Safety of Long-Term Dupilumab Treatment in Adults With Moderate-to-Severe Atopic Dermatitis: Results From an Open-Label Extension Trial up to 172 Weeks

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BACKGROUND

- Atopic dermatitis (AD) is a chronic systemic inflammatory disease requiring long-term management; however, sustained AD treatment with systemic immunosuppressants can be limited due to safety concerns and side effects
- Data from an open-label extension (OLE) study (NCT01949311) have previously demonstrated acceptable safety of dupilumab in adult patients up to 148 weeks of treatment[1]

OBJECTIVE

- **To evaluate the long-term safety of dupilumab in adults with moderate-to-severe AD up to 172 weeks**

METHODS

- Adult patients ≥ 18 years of age with moderate-to-severe AD who had previously participated in any dupilumab parent study (phase 1–3) were enrolled in this long-term, multicenter, OLE study with an initial duration of 3 years
- Protocol amendments in June 2017 and January 2018 allowed for patient re-entry and treatment extension of up to 5 years in certain countries
- This analysis examined the overall population of patients treated with 300 mg dupilumab weekly (qw)[a] in the safety analysis set at time of data cutoff (November 2019)
- Concomitant treatments for AD, including topical corticosteroids (TCS) and topical calcineurin inhibitors, were permitted
- Data shown are for the overall study population
- Because the OLE trial lacks a control arm, safety results from the LIBERTY AD CHRONOS 52-week study (NCT02260986) in adults with moderate-to-severe AD receiving dupilumab 300 mg qw plus TCS are provided as a comparison

[a]Dupilumab 300 mg qw dose is not approved by FDA/EMA

RESULTS

Table 1. Baseline demographics and disease characteristics in the OLE study.

		N = 2,677
Age, mean (SD), years		39.2 (13.4)
Duration of AD, mean (SD), years		29.0 (14.8)
Male sex, n (%)		1,611 (60.2)
Race, n (%)		
White		1,936 (72.3)
Black		147 (5.5)
Asian		541 (20.2)
Other/not reported		53 (1.9%)
	Parent study	**Current study**
EASI, mean (SD)	32.8 (13.2)	16.4 (14.6)
IGA score, mean (SD)	3.5 (0.5)	2.7 (1.0)
IGA score, n (%)		
0/1	0	320 (12.0)
2	0	610 (22.8)
3	1,343 (50.2)	1,288 (48.1)
4	1,301 (48.6)	459 (17.1)
PP-NRS score, mean (SD)	7.1 (1.9)	5.0 (2.5)

BMI, body mass index; EASI, Eczema Area and Severity Index; IGA, Investigator's Global Assessment; PP-NRS, Peak Pruritus Numerical Rating Scale; SD, standard deviation.

Table 2. Patient disposition in LIBERTY AD OLE.

n (%)	N = 2,677
Patients who completed up to Week 52	2,207 (82.4)
Patients who completed up to Week 100	1,064 (39.7)
Patients who completed up to Week 148	534 (19.9)
Patients who completed up to Week 172	253 (9.5)
Patients with treatment duration > 172 weeks	215 (8.0)
Patients who completed the study	1,084 (40.5)
Patients ongoing	249 (9.3)
Patients withdrawn from the study[a]	1,344 (50.2)
Study terminated by sponsor[b]	810 (30.3)
Withdrawal by patient[c]	230 (8.6)
Adverse event[d]	111 (4.1)
Lost to follow-up	69 (2.6)
Lack of efficacy	57 (2.1)
Protocol deviation	36 (1.3)
Pregnancy	17 (0.6)
Physician decision	10 (0.4)
Unknown	4 (0.1)

Patient attrition over time may enrich for patients who tolerate or respond well to dupilumab.
The mean study drug injection compliance was high (98.9%), with most patients having ≥ 80% compliance during the study.
Most patient withdrawals were due to regulatory approval and commercialization of dupilumab.
[a]These patients completed the treatment and end-of-study periods. [b]Regulatory approval/commercialization. [c]Includes reasons of relocation, desire for pregnancy, unwillingness to discontinue treatment for 12 weeks, work/school conflict, and personal reasons not specified. [d]Includes patients withdrawn from the study, both those receiving treatment at the time of withdrawal and those not receiving treatment during the safety follow-up period.

Table 3. Overall safety in comparison with CHRONOS.

	LIBERTY AD OLE (November 2019)			CHRONOS Week 52					
	Dupilumab 300 mg qw (N = 2,677)			Placebo + TCS (n = 315)			Dupilumab 300 mg qw + TCS (n = 315)		
	Events, n	Patients, n (%)	nP/100PY	Events, n	Patients, n (%)	nP/100PY	Events, n	Patients, n (%)	nP/100PY
TEAE	14,169	2,268 (84.7)	170.2	1,520	268 (85.1)	325.1	1,500	263 (83.5)	322.4
Severe TEAE	365	254 (9.5)	5.0	46	28 (8.9)	10.3	24	17 (5.4)	5.9
SAE	365	265 (9.9)	5.2	24	16 (5.1)	5.8	11	10 (3.2)	3.4
SAE drug-related	37	32 (1.2)	0.6	3	3 (1.0)	1.1	2	2 (0.6)	0.7
Leading to treatment discontinuation	117	96 (3.6)	1.8	30	26 (8.3)	8.3	10	9 (2.9)	2.6

Patients enrolled from October 2013 received subcutaneous dupilumab 200 mg qw (400 mg loading dose). Following protocol amendment on 12 December 2013, patients received 300 mg qw based on the dose regimens selected for phase 3 studies. nP/100PY, number of patients with ≥ 1 event per 100 patient-years; SAE, serious adverse event; TEAE, treatment-emergent adverse event.

Table 4. Patients with ≥ 5% incidence of TEAEs in the OLE study by Preferred Term.

PT	LIBERTY AD OLE (November 2019)		CHRONOS Week 52			
	Dupilumab 300 mg qw (N = 2,677)		Placebo + TCS (n = 315)		Dupilumab 300 mg qw + TCS (n = 315)	
	n (%)	nP/100PY	n (%)	nP/100PY	n (%)	nP/100PY
Nasopharyngitis	763 (28.5)	18.5	62 (19.7)	24.9	62 (19.7)	24.2
Conjunctivitis[a]	528 (19.7)	11.6	25 (7.9)	9.2	61 (19.4)	23.4
Atopic dermatitis	441 (16.5)	9.3	147 (46.7)	74.3	55 (17.5)	20.7
Upper respiratory tract infection	358 (13.4)	7.4	32 (10.2)	12.0	43 (13.7)	15.8
Headache	217 (8.1)	4.3	19 (6.0)	7.0	25 (7.9)	9.0
Oral herpes	193 (7.2)	3.8	9 (2.9)	3.2	15 (4.8)	5.2
Injection-site reaction	138 (5.2)	2.7	25 (7.9)	9.4	61 (19.4)	24.5

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

Table 6. Conjunctivitis[a] deep dive.

	LIBERTY AD OLE (November 2019)		CHRONOS Week 52			
	Dupilumab 300 mg qw (N = 2,677)		Placebo + TCS (n = 315)		Dupilumab 300 mg qw + TCS (n = 315)	
Number of events	860		29		91	
Not recovered/not resolved	87		1		7	
Recovered/resolved	745		27		81	
Recovered/resolved with sequelae	9		0		1	
Recovering/resolving	18		1		2	
	n (%)	nP/100PY	n (%)	nP/100PY	n (%)	nP/100PY
Patients with ≥ 1 event of conjunctivitis	528 (19.7)	11.2	25 (7.9)	9.2	61 (19.4)	22.6
Related to study drug	255 (9.5)	5.0	5 (1.6)	1.8	15 (4.8)	5.2
Mild event	244 (9.1)	4.8	15 (4.8)	5.4	31 (9.8)	11.0
Moderate event	258 (9.6)	5.1	9 (2.9)	3.2	28 (8.9)	10.0
Severe event	26 (1.0)	0.5	1 (0.3)	0.4	2 (0.6)	0.7
Event leading to treatment discontinuation	14 (0.5)	0.3	0	0	0	0

[a]Includes the following PTs: conjunctivitis, conjunctivitis allergic, conjunctivitis bacterial, conjunctivitis viral, and atopic keratoconjunctivitis.

Table 5. Baseline demographics – patients with conjunctivitis.

	Conjunctivitis (n = 528)	No conjunctivitis (n = 2,149)
Age, mean (SD), years	39.4 (12.1)	39.1 (13.7)
Male sex, n (%)	333 (63.1)	1,278 (59.5)
Duration of AD, mean (SD), years	32.2 (14.2)	29.3 (14.9)
Race, n (%)		
White	413 (78.2)	1,523 (70.9)
Black	20 (3.8)	127 (5.9)
Asian	80 (15.2)	461 (21.5)
Other/not reported	15 (2.8)	38 (1.8)
EASI, mean (SD)	19.9 (15.3)	15.5 (14.3)
IGA score, mean (SD)	2.9 (0.9)	2.6 (1.0)
IGA score, n (%)		
0/1	44 (8.4)	276 (12.9)
2	85 (16.1)	525 (24.4)
3	275 (52.1)	1,013 (47.1)
4	124 (23.5)	335 (15.6)
PP-NRS score, mean (SD)	5.3 (2.4)	4.9 (2.5)

CONCLUSION

- **In this interim analysis of dupilumab 300 mg qw in adult patients with moderate-to-severe AD up to 172 weeks, safety data are consistent with the known safety profile of dupilumab observed in controlled studies**
- **Exposure-adjusted incidence rates (EAIR) of TEAEs were lower than previously reported rates of AEs at 52 weeks and declined over time**
- **EAIR of conjunctivitis was comparable with CHRONOS placebo but > 50% lower than that observed for the 300 mg qw treatment arm**
- **EAIR of conjunctivitis remained stable despite the extended treatment period and tended toward higher incidence in patients with more severe AD at baseline**
- **In patients with conjunctivitis, > 95% of events were mild/moderate, > 85% were reported as recovered/resolved, and only 0.5% discontinued treatment due to conjunctivitis**

Reference: 1. Beck LA, et al. Am J Clin Dermatol. 2020;21:567-77.

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