Dupilumab With Concomitant Topical Corticosteroids in Atopic Dermatitis Patients Who Are Inadequately Controlled With or Medically Inadvisable for Cyclosporine A: a Phase 3 Clinical Trial (LIBERTY AD CAFÉ)

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BACKGROUND

- Atopic dermatitis (AD) is a chronic inflammatory skin disease often associated with atopic comorbidities[1]
- Cyclosporine A (CsA) is a potent immunosuppressant approved for AD in several countries, but risk of side effects limits its long-term use use
- Dupilumab is a fully human monoclonal antibody that binds specifically to the interleukin (IL)-4 receptor alpha (IL-4Rα) subunit and inhibits signaling of both IL-4 and IL-13, key drivers of type 2/Th2-mediated inflammation in AD[3]
- Dupilumab is approved by the US Food and Drug Administration (FDA) for treatment of adult patients with moderate-to-severe AD whose disease is not adequately controlled with topical prescription therapies or when those therapies are not advisable, and can be used with or without topical corticosteroids (TCS)

OBJECTIVE

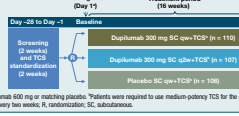
- **To evaluate efficacy and safety of dupilumab with concomitant TCS in adults with AD with inadequate response to or intolerance of CsA, or for whom CsA was medically inadvisable**

METHODS

Study design

- LIBERTY AD CAFÉ (ClinicalTrials.gov: NCT02755649; EudraCT: 2015-002653-35) was a randomized, double-blind, placebo-controlled, parallel-group phase 3 clinical trial (**Figure 1**)
- Patients were randomized 1:1:1 to receive 16 weeks of SC dupilumab 300 mg qw, q2w, or placebo
- All patients received concomitant medium-potency TCS
- Patients were stratified by baseline Investigator's Global Assessment (IGA) score (3 vs 4) and prior CsA exposure

Figure 1. Study design.



*Dupilumab 600 mg or matching placebo. ^aPatients were required to use medium-potency TCS for the entire treatment period. qw, every week; q2w, every two weeks; R, randomization; SC, subcutaneous.

Patient eligibility

Key inclusion criteria were

- Age ≥ 18 years; Eczema Area and Severity Index (EASI) ≥ 20; IGA = 3 or 4
- Documented history (within 6 months before screening visit) of inadequate response to treatment with TCS
- Documented history by a physician of either
  - No prior CsA exposure and not currently a candidate for CsA treatment due to
    - Medical contraindications (e.g. uncontrolled hypertension on medication), or
    - Use of prohibited concomitant medications, or
    - Increased susceptibility to CsA-induced renal damage (elevated creatinine) and/or liver damage (elevated function tests), or
    - Increased risk of serious infections, or
    - Hypersensitivity to CsA active substance or excipients, or
  - Previously exposed to CsA, and CsA treatment should not be continued or restarted due to
    - Intolerance and/or unacceptable toxicity, or
    - Inadequate response to CsA (defined as flare of AD on CsA tapering after a maximum of 6 weeks of high dose [5 mg/kg/day] to maintenance dose [2–3 mg/kg/day] or a flare after a minimum of 3 months on maintenance dose), or
    - Requirement for CsA at doses > 5 mg/kg/day, or duration beyond those specified in the prescribing information (> 1 year)

Outcomes

- Primary endpoint
  - Proportion of patients with ≥ 75% improvement from baseline in EASI score (EASI-75) at Week 16
- Secondary endpoints
  - Percent change in EASI and SCORing AD (SCORAD) at Week 16
  - Percent change in weekly average of peak daily pruritus Numerical Rating Scale (NRS) at Week 2 and Week 16
  - Proportion of patients with ≥ 4-point improvement in Patient-Oriented Eczema Measure (POEM) and Dermatology Life Quality Index (DLQI) at Week 16
  - Proportions of patients reporting "no problem" on the pain/discomfort subscale on the generic 5-dimension 3-level EuroQol scale (EQ-5D) (among patients reporting moderate-severe pain/discomfort at baseline)
- Safety was assessed for the 16-week treatment period

RESULTS

Patient disposition and baseline characteristics

- 390 patients were screened and 325 randomized to 300 mg dupilumab q2w+TCS (n = 107), 300 mg dupilumab qw+TCS (n = 110), or placebo+TCS (n = 108)
- 318 patients completed the trial: 95.4% of patients in the placebo group, 100% in the dupilumab q2w group, and 98.2% in the dupilumab qw group
- Baseline demographic and disease characteristics were similar among treatment groups (**Table 1**)

Table 1. Baseline characteristics.

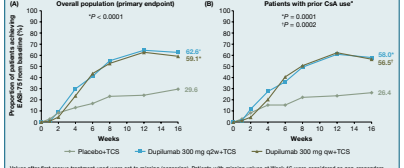
	Score range	Placebo+TCS (n = 108)	Dupilumab 300 mg q2w+TCS (n = 107)	Dupilumab 300 mg qw+TCS (n = 110)
Age, years, median (IQR)	–	37.5 (29.0, 49.0)	38.0 (25.0, 47.0)	38.0 (29.0, 48.0)
Male, n (%)	–	68 (63)	65 (61)	66 (60)
EASI, median (IQR)	0–72	31.7 (24.2, 40.7)	31.6 (25.2, 39.2)	31.1 (24.5, 39.0)
SCORAD, median (IQR)	0–102	67.5 (58.5, 76.6)	66.7 (61.1, 76.2)	66.1 (55.4, 75.4)
Weekly average of peak pruritus NRS, median (IQR)	0–10	6.9 (4.9, 8.1)	7.0 (5.4, 8.0)	6.4 (5.2, 7.7)
Patients with IGA = 4, n (%)	0–4	52 (48.1)	50 (46.7)	52 (47.3)
Prior CsA treatment,[a] n (%)				
Yes	–	72 (66.7)	69 (64.5)	69 (62.7)
No	–	36 (33.3)	38 (35.5)	41 (37.3)
DLQI, median (IQR)	0–30	13.0 (7.0, 19.5)	14.0 (8.0, 22.0)	13.0 (7.0, 21.0)
POEM, median (IQR)[b]	0–28	19.0 (14.0, 24.0)	20.0 (15.0, 24.0)	19.0 (14.0, 24.0)
EQ-5D pain/discomfort domain, n (%)				
"I have no pain or discomfort"	–	26 (24.1)	29 (27.1)	25 (22.7)
"I have moderate pain or discomfort"	–	73 (67.6)	69 (64.5)	75 (68.2)
"I have extreme pain or discomfort"	–	9 (8.3)	9 (8.4)	10 (9.1)

[a]Ratio of prior CsA use/CsA-naive patients was required by trial stratification. [b]Placebo+TCS: n = 107.
IQR, interquartile range (Q1, Q3); Q1, first quartile; Q3, third quartile.

Efficacy

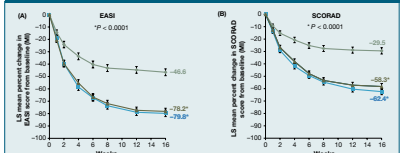
- A significantly higher number of patients treated with dupilumab+TCS achieved EASI-75 at Week 16 vs placebo+TCS (primary endpoint; $P < 0.0001$ each dose group vs placebo+TCS (**Figure 2A**)
- Among patients with prior exposure to CsA, significantly more receiving dupilumab+TCS achieved EASI-75 vs placebo+TCS (**Figure 2B**)
- Dupilumab+TCS induced significantly greater reduction from baseline in EASI and SCORAD vs placebo+TCS (**Figure 3A** and **3B**)
- Dupilumab+TCS induced a significantly greater reduction in weekly average of peak daily pruritus NRS from baseline vs placebo +TCS (**Figure 4**)

Figure 2. Proportion of patients of the overall study population (A) and patients with prior CsA use (B) achieving EASI-75 at Week 16 (primary endpoint).



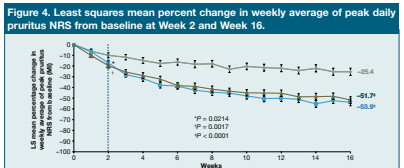
Values after first rescue treatment used were set to missing (censoring). Patients with missing values at Week 16 were considered as non-responders. *Placebo, n/N1 = 19/72; dupilumab 300 mg qw, n/N1 = 39/69; dupilumab 300 mg q2w, n/N1 = 40/69.
n, number of patients with EASI-75; N1, number of patients in treatment group with prior CsA use.

Figure 3. Least squares mean percent change in EASI (A) and SCORAD score (B) from baseline to Week 16.



Error bars are ± SE.
LS, least squares; MI, multiple imputation method with censoring after rescue treatment use; SE, standard error.

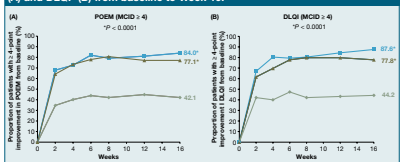
Figure 4. Least squares mean percent change in weekly average of peak daily pruritus NRS from baseline at Week 2 and Week 16.



Error bars are ± SE.
LS, least squares; MI, multiple imputation method with censoring after rescue treatment use; SE, standard error.

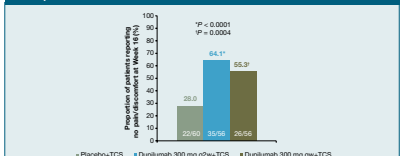
- Significantly higher proportions of patients in the dupilumab+TCS groups achieved ≥ 4-point improvement in POEM and DLQI (among patients with baseline values of ≥ 4) by Week 16 vs placebo+TCS (**Figure 5A** and **5B**)
- Dupilumab+TCS improved EQ-5D pain/discomfort score at Week 16 vs placebo+TCS (**Figure 6**)
- Outcomes were comparable to those at Week 52 for a CAFÉ-like subgroup of patients in LIBERTY AD CHRONOS (52-week randomized placebo-controlled phase 3 study of dupilumab+TCS; ClinicalTrials.gov: NCT02260986)[4,5]
  - Significantly more patients treated with dupilumab+TCS achieved EASI-75 at Week 52 vs placebo+TCS in the LIBERTY AD CHRONOS trial and confirm the 16-week data in this study (**Figure 7**)

Figure 5. Proportion of patients achieving a ≥ 4-point improvement in POEM[a] (A) and DLQI[a] (B) from baseline to Week 16.



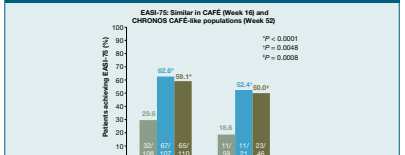
[a]Subset of patients with POEM ≥ 4 at baseline; [a]Subset of patients with DLQI ≥ 4 at baseline
All observed values. Values after first rescue treatment used were set to missing (censoring). Patients with missing values at Week 16 were considered non-responders. MCID, minimal clinically important difference.

Figure 6. Proportions of patients reporting "no pain/discomfort" on the EQ-5D pain/discomfort subscale at Week 16.[a]



[a]Among patients who reported moderate or severe pain/discomfort at baseline. Values after first rescue treatment used were set to missing (censoring). Patients with missing scores at Week 16 were considered non-responders.

Figure 7. Comparison of CAFÉ and subgroup analysis of CAFE-like patients in CHRONOS.



Safety

- All treatment groups had similar rates of adverse events (AEs) and serious AEs (SAEs) (**Table 2**)
- Conjunctivitis was more frequent with dupilumab+TCS groups, while the placebo+TCS group had higher rates of non-herpetic skin infections (**Table 2**)
- Similar proportions of patients in each treatment group reported herpes viral infections (**Table 2**)

Table 2. Overall summary of number of patients with AEs through the 16-week treatment period – SAF.

Patients with, n (%)	Placebo+TCS (n = 108)	Dupilumab 300 mg q2w+TCS (n = 107)	Dupilumab 300 mg qw+TCS (n = 110)
Any TEAE	75 (69.4)	77 (72.0)	76 (69.1)
Any drug-related TEAE	20 (18.5)	36 (33.6)	37 (33.6)
Any TEAE causing discontinuation of study drug permanently	1 (0.9)	0	2 (1.8)
Conjunctivitis[a]	12 (11.1)	30 (28.0)	18 (16.4)
Skin infection (adjudicated; excluding herpetic infections)	9 (8.3)	2 (1.9)	4 (3.6)
Herpes viral infections	6 (5.6)	5 (4.7)	8 (7.3)
Any death	0	0	0
Any TE SAE	2 (1.9)	2 (1.9)	2 (1.8)
Any drug-related TE SAE	0	0	0
Any TE SAE causing discontinuation of study drug permanently	0	0	1 (0.9)
Any severe TEAE	10 (9.3)	5 (4.7)	3 (2.7)

[a]Includes MedDRA PTs of conjunctivitis, conjunctivitis allergic, conjunctivitis bacterial, conjunctivitis viral, and atopic keratoconjunctivitis.
MedDRA, Medical Dictionary for Regulatory Activities; PT, Preferred Term; SAF, safety analysis set (all randomized patients who received any study drug; was based on treatment received [as treated]); TE, treatment-emergent; TEAE, treatment-emergent adverse event.

CONCLUSIONS

- **16 weeks of dupilumab with concomitant TCS significantly improved signs and symptoms of AD compared with placebo in adult patients with AD and a history of inadequate response or intolerance to TCS and CsA, or for whom CsA treatment is medically inadvisable**
- **In this study, dupilumab was well tolerated with an acceptable safety profile**
- **Results in this study are similar to other phase 3 studies (16- and 52-week) of dupilumab with or without concomitant TCS[1,4,6–8]**
- **These data support the use of dupilumab in adult patients with moderate-to-severe AD**
  - **Who have previously used CsA and stopped it due to intolerance or lack of efficacy**
  - **Who are not candidates for CsA because of medical conditions or use of contraindicated concomitant medications**

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Disclosures

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