Effect of Dupilumab on Global Individual Signs Score in Adults With Moderate-to-Severe Atopic Dermatitis: Combined Results From Four Phase 3 Trials

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BACKGROUND

- Atopic dermatitis (AD) is a chronic inflammatory skin condition characterized by pruritus, disruption of skin barrier function, and type 2 inflammation¹
- Dupilumab is a fully human VelocImmune®-derived^{2,3} monoclonal antibody that blocks the shared receptor component for interleukin (IL)-4 and IL-13, thus inhibiting signaling of both IL-4 and IL-13, which are key drivers of type 2 inflammation⁴
- Dupilumab is approved for subcutaneous administration every 2 weeks (q2w) for the treatment of patients aged 12 and above with moderate-to-severe AD and adults with moderate-to-severe AD who are candidates for systemic therapy in the EU,⁵ for the treatment of patients aged 12 years and older with moderate-to-severe AD inadequately controlled with topical prescription therapies or when those therapies are not advisable in the USA,⁶ and for use in adult AD patients not adequately controlled with existing therapies in Japan
- In the EU, dupilumab is indicated as an add-on maintenance treatment in patients aged ≥ 12 years with severe asthma with type 2 inflammation characterized by raised blood eosinophils and/or raised fractional exhaled nitric oxide who are inadequately controlled with high-dose inhaled corticosteroid plus another medicinal product for maintenance treatment
- Dupilumab is approved by the US Food and Drug Administration as an add-on maintenance treatment in adult patients with inadequately controlled chronic rhinosinusitis with nasal polyps⁶
- In phase 3 dupilumab AD trials, the overall severity of 4 clinical signs of AD – erythema, infiltration/papulation, excoriation, lichenification – was assessed globally through the investigator-assessed Global Individual Signs Score (GISS; score range 0–12)

OBJECTIVE

- To report the effect of dupilumab on AD clinical signs as measured by GISS in phase 3 trials (LIBERTY AD SOLO 1 & 2,⁷ LIBERTY AD CAFÉ,⁸ and LIBERTY AD CHRONOS⁹) in 1553 adults with moderate-to-severe AD

METHODS

Study design

- These were randomized, placebo-controlled, double-blind, parallel-group, multicenter, phase 3 trials in adults with moderate-to-severe AD; full details on the study design, population, efficacy, and safety have been previously reported^{7–9} and are summarized in **Figure 1**
 - SOLO 1 (NCT02277743) and SOLO 2 (NCT02277769) were identically designed, pivotal trials of 16 weeks of treatment;⁷ for the purpose of this analysis, data from the 2 SOLO trials were pooled
 - CAFÉ (NCT02755649) included patients not adequately controlled with, intolerant to, or medically inadvisable for treatment with cyclosporine A; study drug was administered for 16 weeks⁸
 - CHRONOS (NCT02260986) was a 52-week trial of longer duration⁹
 - Patients received concomitant TCS in all treatment groups of CAFÉ and CHRONOS trials^{8,9}

Figure 1. Design of the studies.

- The studies were conducted in accordance with the provisions of the Declaration of Helsinki, the International Conference on Harmonisation Good Clinical Practice (ICH GCP) guidelines, and applicable regulatory requirements
- The protocol was reviewed and approved by institutional review boards/ethics committees at all study sites; for all patients, written informed consent was obtained prior to any study procedure

Endpoints

- This analysis is focused on the placebo/control group and the dupilumab 300 mg q2w treatment group (approved dose)
- Efficacy endpoints were analyzed in all studies and included
 - Percent change from baseline through end of treatment in total GISS
 - Proportion of patients with different severity scores in the individual components of GISS, namely erythema, infiltration/papulation, excoriation, and lichenification

Analysis

- Efficacy was analyzed in all randomized patients (full analysis set)
- Continuous endpoints were analyzed using an analysis of covariance (ANCOVA) model with baseline measurement as covariate and the treatment, randomization strata (baseline disease severity), region for all studies, and study identifier in SOLO 1 & 2 only as fixed factors; missing values were imputed using multiple imputation, and patients with rescue medication were considered “missing” first, then imputed by multiple imputation
- Categorical endpoints were analyzed descriptively using all observed values and no imputation

RESULTS

- 1553 patients were included in this analysis
- Demographics and baseline characteristics were similar among treatment groups and showed considerable disease burden at baseline (**Table 1**)

Efficacy

- Early improvement with dupilumab vs placebo was observed in total GISS as early as Week 1 in SOLO 1 & 2 and Week 2 in CAFÉ and CHRONOS, and sustained through end of treatment (**Figure 2**)

Table 1. Baseline demographics and disease characteristics.

	Score range	SOLO 1 & 2		CAFÉ		CHRONOS	
		Placebo qw (n = 460)	Dupilumab 300 mg q2w (n = 457)	Placebo qw + TCS (n = 108)	Dupilumab 300 mg q2w + TCS (n = 107)	Placebo qw + TCS (n = 315)	Dupilumab 300 mg q2w + TCS (n = 106)
Age, years	–	38.4 (14.03)	38.3 (14.37)	38.9 (13.35)	37.5 (12.89)	36.6 (13.01)	39.6 (13.98)
Male sex, n (%)	–	250 (54.3)	267 (58.4)	68 (63.0)	65 (60.7)	193 (61.3)	62 (58.5)
Disease duration, years	–	28.8 (14.43)	27.9 (15.20)	29.2 (14.72)	29.6 (15.61)	27.5 (14.34)	30.1 (15.53)
Total GISS	0–12	9.1 (1.82)	9.0 (1.80)	9.4 (1.63)	9.3 (1.64)	8.7 (1.84)	8.9 (2.04)
Erythema score	0–3	2.4 (0.55)	2.4 (0.56)	2.5 (0.50)	2.4 (0.56)	2.4 (0.56)	2.4 (0.59)
Infiltration/papulation score	0–3	2.3 (0.59)	2.3 (0.55)	2.4 (0.53)	2.3 (0.58)	2.2 (0.56)	2.2 (0.63)
Excoriation score	0–3	2.1 (0.71)	2.1 (0.72)	2.2 (0.69)	2.2 (0.64)	2.0 (0.72)	2.0 (0.78)
Lichenification score	0–3	2.3 (0.67)	2.2 (0.72)	2.3 (0.62)	2.4 (0.60)	2.1 (0.64)	2.3 (0.66)

Figure 2. Percent change in total GISS scores from baseline through end of treatment in SOLO, CAFÉ, and CHRONOS trials.

- An analysis of severity among GISS components showed rapid, sustained, and consistent improvement with dupilumab in different severity strata in all trials (**Figures 3–6**)
- The majority of patients treated with dupilumab had absent or mild excoriation at Week 2 in SOLO 1 & 2 and CAFÉ and Week 4 in CHRONOS (**Figure 5**); erythema in CHRONOS by Week 4; as well as absent or mild infiltration/papulation, and lichenification at Week 4 in all trials (**Figures 3, 4, and 6**)

Figure 3. Categorical change in severity of ERYTHEMA over time in (A) SOLO; (B) CAFÉ; and (C) CHRONOS trials.

Figure 4. Categorical change in severity of INFILTRATION/PAPULATION over time in (A) SOLO; (B) CAFÉ; and (C) CHRONOS trials.

- At the end of each study, a majority of patients had absent or mild severity in erythema (**Figure 3**), infiltration/papulation (**Figure 4**), excoriation (**Figure 5**), and even lichenification (**Figure 6**)

Safety

- Dupilumab was generally well tolerated with a favorable safety profile; overall rates of adverse events were similar across all 3 treatment groups^{2–9}

Figure 5. Categorical change in severity of EXCORIATION over time in (A) SOLO; (B) CAFÉ; and (C) CHRONOS trials.

Figure 6. Categorical change in severity of LICHENIFICATION over time in (A) SOLO; (B) CAFÉ; and (C) CHRONOS trials.

CONCLUSIONS

- Dupilumab 300 mg q2w as monotherapy or with concomitant TCS, compared with control, resulted in rapid improvement in total GISS and individual signs consistently across all 4 trials, and results were maintained until the end of treatment
- Improvements were seen with dupilumab treatment vs control over time in all individual AD signs assessed by GISS, including erythema, infiltration/papulation, excoriation, and lichenification
- The majority of patients had moderate or severe signs at baseline and achieved absent or mild signs by the end of treatment; even lichenification showed an early significant improvement

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