Favorable Safety and Sustained Efficacy With Long-Term Dupilumab Treatment in Adults With Moderate-to-Severe Atopic Dermatitis: An Analysis up to 3 Years (LIBERTY AD OLE)

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BACKGROUND

- Atopic dermatitis (AD) is a chronic inflammatory skin condition characterized by intense pruritus, disruption of skin barrier function, and type 2 inflammation[1]
- Moderate-to-severe AD typically requires long-term treatment[1]
  - Continuous, long-term use of conventional treatments such as higher-potency topical corticosteroids (TCS), oral corticosteroids, ultraviolet therapy, and systemic immunosuppressants is not recommended due to risk of adverse events (AEs) or lack of efficacy data
- Dupilumab is a fully human[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 inflammation in multiple diseases[4]

OBJECTIVE

- **To report the safety and efficacy of open-label dupilumab for up to 3 years of treatment in adult patients with moderate-to-severe AD**

METHODS

Study design

- This is an analysis of an ongoing phase 3, multicenter, open-label extension (OLE) trial in adults with moderate-to-severe AD (NCT01949311) with a data cutoff date of December 1, 2018; an analysis with a cutoff date of April 11, 2016 has been previously reported[5]
- Main inclusion criteria: participated in previous phase 1–3 dupilumab studies (including patients in the placebo groups)[6–15] and adequately completed the required assessments of the parent studies; or screened for a phase 3 study (NCT02277743 or NCT02277769) but not randomized due to randomization closure; and provided signed informed consent
- Main exclusion criteria: patients who had an AE deemed related to dupilumab in the parent study and that led to treatment discontinuation; patients who had a serious AE (SAE) deemed related to dupilumab in the parent study
- Treatment: dupilumab subcutaneous (SC) 300 mg weekly (qw)
  - The planned duration was up to 3 years of treatment or until regulatory approval of dupilumab in the respective participating country
  - Country/region-specific protocol amendments (France, Germany, Poland, Finland, Japan) permitted treatment continuation for more than 3 years

RESULTS

Table 1. Baseline demographics and disease characteristics.

Characteristic	N = 2,677
Age, mean (SD), years	39.2 (13.4)
Male, n (%)	1,611 (60.2)
Race, n (%)	
White	1,936 (72.3)
Black/African American	147 (5.5)
Asian	541 (20.2)
Other/not reported	53 (2.0)
BMI, mean (SD), kg/m^2	26.37 (5.6)
Patients with current history of Atopic/ Allergic Conditions, n (%)	2,627 (98.1)
Atopic dermatitis	2,616 (97.7)
Other allergies	1,749 (65.3)
Allergic rhinitis	1,332 (49.8)
Asthma	1,105 (41.3)
Food allergy	1,010 (37.7)
Allergic conjunctivitis	740 (27.6)
Hives	368 (13.7)
Chronic rhinosinusitis	173 (6.5)
Atopic keratoconjunctivitis	78 (2.9)
Nasal polyps	63 (2.4)
Eosinophilic esophagitis	13 (0.5)

	Current study	Parent study
Duration of AD, mean (SD), years	29.9 (14.8)	29.0 (14.8)
EASI, mean (SD), range 0–72	16.4 (14.6)	32.8 (13.2)
EASI-75, n (%)	884 (33.0)	–
IGA, mean (SD), range 0–4	2.7 (1.0)	3.5 (0.5)
0 or 1, n (%)	320 (11.9)	0
2, n (%)	610 (22.8)	0
3, n (%)	1,288 (48.1)	1,343 (50.2)
4, n (%)	459 (17.1)	1,301 (48.6)
Peak Pruritus NRS, mean (SD)	5.0 (2.5)	7.1 (1.9)
Patients with Peak Pruritus NRS, n (%)		
≥ 3	1,769 (66.1)	2,528 (94.4)
≥ 4	1,505 (56.2)	2,437 (91.0)
POEM score, mean (SD)	14.7 (8.0)	20.5 (5.9)
DLQI score, mean (SD)	8.5 (7.1)	14.7 (7.4)

BMI, body mass index; EASI-75, ≥ 75% improvement from BL of parent study in EASI; IGA, Investigator's Global Assessment; SD, standard deviation; EASI, Eczema Area and Severity Index; NRS, Peak Pruritus Numerical Rating Scale; POEM, Patient-Oriented Eczema Measure; DLQI, Dermatology Life Quality Index.

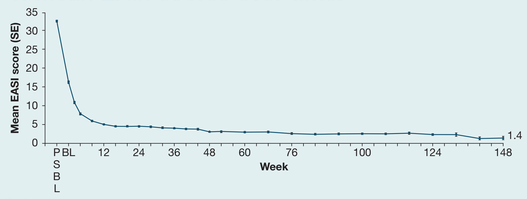
Table 2. Patient disposition.

	February 2019 database lock, n (%)
Safety Analysis Set	2,677
Completed up to 1 year	2,207 (82.4)
Completed up to 2 years	1,028 (38.4)
Completed up to 3 years	347 (13.0)
Completed study	1,061 (39.6)
Patients ongoing	291 (10.9)
Withdrawn from study	1,325 (49.5)
Study terminated by sponsor	552 (20.6)
Withdrawal by patient	492 (18.4)
AE	100 (3.7)
Lost to follow-up	64 (2.4)
Lack of efficacy	50 (1.9)
Protocol deviation	32 (1.2)
Pregnancy	17 (0.6)
Physician decision	14 (0.5)
Unknown	4 (0.1)

Of the 492 Withdrawals by patient, 255 were due to availability of commercial drug or study termination.
The mean study drug injection compliance was high (98.15%), with most patients having ≥ 80% compliance during the study.

Efficacy

Figure 1. Mean EASI scores over time.



PSBL, parent study BL; SE, standard error.

Figure 2. Mean Peak Pruritus NRS scores over time.

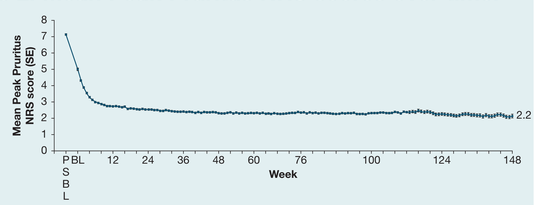


Figure 3. Mean POEM scores over time.

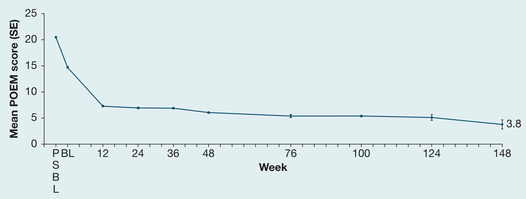
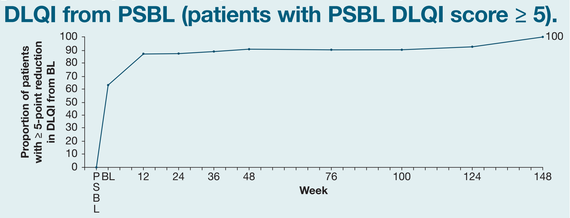


Figure 4. Proportion of patients with ≥ 5-point reduction in DLQI from PSBL (patients with PSBL DLQI score ≥ 5).



Safety

- Due to the lack of a control arm in this OLE study, a safety comparison with the dupilumab 300 mg qw + TCS and placebo + TCS groups from the 52-week CHRONOS study is provided[7]

Table 3. Most common AEs: comparison between OLE and CHRONOS studies.

PT (≥ 5% of patients in OLE)	OLE (AD-1225) Dupilumab 300 mg qw N = 2,677		CHRONOS (AD-1224) Week 52 Placebo + TCS n = 315		CHRONOS (AD-1224) Week 52 Dupilumab 300 mg qw + TCS n = 315	
	n (%)	nP/100 PY	n (%)	nP/100 PY	n (%)	nP/100 PY
Nasopharyngitis	752 (28.1)	19.16	62 (19.7)	24.93	62 (19.7)	24.16
Conjunctivitis[a]	521 (19.5)	11.96	25 (7.9)	9.24	61 (19.4)	23.37
AD	438 (16.4)	9.61	147 (46.7)	74.32	55 (17.5)	20.71
Upper respiratory tract infection	350 (13.1)	7.56	32 (10.2)	12.03	43 (13.7)	15.85
Headache	216 (8.1)	4.54	19 (6.0)	6.98	25 (7.9)	8.97
Oral herpes	188 (7.0)	3.91	9 (2.9)	3.20	15 (4.8)	5.21
Injection-site reaction	138 (5.2)	2.82	25 (7.9)	9.39	61 (19.4)	24.46

[a]Includes the following PTs: conjunctivitis, conjunctivitis allergic, conjunctivitis bacterial, conjunctivitis viral, and atopic keratoconjunctivitis. MedDRA, Medical Dictionary for Regulatory Activities; PT, MedDRA Preferred Term.

Table 4. Safety overview: comparison between OLE trial and results from the CHRONOS trial.

	OLE (AD-1225) Dupilumab 300 mg qw N = 2,677			CHRONOS (AD-1224) Week 52, final data set Placebo + TCS n = 315			Dupilumab 300 mg qw + TCS n = 315		
	Events	n (%)	nP/100 PY	Events	n (%)	nP/100 PY	Events	n (%)	nP/100 PY
TEAE	13,826	2,264 (84.6)	173.74	1,520	268 (85.1)	325.08	1,500	263 (83.5)	322.43
Severe TEAE	355	246 (9.2)	5.08	46	28 (8.9)	10.31	24	17 (5.4)	5.88
SAE	354	256 (9.6)	5.28	24	16 (5.1)	5.75	11	10 (3.2)	3.40
SAE related to study drug	36	31 (1.2)	0.61	3	3 (1.0)	1.06	2	2 (0.6)	0.68
TEAE leading to study drug discontinuation	116	95 (3.5)	1.87	30	25 (7.9)	8.31	10	9 (2.9)	2.58

TEAE, treatment-emergent adverse events.

CONCLUSIONS

- **The safety profile observed in this large open-label study over 3 years is consistent with the known safety profile of dupilumab previously observed in controlled studies; no new safety signals associated with the use of dupilumab in adult patients with moderate-to-severe AD were identified**
- **Long-term treatment with dupilumab showed sustained efficacy in multiple measures of disease assessment, reducing signs and symptoms of AD and improving quality of life in the cohort of patients who completed up to 3 years of treatment. Few patients discontinued treatment, and compliance to treatment was high**

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