recent report stated that, in patients with ≥ 4-point improvement in pruritus NRS after upadacitinib treatment who were re-randomized to placebo or upadacitinib, loss of itch response (< 4-point improvement in daily pruritus NRS relative to baseline) was seen rapidly in patients who transitioned to placebo [22].

A limitation of these analyses is that they are post hoc.

## CONCLUSIONS

In CHRONOS, adult patients with moderate-to-severe AD treated with dupilumab + TCS achieved optimal itch response rapidly and considerably earlier than the 6 months proposed per the T2T concept (median time to response 29 days). Most patients treated with dupilumab + TCS achieved optimal itch response until week 52, and this response was maintained for most of the treatment period. In SOLO-CONTINUE, optimal itch response was maintained by a higher percentage of patients when they continued dupilumab monotherapy, compared with patients who transitioned to placebo. Dose spacing, which is sometimes observed in real-world clinical practice, led to loss of itch response in some

patients. However, a majority of patients switching to dupilumab q4w still maintained optimal itch response.

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***Author Contributions.*** Sonja Ständer and Mike Bastian contributed to the concept and design of this work. Eric L. Simpson and Diamant Thaçi acquired data. Zhen Chen conducted the statistical analyses on the data. Sonja Ständer, Gil Yosipovitch, Eric L. Simpson, Brian S. Kim, Kenji Kabashima, Diamant Thaçi, Martin Metz, Zhen Chen, Sandra Hagen, and Mike Bastian interpreted the data, provided critical feedback on the manuscript, approved the final manuscript for submission, and were accountable for the accuracy and integrity of the manuscript.

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

### *Declarations*

***Conflict of Interest.*** Sonja Ständer is an investigator for Celldex, Galderma, GSK, Incyte, Kiniksa Pharmaceuticals, and Trevi Therapeutics; a consultancy/advisory board member for AbbVie, Almirall, Beiersdorf, Clexio Biosciences, Eli Lilly, Galderma, Incyte, Integrity CE, Kiniksa Pharmaceuticals, KliRNA Biotech, Pfizer, Professor Paul Gerson Unna Academy, Sanofi, Touch IME, Vifor Pharma, and WebMD; and a speaker for AbbVie, BMS, Eli Lilly, FOMF, Galderma, LEO Pharma, L'Oréal, MEDahead, moroscience, Novartis, Pfizer, Professor Paul Gerson Unna Academy, Sanofi, UCB, and Vifor Pharma. Gil Yosipovitch is an advisory board member for AbbVie, Almirall, Amgen, Arcutis, Celldex, Eli Lilly, Escient Health, Galderma, GSK, Kamari, LEO Pharma, Novartis, Pfizer, Pierre Fabre, Regeneron Pharmaceuticals Inc., Sanofi, and Vifor Pharma; received grants/research funding from AbbVie, Celldex, Galderma, Eli Lilly, Escient, LEO Pharma, Novartis, Pfizer, and Sanofi-Regeneron Pharmaceuticals Inc.; and is an investigator for Sanofi-Regeneron Pharmaceuticals Inc. Eric L. Simpson has received personal fees from AbbVie, Amgen, Arcutis Biotherapeutics, Areteia Therapeutics, BMS, CorEvitas, Corvus, Dermira, Eli Lilly, Evelo Biosciences, FIDE, Forte Biosciences, Galderma, Gilead, GlaxoSmithKline, Impetus Healthcare, Incyte, Innovaderm Research,

Janssen, Johnson & Johnson, Kyowa Kirin Pharmaceutical Development, LEO Pharma, Merck, Numab Therapeutics, Pfizer, Physicians World, PRImE, Recludix Pharma, Regeneron Pharmaceuticals Inc., Roivant Sciences, Sanofi/Genzyme, Sitryx Therapeutics, Trevi Therapeutics, and Valeant; and reports grants (or serves as Principal investigator) for AbbVie, Acrotech, Amgen, Arcutis Biotherapeutics, Aslan Pharmaceuticals, Castle Biosciences, CorEvitas, Dermavant, Dermira, Incyte, Lilly, Kymab, Kyowa Kirin, LEO Pharma, National Jewish Health, Pfizer, Regeneron Pharmaceuticals Inc., Sanofi, Target, and VeriSkin. Brian S. Kim is co-founder of Alys Pharmaceuticals; has served as a consultant for 23andMe, ABRAX Japan, AbbVie, Amgen, Attovia Therapeutics, Cara Therapeutics, Clexio Biosciences, Eli Lilly and Company, Escient Pharmaceuticals, Evommune, Galderma, LEO Pharma, Micreos, Novartis, Pfizer, Recens Medical, Regeneron, Sanofi, Septerna, Teva, Trevi Therapeutics, Triveni Bio, WebMD; has stock in ABRAX Japan, Alys Pharmaceuticals, Attovia Therapeutics, Locus Biosciences, Recens Medical, and Triveni Bio; holds a patent for the use of JAK1 inhibitors for chronic pruritus. Kenji Kabashima has received honoraria for lectures from Eli Lilly, Japan Tobacco, LEO Pharma, Maruho, Mitsubishi Tanabe Pharma, and Procter & Gamble; and research grants from Kyoto Hakko Kirin, Mitsubishi Tanabe Pharma, and Ono Pharmaceutical. Diamant Thaçi is an advisor, speaker, or consultant for AbbVie, Almirall, Amgen, Boehringer Ingelheim, Bristol Myers Squibb, Celltrion, Galderma, Janssen, Kyowa Kirin, LEO Pharma, Lilly, L'Oréal, New Bridge, Novartis, Pfizer, Regeneron Pharmaceuticals Inc., Sanofi/Genzyme, Target RWE, UCB, and Vichy. Martin Metz has received honoraria as a speaker and/or advisor for AbbVie, ALK-Abello, Almirall, Amgen, argenx, AstraZeneca, Bayer, Beiersdorf, Celldex, Celltrion, Escient Pharmaceuticals, Galderma, GSK, Incyte, Jasper, Novartis, Pfizer, Pharvaris, Regeneron Pharmaceuticals Inc., Sanofi, Teva, Third Harmonic Bio, and Vifor Pharma. Zhen Chen and Sandra Hagen are employees and shareholders of Regeneron Pharmaceuticals Inc. Mike Bastian is an employee and may hold stock and/or stock options in Sanofi.

***Ethical Approval.*** The study was conducted in accordance with the Declaration of Helsinki, the International Conference on Harmonisation Good Clinical Practice guideline, and applicable regulatory requirements. An independent data and safety monitoring committee conducted blinded monitoring of patient safety data. The local institutional review board or ethics committee at each study center oversaw trial conduct and documentation. Signed written informed consent was obtained from all patients participating in both trials.



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