Dupilumab Treatment Results in Rapid Improvement in Itch in Adult and Adolescent Patients With Moderate-to-Severe Atopic Dermatitis (LIBERTY AD SOLO 1 and 2 and ADOL trials)

Gil Yosipovitch[1], Chih-ho Hong[2,3], Eric L. Simpson[4], Zhen Chen[5], Ana Rossi[6]

[1]University of Miami, Miami, FL, USA; [2]University of British Columbia, Surrey, BC, Canada; [3]Probity Medical Research, Waterloo, ON, Canada; [4]Oregon Health and Science University, Portland, OR, USA; [5]Regeneron Pharmaceuticals, Inc., Tarrytown, NY, USA; [6]Sanofi Genzyme, Cambridge, MA, USA

INTRODUCTION

- Atopic dermatitis (AD) is a chronic, type 2 inflammatory skin disease characterized by eczematous lesions and intense pruritus/itch
- Pruritus/itch is one of the defining features of AD
  - Itch is responsible for a significant portion of the patient's disease burden
  - Itch impacts sleep quality, which worsens with the severity of itch[1,2]
  - Itch has a profound impact on daily lives of patients
- Improvement in itch is therefore an important marker of treatment benefit
- Dupilumab is a fully human[3,4] monoclonal antibody that blocks the shared receptor component for interleukin (IL)-4 and IL-13, inhibiting signaling of both IL-4 and IL-13, which are key drivers of type 2-mediated inflammation in multiple diseases[5,6]
- Dupilumab has previously been demonstrated to significantly improve measures of itch in both adults and adolescents with moderate-to-severe AD;[7–9] however, until now, data published have concentrated on a weekly timescale

OBJECTIVE

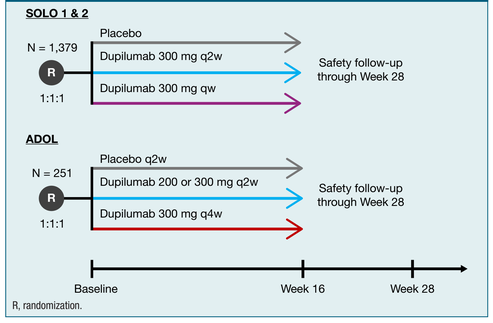
- **This post hoc analysis assesses the time to onset (in days) of improvement in pruritus in dupilumab- vs placebo-treated adult and adolescent patients with AD in the LIBERTY AD SOLO 1 (NCT02277743), LIBERTY AD SOLO 2 (NCT02277769), and LIBERTY AD ADOL (NCT03054428) studies**

METHODS

Study design

- Detailed descriptions of the study populations and methodologies have been previously published,[7–9] and are summarized below and in **Figure 1**
  - SOLO 1 (NCT02277743) and SOLO 2 (NCT02277769): adult patients received 300 mg dupilumab every week (qw), or every 2 weeks (q2w), or placebo
    - SOLO 1 and 2 had identical study designs; data from these trials have been pooled in this analysis (SOLO)
  - ADOL (NCT03054428): adolescent patients received 200/300 mg dupilumab q2w, 300 mg every 4 weeks (q4w) or placebo

Figure 1. Study designs.



R, randomization.

Outcomes

- Improvement in itch was quantified through
  - Least squares (LS) mean percent change from baseline in daily Peak Pruritus Numerical Rating Scale (NRS) from Day 2 to Day 15
  - Proportion of patients achieving ≥ 3-point improvement from baseline in daily Peak Pruritus NRS score (clinically meaningful response[10–12]) from Day 2 through Day 15

Analysis

- Efficacy was analyzed in the full analysis set which included all randomized patients
- Analysis of daily Peak Pruritus NRS score was performed using an analysis of covariance (ANCOVA) model with baseline measurement as covariate, and the treatment and randomization strata as fixed factors (study identifier was also used as fixed factor for the analysis of pooled SOLO data)
- Responder analyses were conducted using a Cochran–Mantel–Haenszel test stratified by baseline disease severity (Investigator's Global Assessment [IGA] = 3 vs IGA = 4) in both SOLO and ADOL, and additionally by baseline weight group (< 60 kg vs ≥ 60 kg) in ADOL
- Missing values were imputed using the last observation carried forward method
- Safety was assessed among patients who received ≥ 1 dose of any study drug

RESULTS

Baseline characteristics

- Baseline characteristics were comparable among treatment groups within trials (**Table 1**)
- Adolescents had marginally higher AD severity than adults, as assessed by IGA and Eczema Area and Severity Index (EASI)
- Baseline Peak Pruritus NRS scores (standard deviation [SD]) in adults were 7.3 (1.9)/7.4 (1.8)/7.4 (1.8) for qw/q2w/placebo groups, respectively, and 7.5 (1.5)/7.5 (1.8)/7.7 (1.6) for q2w/q4w/placebo groups, respectively, in adolescents

Efficacy

- Primary efficacy endpoints are displayed in **Table 2**
- Dupilumab treatment vs placebo resulted in significant improvement in pruritus, as measured by LS mean percent change in Peak Pruritus NRS score: in adults as early as Day 2 for q2w ($P = 0.0033$) and Day 3 for qw ($P < 0.0001$) and in adolescents as early as Day 5 for q2w ($P = 0.0265$) and Day 6 for q4w ($P = 0.0095$; **Figure 2**)
- At Day 15 in adults, LS mean percent change (standard error [SE]) was –22.5 (1.4)/–24.7 (1.4)/–3.4 (1.4) for qw/q2w/placebo groups, respectively ($P < 0.0001$ for both doses); corresponding values in adolescents were –25.3 (2.7)/–21.8 (2.7)/–5.7 (2.6) for q2w/q4w/placebo groups, respectively ($P < 0.0001$ for both doses; **Figure 2**)
- A higher proportion of patients in the dupilumab q2w group showed a clinically meaningful response (≥ 3-point improvement) in daily Peak Pruritus NRS scores vs placebo as early as Day 4 in adults and Day 13 in adolescents ($P < 0.01$ and $P < 0.05$, respectively, vs placebo; **Figure 3**)

Safety

- Safety data were consistent with the known dupilumab safety profile (**Table 3**)

Table 1. Baseline disease characteristics.

	Adult patients (SOLO 1 & 2 pooled)			Adolescent patients (ADOL)		
	Placebo (n = 460)	Dupilumab 300 mg q2w (n = 457)	Dupilumab 300 mg qw (n = 462)	Placebo (n = 85)	Dupilumab 200 mg or 300 mg q2w (n = 82)	Dupilumab 300 mg q4w (n = 84)
Age, mean (SD), years	38.4 (14.0)	38.3 (14.4)	38.2 (14.5)	14.5 (1.8)	14.5 (1.7)	14.4 (1.6)
Male, n (%)	250 (54.3)	267 (58.4)	281 (60.8)	53 (62.4)	43 (52.4)	52 (61.9)
Duration of AD, mean (SD), years	28.8 (14.4)	27.9 (15.2)	27.6 (15.4)	12.3 (3.4)	12.5 (3.0)	11.9 (3.2)
Patients with IGA score = 4, n (%)	225 (49)	223 (49)	218 (47)	46 (54)	43 (52)	46 (55)
EASI score, mean (SD)	34.0 (14.4)	32.4 (13.3)	32.5 (13.3)	35.5 (14.0)	35.3 (13.8)	35.8 (14.8)
Peak Pruritus NRS score, mean (SD)	7.4 (1.8)	7.4 (1.8)	7.3 (1.9)	7.7 (1.6)	7.5 (1.5)	7.5 (1.8)
SCORAD score, mean (SD)	68.8 (14.5)	67.1 (13.7)	67.5 (13.3)	70.4 (13.3)	70.6 (13.9)	69.8 (14.1)
BSA affected by AD, mean (SD), %	55.8 (23.3)	53.7 (22.2)	54.1 (22.3)	56.4 (24.1)	56.0 (21.4)	56.9 (23.5)
POEM score, mean (SD)	20.6 (5.9)	20.3 (6.0)	20.7 (5.9)	21.1 (5.4)	21.0 (5.0)	21.1 (5.5)
(C)DLQI score, mean (SD)	15.1 (7.5)	14.7 (7.3)	15.1 (7. 5)	13.1 (6.7)	13.0 (6.2)	14.8 (7.4)

EASI scores reported on scale from 0 to 72, Peak Pruritus NRS scores reported on scale from 0 to 10, SCORAD scores reported on scale from 0 to 103, POEM scores reported on scale from 0 to 28, (C)DLQI scores reported on scale from 0 to 30. BSA, Body Surface Area; (C)DLQI, (Children's) Dermatology Life Quality Index; N/A, not applicable; POEM, Patient-Oriented Eczema Measure; SCORAD, SCORing Atopic Dermatitis.

Table 2. Primary efficacy endpoints at Week 16.

	Adult patients (SOLO 1 & 2 pooled)			Adolescent patients (ADOL)		
	Placebo (n = 460)	Dupilumab 300 mg q2w (n = 457)	Dupilumab 300 mg qw (n = 462)	Placebo (n = 85)	Dupilumab 200 mg or 300 mg q2w (n = 82)	Dupilumab 300 mg q4w (n = 84)
Proportion of patients achieving IGA score 0/1, and ≥ 2-point reduction from baseline, %	11.7	38.9***	38.1***	4.7	24.4***	20.2**
Proportion of patients achieving EASI-75,[a] %	18.9	54.5***	59.3***	15.30	45.1***	47.6***

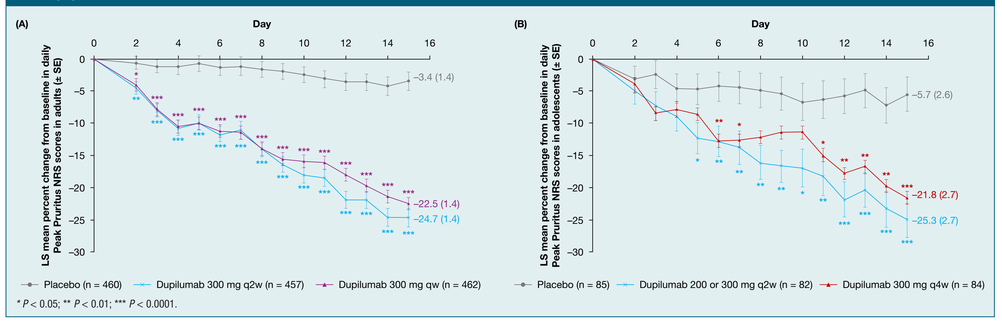
All observed values regardless of rescue treatment use; missing patients were considered as non-responders. [a]Co-primary endpoint for adults and adolescents in Europe and Japan, key secondary endpoint in the USA.
** $P < 0.01$, *** $P < 0.001$. EASI-75, 75% improvement from baseline in EASI.

Table 3. Safety assessment during the treatment period.

Patients with event, n (%)	Adult patients (SOLO 1 & 2 pooled)			Adolescent patients (ADOL)		
	Placebo (n = 456)	Dupilumab 300 mg q2w (n = 465)	Dupilumab 300 mg qw (n = 455)	Placebo (n = 85)	Dupilumab 200/300 mg q2w (n = 82)	Dupilumab 300 mg q4w (n = 83)
≥ 1 TEAE	313 (68.6)	321 (69.0)	307 (67.5)	59 (69.4)	59 (72.0)	53 (63.9)
TEAE leading to permanent study discontinuation	7 (1.5)	6 (1.3)	7 (1.5)	1 (1.2)	0	0
Death	0	0	1 (0.2)[a]	0	0	0
Treatment-emergent SAE	24 (5.3)	11 (2.4)	10 (2.2)	1 (1.2)	0	0
TEAEs occurring in ≥ 5% of patients in any group in any trial (PT)						
Dermatitis atopic	148 (32.5)	62 (13.3)	59 (13.0)	21 (24.7)	15 (18.3)	15 (18.1)
Nasopharyngitis	39 (8.6)	42 (9.0)	45 (9.9)	4 (4.7)	3 (3.7)	9 (10.8)
Upper respiratory tract infection	10 (2.2)	13 (2.8)	20 (4.4)	15 (17.6)	10 (12.2)	6 (7.2)
Headache	24 (5.3)	40 (8.6)	33 (7.3)	9 (10.6)	9 (11.0)	4 (4.8)
Injection-site reaction	28 (6.1)	51 (11.0)	72 (15.8)	1 (1.2)	0	1 (1.2)
Conjunctivitis[b]	10 (2.2)	45 (9.7)	33 (7.3)	4 (4.7)	8 (9.8)	9 (10.8)

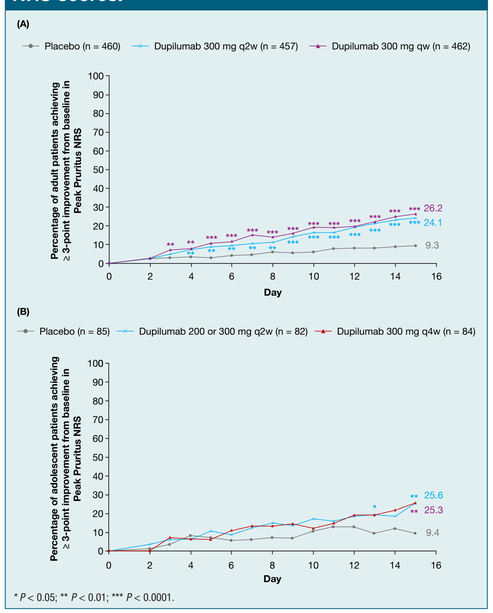
[a]Death was unrelated to treatment (for a full description of the events, see Simpson, et al. 2016[7]); [b]Includes the following PTs: conjunctivitis, conjunctivitis bacterial, conjunctivitis viral, conjunctivitis allergic, and atopic keratoconjunctivitis. MedDRA, Medical Dictionary for Regulatory Activities; PT, MedDRA Preferred Term; SAE, serious adverse event; TEAE, treatment-emergent adverse event.

Figure 2. LS mean percent change from baseline in daily Peak Pruritus NRS from Day 2 to Day 15 in (A) adults and (B) adolescents.



* $P < 0.05$; ** $P < 0.01$; *** $P < 0.0001$.

Figure 3. Proportion of (A) adult and (B) adolescent patients achieving ≥ 3-point improvement from baseline through Day 15 in daily Peak Pruritus NRS scores.



* $P < 0.05$; ** $P < 0.01$; *** $P < 0.0001$.

CONCLUSIONS

- **Treatment with dupilumab (q2w approved dose) resulted in rapid and significant improvement in itch as early as Day 2 in adult patients, and Day 5 in adolescent patients with moderate-to-severe AD**
- **Clinically meaningful improvement was observed after the first dose in both adults and adolescents**
- **Dupilumab was well tolerated with an acceptable safety profile**

References

1. Zachariae R, et al. Acta Derm Venereol. 2012;92:508-14. 2. Ramirez FD, et al. JAMA Pediatr. 2019;173:e190025. 3. Macdonald LE, et al. Proc Natl Acad Sci U S A. 2014;111:5147-52. 4. Murphy AJ, et al. Proc Natl Acad Sci U S A. 2014;111:5153-8. 5. Gandhi NA, et al. Expert Rev Clin Immunol. 2017;13:425-37. 6. Gandhi NA, et al. Nat Rev Drug Discov. 2016;15:35-50. 7. Simpson EL, et al. N Engl J Med. 2016;375:2335-48. 8. Simpson EL, et al. Data presented at the 27th Annual Congress of the European Academy of Dermatology and Venereology; Paris, France; September 12–16, 2018. 9. Simpson EL, et al. JAMA Derm. 2019; Nov 6 (Epub ahead of print). doi:https://doi.org/10.1001/jamadermatol.2019.3336. 10. Phan NQ, et al. Acta Derm Venereol. 2012;92:502-7. 11. Simpson EL, et al. J Am Acad Dermatol. 2017;76 Suppl 1: abstract 93. 12. Yosipovitch G, et al. J Am Acad Dermatol. 2017;76 Suppl 1: abstract 278.

Acknowledgments

Data first presented at the 76th Annual American Academy of Allergy, Asthma & Immunology Conference (AAAAI 2020); Virtual Conference; March 13–16, 2020.
Research sponsored by Sanofi and Regeneron Pharmaceuticals, Inc. ClinicalTrials.gov Identifiers: NCT02277743 (LIBERTY AD SOLO 1), NCT02277769 (LIBERTY AD SOLO 2), and NCT03054428 (LIBERTY AD ADOL). Medical writing/editorial assistance provided by Luke Shelton, PhD, of Excerpta Medica, funded by Sanofi Genzyme and Regeneron Pharmaceuticals, Inc.

Disclosures

Yosipovitch G: Bayer, Eli Lilly, Galderma, Menlo Therapeutics, Novartis, Regeneron Pharmaceuticals, Inc., Sanofi, Sienna Biopharmaceuticals, Trevi Therapeutics – advisory board member; Galderma, Kiniska, LEO Pharma, Novartis, Pfizer, Sun – grants/research funding. **Hong CH:** Centocor, Cutanea, Dermavant, GSK, MedImmune – investigator; sanofi-aventis – consultant; Boehringer Ingelheim – investigator, consultant; Cipher – speaker; Bausch Health, Roche – speaker, consultant; AbbVie, Amgen, Celgene, Eli Lilly, Galderma, Janssen, LEO Pharma, Novartis, Regeneron Pharmaceuticals, Inc. – speaker, investigator, consultant. **Simpson EL:** AbbVie, Eli Lilly, Galderma, Kyowa Hakko Kirin, LEO Pharma, Merck, Pfizer, Regeneron Pharmaceuticals, Inc. – investigator; AbbVie, Boehringer Ingelheim, Dermavant, Eli Lilly, Forte Bio, Incyte, LEO Pharma, Menlo Therapeutics, Pfizer, Pierre Fabre Dermo Cosmétique, Regeneron Pharmaceuticals, Inc., Sanofi Genzyme, Valeant – consultant honorarium. **Chen Z:** Regeneron Pharmaceuticals, Inc. – employees and shareholders. **Rossi A:** Sanofi Genzyme – employee, may hold stock and/or stock options in the company.

Presented at the Maui Derm Connect Virtual Dermatology Conference; Virtual Conference; September 23–26, 2020.