Dupilumab in Moderate-to-Severe Atopic Dermatitis: Pooled Efficacy Results From Two Identically Designed Randomized Phase 3 Trials (SOLO 1 & 2)

Carlos Ferrándiz[1], Pablo de la Cueva Dobao[2], Eric L. Simpson[3], Rick Zhang[4], Abhijit Gadkari[5], Laurent Eckert[6], Bolanle Akinlade[5], Marius Ardeleanu[5]

[1]Hospital Universitario Germans Trias i Pujol, Barcelona, Spain; [2]Hospital Universitario Infanta Leonor, Madrid, Spain; [3]Oregon Health & Science University, Portland, OR, USA; [4]Regeneron Pharmaceuticals, Inc., Basking Ridge, NJ, USA; [5]Regeneron Pharmaceuticals, Inc., Tarrytown, NY, USA; [6]Sanofi, Chilly-Mazarin, France

BACKGROUND

- Atopic dermatitis (AD) is a chronic inflammatory skin disorder with reddened, dry, excoriated, pruritic skin lesions that can affect a large area of the body[1,2]
- Dupilumab is a fully human anti-interleukin (IL)-4 receptor alpha monoclonal antibody that inhibits signaling of IL-4 and IL-13, type 2/Th2 cytokines that have been implicated in numerous atopic/allergic diseases, including asthma and AD[3]
- Dupilumab is approved by the US 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
- Two identically designed pivotal phase 3 trials – SOLO 1 (ClinicalTrials.gov Identifier NCT02277743; EudraCT number 2014-001198-15) and SOLO 2 (NCT02277769; 2014-002619-40) – independently demonstrated the efficacy and safety of dupilumab administered for 16 weeks in patients with moderate-to-severe AD[4]
- The identical designs of these studies permitted pooling of the efficacy and safety outcomes

OBJECTIVES

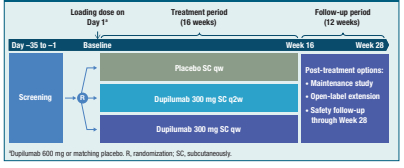
- **To report pooled efficacy results from SOLO 1 and SOLO 2**
- **To present pooled safety outcomes of the studies**

METHODS

Study design

- SOLO 1 and SOLO 2 were randomized, double-blind, multinational, placebo-controlled trials with identical study designs, conducted at separate sites in North America, Europe, and Asia (**Figure 1**)

Figure 1. SOLO 1 and SOLO 2: pivotal phase 3 studies with identical study design.



*Dupilumab 600 mg or matching placebo. R, randomization; SC, subcutaneously.

Patient eligibility

- Key inclusion criteria included: age ≥ 18 years, moderate-to-severe AD for ≥ 3 years prior to screening, Investigator's Global Assessment (IGA) score ≥ 3 (moderate-to-severe; scale 0–4), Eczema Area and Severity Index (EASI) score ≥ 16 (scale 0–72), and AD inadequately controlled with/inadvisable for topical medications
- Key exclusion criteria included: active chronic or acute infection requiring systemic treatment within 2 weeks before baseline, or history of immunosuppressive condition

Presented at the 2017 Fall Clinical Dermatology Conference; Las Vegas, NV, USA; October 12-15, 2017.

Treatments

- Patients were randomized (1:1:1) to subcutaneous dupilumab 300 mg every week (qw) or 300 mg every 2 weeks (q2w), or placebo qw, for 16 weeks
- Loading dose on Day 1: 600 mg dupilumab or matching placebo

Outcomes

- Primary and co-primary efficacy endpoints
  - Proportion of patients at Week 16 achieving IGA score of 0/1 (clear/almost clear) and ≥ 2-point improvement from baseline (primary)
  - Proportion of patients at Week 16 achieving 75% improvement from baseline in EASI score (EASI-75) (co-primary endpoint in the EU and Japan; key secondary endpoint in other regions)
- Secondary efficacy endpoints
  - Proportion of patients achieving ≥ 4-point improvement in weekly average of peak pruritus numerical rating scale (NRS) score (key secondary endpoint)
  - Percent change in EASI score and SCORing Atopic Dermatitis (SCORAD) total score
  - Percent change in Patient-Oriented Eczema Measure (POEM) score, Hospital Anxiety and Depression Scale (HADS) total score, and Dermatology Life Quality Index (DLQI) score
- Pooled safety outcomes are reported

RESULTS

Baseline demographics and disease characteristics

- A total of 1,379 patients were enrolled (SOLO 1: 671; SOLO 2: 708)
- All treatment groups had similar baseline characteristics (**Table 1**)

Table 1. Baseline disease characteristics.

	Placebo qw (n = 460)	Dupilumab 300 mg q2w (n = 457)	Dupilumab 300 mg qw (n = 462)
Duration of AD, median (Q1, Q3), years	27 (19.0, 39.0)	26 (17.0, 38.0)	25 (17.0, 39.0)
EASI score, mean (SD)	34.0 (14.38)	32.4 (13.32)	32.5 (13.34)
IGA score (range 0–4), n (%)			
3 (moderate)	234 (51)	234 (51)	244 (53)
4 (severe)	225 (49)	223 (49)	218 (47)
SCORAD total score, mean (SD)	68.8 (14.45)	67.1 (13.71)	67.5 (13.34)
BSA affected, mean (SD), %	55.8 (23.25)	53.7 (22.21)	54.1 (22.29)
Peak pruritus NRS score, mean (SD)	7.4 (1.81)	7.4 (1.76)	7.3 (1.94)
POEM score, mean (SD)	20.6 (5.93)	20.3 (5.96)	20.7 (5.91)
HADS total score, mean (SD)	13.2 (8.33)	13.0 (7.43)	13.7 (8.15)
DLQI score, mean (SD)	15.1 (7.47)	14.7 (7.25)	15.1 (7.47)

BSA, body surface area; Q1, quartile 1; Q3, quartile 3; SD, standard deviation.

Clinical efficacy

- Significantly more patients in both dupilumab dose groups compared with placebo achieved both IGA score 0/1 and ≥ 2-point improvement at Week 16 ($P < 0.0001$ vs placebo, each dose group) (**Figure 2A**)
- Significantly more patients in both dupilumab dose groups compared with placebo achieved EASI-75 at Week 16 ($P < 0.0001$ vs placebo, each dose group) (**Figure 2B**)
- In both dose groups, dupilumab resulted in significantly greater percent reductions (improvements) from baseline to Week 16 compared with placebo in
  - EASI scores ($P < 0.0001$ vs placebo, each dose group) (**Figure 3A**)
  - SCORAD total scores ($P < 0.0001$ vs placebo, each dose group) (**Figure 3B**)

Pruritus

- Significantly more patients in both dupilumab dose groups compared with placebo achieved a ≥ 4-point improvement in weekly peak pruritus NRS score at Week 16 ($P < 0.0001$ vs placebo, each dose group) (**Figure 4A**)
- Significant improvements in the proportion of patients achieving ≥ 4-point improvement in weekly peak pruritus NRS score were observed as early as Week 2 ($P < 0.0001$ vs placebo, each dose group) (**Figure 4A**)

Figure 2. IGA 0/1 and ≥ 2-point improvement from baseline (A) and EASI-75 (B) at Week 16.

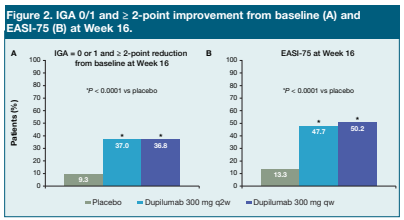
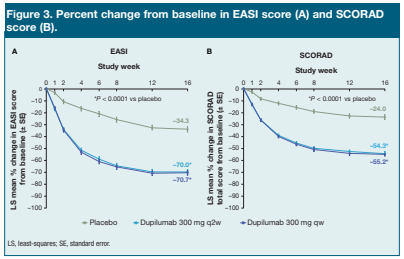


Figure 3. Percent change from baseline in EASI score (A) and SCORAD score (B).



LS, least-squares; SE, standard error.

Patient-reported symptoms and quality of life

- In both dose groups, compared with placebo, dupilumab significantly improved symptoms of AD, including impact on sleep (**Figure 4B**); symptoms of anxiety and depression (**Figure 5A**); and quality of life (**Figure 5B**) ($P < 0.0001$, dupilumab vs placebo, all comparisons)

Safety

- Rates of adverse events (AEs) were similar in the 3 treatment groups (dupilumab qw, dupilumab q2w, and placebo) (**Table 2**)
- The most common AEs were nasopharyngitis, injection-site reactions, and AD exacerbations
- Conjunctivitis and injection-site reactions were more frequent in dupilumab-treated patients, and exacerbations of AD and skin infections were more frequent in placebo-treated patients
- The overall infection rate was not increased in the dupilumab groups compared with placebo

Figure 5. Change from baseline in HADS total score (A) and DLQI score (B).

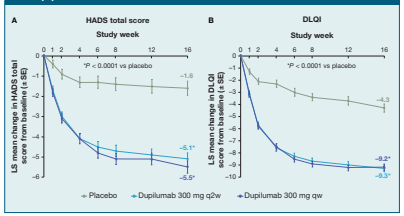


Figure 4. Proportions of patients achieving peak pruritus NRS score improvement of ≥ 4 points at Week 16 (A), and change from baseline in POEM score (B).

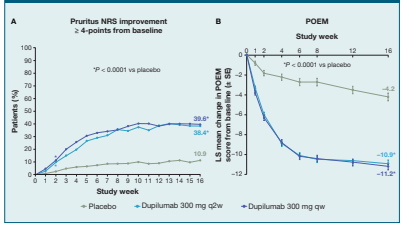


Table 2. Adverse events.

Event	Placebo qw (n = 456)	Dupilumab 300 mg q2w (n = 465)	Dupilumab 300 mg qw (n = 455)
	Patients with AE, n (%)		
≥ 1 AE	313 (69)	321 (69)	307 (67)
≥ 1 SAE	24 (5)	11 (2)	10 (2)
Death	0 (0)	1 (< 1)[a]	1 (< 1)
AEs leading to treatment discontinuation	7 (2)	6 (1)	7 (2)
Infections and infestations[b]	139 (30)	145 (31)	142 (31)
Skin infections (adjudicated)	44 (10)	27 (6)	29 (6)
Herpes viral infections[c]	17 (4)	25 (5)	21 (5)
Nasopharyngitis[d]	39 (9)	42 (9)	45 (10)
Conjunctivitis[d]	3 (1)	20 (4)	16 (4)
Upper respiratory tract infection[d]	10 (2)	13 (3)	20 (4)
Injection-site reaction[d]	28 (6)	51 (11)	72 (16)
Atopic dermatitis[d]	148 (32)	62 (13)	59 (13)
Headache[d]	24 (5)	40 (9)	33 (7)
Allergic conjunctivitis[d]	4 (1)	14 (3)	10 (2)

[a]Death occurred during the post-treatment period. [b]MedDRA System Organ Class; [c]MedDRA High Level Term; [d]MedDRA Preferred Term. MedDRA, Medical Dictionary for Regulatory Activities; SAE, serious adverse event.

CONCLUSIONS

- **In a pooled analysis of SOLO 1 and 2, both dose regimens of dupilumab significantly improved signs (including the primary and co-primary endpoints) and symptoms of AD (including pruritus, symptoms of anxiety and depression, and quality of life) compared with placebo**
- **The results of the pooled analyses were consistent with those presented separately for each study, and with previous studies of dupilumab in AD[4-7]**
- **There were no major safety issues related to dupilumab treatment**

References

1. Hanifin JM, Rajka G. Acta Dermatovener (Stockholm). 1980;60 Suppl 92:44-7.
2. Eichenfield LF, et al. J Am Acad Dermatol. 2014;70:338-51.
3. Gandhi NA, et al. Nature Rev Drug Disc. 2016;15:35-50.
4. Simpson EL, et al. N Engl J Med. 2016;375:2335-48.
5. Beck LA, et al. N Engl J Med. 2014;371:130-9.
6. Thaçi D, et al. Lancet. 2016;387:40-52.
7. Simpson EL, et al. J Am Acad Dermatol. 2016;75:506-15.

Acknowledgments

Research sponsored by Sanofi and Regeneron Pharmaceuticals, Inc. ClinicalTrials.gov Identifiers: NCT02277743; NCT02277769. Medical writing/editorial assistance provided by Vicki Schwartz, PhD, of Excerpta Medica, funded by Sanofi Genzyme and Regeneron Pharmaceuticals, Inc.

Data first presented at the 45th Congreso Nacional de Dermatología y Venereología (AEDV 2017); Madrid, Spain; May 10–13, 2017.

Disclosures

Ferrándiz C: AbbVie, Almirall, Amgen, Celgene, Janssen-Cilag, LEO Pharma, Lilly, Merck Sharp & Dohme, Novartis, Pfizer – consultant and/or speaker and/or investigator.
de la Cueva Dobao P: AbbVie, Almirall, Biogen, Boehringer, Celgene, Janssen, LEO Pharma, Lilly, Merck Sharp & Dohme, Novartis, Pfizer, Sanofi – grants/speaker/consultant/research.
Simpson EL: Amgen, Celgene, Chugai, Galderma, Regeneron Pharmaceuticals, Inc. – grants/research support; Anacor, Asubio, Celgene, Galderma, Genentech, Medicis, Merck – consultant.
Zhu X, Gadkari A, Akinlade B, Ardeleanu M: Regeneron Pharmaceuticals, Inc. – employees and shareholders.
Eckert L: Sanofi – employee and may hold stock and/or stock options in the company.