 ORIGINAL ARTICLE Journal of Drugs in Dermatology

Efficacy of Dupilumab in Different Racial Subgroups of Adults With Moderate-to-Severe Atopic Dermatitis in Three Randomized, Placebo-Controlled Phase 3 Trials

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ABSTRACT

Dupilumab, a monoclonal antibody that blocks the shared receptor subunit for interleukin (IL)-4 and IL-13, is currently approved for the treatment of adults with inadequately controlled moderate-to-severe atopic dermatitis (AD). The efficacy and safety of dupilumab for AD among racial subgroups is unknown. This post hoc analysis from three phase 3 trials assessed the efficacy and safety of dupilumab vs placebo by racial subgroup (White, Asian, Black/African American). Data from LIBERTY AD SOLO 1 (NCT02277743), SOLO 2 (NCT02277769), and CHRONOS (NCT02260986) were pooled. Outcomes included mean and percent change from baseline to week 16 in the key therapeutic domains Eczema Area and Severity Index (EASI), Peak Pruritus Numerical Rating Scale (NRS), Dermatology Life Quality Index (DLQI), and Patient-Oriented Eczema Measure, as well as Investigator's Global Assessment and pain or discomfort assessed by the European Quality of Life-5 Dimensions 3 level questionnaire.

A total of 2,058 patients (White n=1,429, Asian n=501, Black/African American n=128) were included in the current analysis. Baseline demographics and disease characteristics were balanced between treatment groups and racial subgroups. In the three trials, dupilumab significantly (P<0.0001) improved all assessed outcomes compared with placebo in the White and Asian subgroups. In the smaller Black/African American subgroup, dupilumab significantly (P<0.0001) improved EASI endpoints and mean changes in Peak Pruritus NRS and DLQI vs placebo, with positive numeric trends favoring dupilumab in all other endpoints.

Dupilumab was generally well tolerated, with an acceptable safety profile in all racial subgroups. Serious adverse events occurred more frequently with placebo; treatment discontinuations due to adverse events were rare in all treatment groups.

Significant clinical improvement and a favorable benefit-risk profile can be achieved with dupilumab treatment in patients of White, Asian, and Black/African American racial subgroups with moderate-to-severe AD inadequately controlled with topical medications.

ClinicalTrials.gov identifiers: NCT02277743, NCT02277769, NCT02260986

J Drugs Dermatol. 2019;18(8):804-813.

INTRODUCTION

Atopic dermatitis (AD) is a clinically defined, chronic skin condition characterized by intense itch, disruption of the skin barrier, and upregulation of type 2 immune responses.[1-3] The disease has an adverse impact on quality of life (QoL) and is associated with sleep loss, anxiety, and depression.[4,5] Considerable heterogeneity in AD characteristics and disease course has been noted between racial groups and region.[6,7] Genetic variations that influence AD incidence,

presentation, and severity include differential expression of specific polymorphisms in type 2 signaling pathway genes, including those of interleukin (IL)-4 and IL-13 and their receptors, and variations in skin barrier gene mutations.[6] Disease presentation can also vary among racial subgroups, with Asian patients presenting with better demarcated lesions and increased scaling and lichenification compared with White patients.[6] Darker-skinned patients can have perifollicular accentuation and scattered distinct papules on the extensors and trunk, and erythema may be missed when assessing AD lesions.[6] AD prevalence also varies by racial subgroup, having been reported more often in Asians and Blacks than in Whites.[6,8] Therefore, diagnosis and severity assessment should consider racial differences in genetics, presentation, and prevalence. However, current guidelines do not propose any differences in the diagnosis and treatment of AD by racial subgroup,[9-11] and no practical evidence exists to show that treatment should be addressed differentially by racial subgroup.

Dupilumab, a fully human VelocImmune®-derived[12,13] monoclonal antibody, blocks the shared receptor subunit for IL-4 and IL-13, thus inhibiting signaling of both IL-4 and IL-13. Dupilumab is approved for subcutaneous administration every two weeks (q2w) for the treatment of patients aged 12 years and older with moderate-to-severe AD inadequately controlled with topical prescription therapies or when those therapies are not advisable in the USA,[14] for the treatment of adult AD patients not adequately controlled with existing therapies in Japan, and for use in adults with moderate-to-severe AD who are candidates for systemic therapy in the EU.[15] Dupilumab is also approved by the US Food and Drug Administration[14] as an add-on maintenance treatment in patients with moderate-to-severe asthma aged ≥12 years with an eosinophilic phenotype or with oral corticosteroid-dependent asthma regardless of eosinophilic phenotype.[16-18] In clinical trials, dupilumab demonstrated significant efficacy in improving signs and symptoms of AD, and an acceptable safety profile.[19-23] Efficacy and safety of dupilumab have also been shown in clinical trials in other type 2 immune diseases, including chronic rhinosinusitis with nasal polyposis, and eosinophilic esophagitis, thus demonstrating the importance of IL-4 and IL-13 as drivers of multiple type 2 atopic/allergic diseases.[24,25]

LIBERTY AD SOLO 1 and SOLO 2 were two identically designed, pivotal, 16-week, phase 3 trials that assessed efficacy and safety of dupilumab monotherapy vs placebo,[21] while the 52-week CHRONOS trial assessed dupilumab with concomitant topical corticosteroids (TCS) vs TCS alone[22] in adults with moderate-to-severe AD. Dupilumab significantly improved skin lesions, symptoms (including pruritus and symptoms of anxiety and depression), and QoL with an acceptable safety profile[21,22] in these randomized, placebo-controlled, double-blinded trials.

As the efficacy and safety of dupilumab among racial subgroups have not been assessed previously, the objective of this report is to present dupilumab efficacy, safety, and pharmacokinetics (PK) among racial subgroups of adult patients with moderate-to-severe AD in an analysis of the SOLO 1, SOLO 2, and CHRONOS trials.

METHODS

Study Designs

Detailed descriptions of the study populations and methodologies of these trials have been published previously.[21,22] All three studies were conducted following guidelines based on the Declaration of Helsinki, International Conference on Harmonisation-Good Clinical Practice, and local applicable regulatory requirements. All patients provided written informed consent prior to undertaking any study procedures.[21,22]

Briefly, in SOLO 1 (NCT02277743) and SOLO 2 (NCT02277769), patients were randomized 1:1:1 to subcutaneous dupilumab 300 mg weekly (qw), q2w, or placebo for 16 weeks. A 35-day screening and washout period preceded study drug administration. In CHRONOS (NCT02260986), patients were randomized 3:1:3 to subcutaneous dupilumab 300 mg qw, q2w, or placebo for 52 weeks with concomitant TCS; concomitant topical calcineurin inhibitors could be used on body locations where TCS were considered inadvisable. A 35-day screening period preceded the study drug administration without a washout period for TCS. In all three trials, a 600 mg loading dose was administered on day 1 to patients receiving dupilumab, while patients in the placebo group received a double dose of placebo.

Patients self-reported their racial subgroup. Due to the very low number or absence of patients of other racial subgroups (American Indian, Alaska Native, Native Hawaiian or other Pacific Islander, Others), this analysis only presented data from White, Asian, and Black/African American patients.

Outcomes

Efficacy outcomes assessed in this analysis included: mean and percent change from baseline to week 16 in Eczema Area and Severity Index (EASI), Peak Pruritus Numerical Rating Scale (NRS), Dermatology Life Quality Index (DLQI), and Patient-Oriented Eczema Measure (POEM); proportion of patients achieving Investigator's Global Assessment (IGA) score 0 or 1 and a reduction of ≥2 points from baseline at week 16; and proportion of patients with no pain or discomfort at week 16 using the European Quality of Life-5 Dimensions 3 level (EQ-5D-3L) questionnaire among patients with at least moderate pain or discomfort at baseline.

Safety outcomes included overall incidence of treatment-emergent adverse events (TEAEs); treatment-emergent serious adverse events (TE-SAEs); TEAEs leading to treatment discontinuation;

deaths; and conjunctivitis from baseline to week 16. The generic term "conjunctivitis" was used to summarize a cluster of Medical Dictionary for Regulatory Activities Preferred Terms including conjunctivitis, allergic conjunctivitis, viral conjunctivitis, bacterial conjunctivitis, and atopic keratoconjunctivitis. Individual TEAEs by racial subgroup were not analyzed due to low numbers of patients in each subgroup.

The PK profile among different racial subgroups was assessed as functional dupilumab levels in serum.[26] The lower limit of quantification of functional dupilumab concentration was 0.078 mg/L in undiluted human serum.

Statistical Analysis

Baseline, efficacy, and safety data for all three studies were pooled. For CHRONOS, efficacy and safety data were used through week 16, with week 52 data not reported due to insufficient numbers of patients in some racial subgroups to enable statistical analyses at that time point.

Efficacy analyses were performed on the full analysis set, which included all randomized patients. Safety analyses by study drug were performed using the safety analysis set, which included all randomized patients who received at least one dose of any study drug. PK analyses were performed on the PK analysis set, which included all patients who had a PK measurement for a particular time point.

All efficacy endpoints except IGA and EQ-5D-3L were analyzed using an ANCOVA model with baseline measurement as covariate, and treatment, region, and baseline IGA strata as fixed factors for all studies, and study identifier. Values after first rescue treatment were set to missing (censored) and imputed using the multiple imputation method. *P* values (nominal) were derived from an ANCOVA model using baseline as covariate, and treatment, subgroup, treatment-by-subgroup interaction, region, and baseline IGA strata as fixed factors. The ANCOVA model was further adjusted with baseline weight (kg) as an additional factor to generate weight-adjusted results for continuous endpoints. IGA and EQ-5D-3L responder analyses were conducted using a Cochran–Mantel–Haenszel (CMH) test stratified by region, baseline disease severity (IGA=3 vs IGA=4), and study identifier. CMH models are not amenable to adjustment with continuous variables, therefore, body weight adjustment analyses were not conducted for responder analyses.

Safety outcomes were summarized using descriptive statistics. Statistical significance of differences in efficacy between the dupilumab dose groups was not investigated.

All analyses were performed using SAS software, version 9.4 (SAS Institute Inc., Cary, NC, USA).

RESULTS

Patients

The pooled analysis population included 1,429 White patients, 501 Asian patients, and 128 Black/African American patients (Table 1). Patient race was self-identified. White patients were enrolled in the United States of America (USA, 29.2%), Poland (16.9%), Germany (14.4%), Canada (12.0%), Spain (4.1%), Estonia (3.8%), the United Kingdom (UK, 3.1%), Italy (2.5%), the Netherlands (2.5%), Australia (2.4%), Hungary (1.9%), France (1.5%), the Czech Republic (1.4%), Lithuania (1.2%), Bulgaria (1.0%), Denmark (1.0%), Finland (0.6%), Romania (0.3%), and New Zealand (0.2%). Asian patients were enrolled in Japan (44.5%), Republic of Korea (21.2%), Canada (15.6%), the USA (11.8%), Singapore (2.8%), Hong Kong (1.0%), the Netherlands (1.0%), the UK (0.8%), Australia (0.6%), New Zealand (0.4%), Germany (0.2%), and Spain (0.2%). Black/African American patients were enrolled in the USA (92.2%) and Canada (7.8%).

Baseline demographics and disease characteristics were generally balanced among treatment groups[21,22] and among racial subgroups in each of the studies (Table 1). Most patients had a median AD duration of >20 years, mean baseline EASI >30, and mean weekly Peak Pruritus NRS >7, showing a high disease burden at baseline.

Efficacy

In the White and Asian subgroups, both dupilumab regimens significantly improved AD signs (EASI, IGA), symptoms (POEM), including itch (Peak Pruritus NRS) and pain/discomfort (EQ-5D-3L), and QoL (DLQI) vs placebo at week 16 (Figure 1A-J, $P<0.0001$). Weight-adjusted analyses support these findings (Figure 2A-H).

In Black/African American patients, both dupilumab regimens led to significant improvement vs placebo in the EASI endpoints (Figure 1A-B) and mean change in Peak Pruritus NRS (Figure 1C) and DLQI (Figure 1E), while only dupilumab 300 mg qw showed significant improvement vs placebo in mean percent change in Peak Pruritus NRS (Figure 1D), POEM endpoints (Figure 1G-H), and proportions of patients achieving the IGA success endpoint (Figure 1I) ($P<0.05$). Weight-adjusted analyses are consistent with these findings (Figure 2).

Safety

Dupilumab was generally well tolerated, with an acceptable safety profile in all three trials.[21,22] TEAEs occurred at similar rates across treatment groups. Conjunctivitis and injection-site reactions were more frequent in the dupilumab-treated groups in all studies, but were mild-to-moderate and rarely led to treatment discontinuation. AD exacerbations and skin infections occurred more frequently in the placebo groups.

TABLE 1.

Baseline Demographics and Clinical Characteristics by Treatment Group and Racial Subgroup

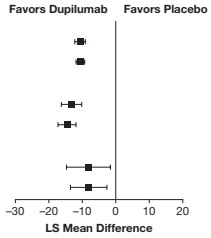
	White			Asian			Black/African American		
	Placebo (n=510)	Dupilumab 300 mg q2w (n=394)	Dupilumab 300 mg qw (n=525)	Placebo (n=189)	Dupilumab 300 mg q2w (n=127)	Dupilumab 300 mg qw (n=185)	Placebo (n=55)	Dupilumab 300 mg q2w (n=25)	Dupilumab 300 mg qw (n=48)
Age, Median (Q1, Q3), Years	38 (26.0, 49.0)	38 (28.0, 49.0)	39 (26.0, 52.0)	33 (24.0, 43.0)	33 (25.0, 42.0)	31 (25.0, 40.0)	41 (27.0, 49.0)	35 (28.0, 48.0)	31.5 (24.0, 44.0)
Male Sex, n (%)	282 (55.3)	230 (58.4)	313 (59.6)	128 (67.7)	83 (65.4)	127 (68.6)	23 (41.8)	9 (36.0)	20 (41.7)
Weight, Median (Q1, Q3), kg	76.4 (65.00, 88.50)	77 (65.70, 88.90)	77 (64.80, 89.00)	65.55 (55.40, 77.30)	64 (56.40, 73.70)	65.3 (59.30, 74.20)	82 (68.10, 102.00)	84.2 (72.50, 92.40)	81.9 (67.00, 105.00)
BMI, Median (Q1, Q3), kg/m^2	25.22 (22.50, 29.15)	25.74 (23.05, 29.22)	25.67 (22.24, 29.10)	23.52 (21.08, 26.96)	23.39 (20.98, 26.13)	23.42 (21.25, 25.87)	29.73 (24.84, 35.18)	29.13 (27.05, 32.74)	29.33 (21.31, 35.00)
Duration of AD, Median (Q1, Q3), Years	28 (18.0, 40.0)	27.5 (18.0, 42.0)	27 (18.0, 42.0)	24 (18.0, 35.0)	23.5 (18.0, 32.0)	23.5 (17.0, 32.0)	27 (18.0, 40.0)	21 (12.0, 28.0)	22 (14.0, 31.0)
EASI, Mean (SD)	32.9 (13.45)	32.3 (13.49)	32.1 (13.33)	35.8 (14.84)	34.0 (13.11)	34.3 (12.90)	30.8 (12.13)	30.9 (12.06)	28.3 (11.01)
Patients With IGA, n (%)									
3	281 (55.1)	211 (53.6)	285 (54.3)	84 (44.4)	56 (44.1)	82 (44.3)	30 (54.5)	12 (48.0)	34 (70.8)
4	229 (44.9)	183 (46.4)	239 (45.5)	104 (55.0)	71 (55.9)	103 (55.7)	25 (45.5)	13 (52.0)	14 (29.2)
Missing	0	0	0	1 (0.5)	0	0	0	0	0
Weekly Average of Peak Pruritus NRS, Mean (SD)	7.4 (1.80)	7.4 (1.71)	7.3 (1.93)	7.4 (1.59)	7.3 (1.76)	7.2 (1.80)	6.9 (2.55)	8.3 (1.57)	6.9 (2.37)
DLQI, Median (Q1, Q3)	14 (9.0, 21.0)	14 (9.0, 20.0)	14 (9.0, 20.0)	14 (9.0, 21.0)	14 (9.0, 21.0)	15 (9.0, 21.0)	11 (6.0, 18.0)	14 (10.0, 20.0)	13 (6.0, 18.0)
POEM, Median (Q1, Q3)	21 (16.0, 26.0)	21 (17.0, 25.0)	21 (17.0, 26.0)	21 (16.0, 25.0)	21 (16.0, 25.0)	21 (15.0, 26.0)	19 (13.0, 24.0)	22 (19.0, 25.0)	19 (13.5, 22.0)
EQ-5D-3L Pain/ Discomfort by Category, n (%)									
No Pain/ Discomfort	110 (21.6)	75 (19.0)	83 (15.8)	30 (15.9)	20 (15.7)	40 (21.6)	19 (34.5)	6 (24.0)	19 (39.6)
Moderate Pain/ Discomfort	301 (59.0)	252 (64.0)	345 (65.7)	105 (55.6)	83 (65.4)	101 (54.6)	27 (49.1)	12 (48.0)	22 (45.8)
Severe Pain/ Discomfort	99 (19.4)	67 (17.0)	96 (18.3)	53 (28.0)	24 (18.9)	44 (23.8)	9 (16.4)	7 (28.0)	7 (14.6)
Missing	0	0	1 (0.2)	1 (0.5)	0	0	0	0	0

AD, atopic dermatitis; BMI, body mass index; DLQI, Dermatology Life Quality Index; EASI, Eczema Area and Severity Index; EQ-5D-3L, European Quality of Life-5 Dimensions 3 level; IGA, Investigator's Global Assessment; NRS, Numerical Rating Scale; POEM, Patient-Oriented Eczema Measure; Q1, first quartile; Q3, third quartile; qw, weekly; q2w, every 2 weeks; SD, standard deviation.

FIGURE 1. Forest plot of change from baseline to week 16: (A) LS mean change in EASI; (B) LS mean percent change in EASI; (C) LS mean change in average of weekly Peak Pruritus NRS; (D) LS mean percent change in average of weekly Peak Pruritus NRS; (E) LS mean change in DLQI; (F) LS mean percent change in DLQI; (G) LS mean change in POEM; (H) LS mean percent change in POEM; (I) Proportion of patients achieving IGA 0 or 1 and ≥2 point improvement; (J) Proportion of patients reporting no pain or discomfort at week 16 based on EQ-5D-3L. DLQI, Dermatology Life Quality Index; EASI, Eczema Area and Severity Index; EQ-5D-3L, European Quality of Life-5 Dimensions 3 level; IGA, Investigator's Global Assessment; LS, least squares; NRS, Numerical Rating Scale; POEM, Patient-Oriented Eczema Measure; qw, weekly; q2w, every 2 weeks; SE, standard error. Solid squares represent difference vs placebo in dupilumab q2w and qw dose groups; error bars show 95% confidence interval; *P* values are for difference vs placebo in dupilumab q2w and qw dose groups.

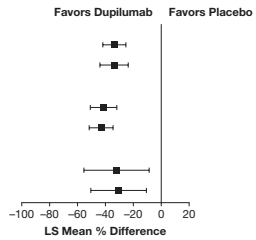
(A)

Subgroup	Placebo Change (SE)	Dupilumab Change (SE)	*P* Value
White			
Dupilumab q2w vs Placebo	−14.91 (0.703)	−25.36 (0.693)	<0.0001
Dupilumab qw vs Placebo	−14.91 (0.703)	−25.47 (0.651)	<0.0001
Asian			
Dupilumab q2w vs Placebo	−10.97 (1.664)	−24.23 (1.615)	<0.0001
Dupilumab qw vs Placebo	−10.97 (1.664)	−25.46 (1.455)	<0.0001
Black/African American			
Dupilumab q2w vs Placebo	−11.88 (1.947)	−20.02 (2.722)	0.0161
Dupilumab qw vs Placebo	−11.88 (1.947)	−19.98 (1.925)	0.0028



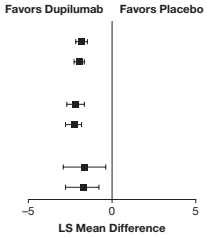
(B)

Subgroup	Placebo % Change (SE)	Dupilumab % Change (SE)	*P* Value
White			
Dupilumab q2w vs Placebo	−44.5 (3.77)	−77.7 (3.83)	<0.0001
Dupilumab qw vs Placebo	−44.5 (3.77)	−78.0 (4.22)	<0.0001
Asian			
Dupilumab q2w vs Placebo	−32.5 (5.15)	−73.8 (4.89)	<0.0001
Dupilumab qw vs Placebo	−32.5 (5.15)	−75.6 (4.47)	<0.0001
Black/African American			
Dupilumab q2w vs Placebo	−39.1 (7.62)	−70.8 (9.09)	0.0079
Dupilumab qw vs Placebo	−39.1 (7.62)	−69.5 (6.70)	0.0030



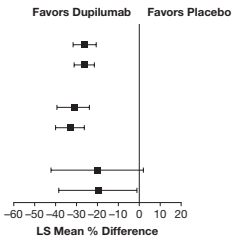
(C)

Subgroup	Placebo Change (SE)	Dupilumab Change (SE)	*P* Value
White			
Dupilumab q2w vs Placebo	−2.29 (0.168)	−4.12 (0.158)	<0.0001
Dupilumab qw vs Placebo	−2.29 (0.168)	−4.24 (0.139)	<0.0001
Asian			
Dupilumab q2w vs Placebo	−1.41 (0.298)	−3.59 (0.285)	<0.0001
Dupilumab qw vs Placebo	−1.41 (0.298)	−3.68 (0.261)	<0.0001
Black/African American			
Dupilumab q2w vs Placebo	−2.18 (0.364)	−3.82 (0.531)	0.0118
Dupilumab qw vs Placebo	−2.18 (0.364)	−3.95 (0.389)	0.0007



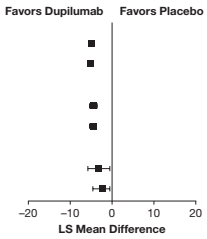
(D)

Subgroup	Placebo % Change (SE)	Dupilumab % Change (SE)	*P* Value
White			
Dupilumab q2w vs Placebo	−28.9 (2.48)	−54.9 (2.46)	<0.0001
Dupilumab qw vs Placebo	−28.9 (2.48)	−55.2 (2.15)	<0.0001
Asian			
Dupilumab q2w vs Placebo	−18.1 (4.17)	−49.4 (4.06)	<0.0001
Dupilumab qw vs Placebo	−18.1 (4.17)	−51.1 (3.65)	<0.0001
Black/African American			
Dupilumab q2w vs Placebo	−30.5 (6.79)	−50.3 (9.55)	0.0775
Dupilumab qw vs Placebo	−30.5 (6.79)	−50.1 (6.71)	0.0404



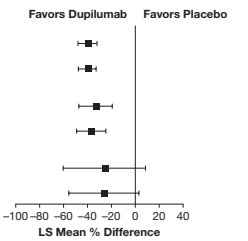
(E)

Subgroup	Placebo Change (SE)	Dupilumab Change (SE)	*P* Value
White			
Dupilumab q2w vs Placebo	−5.42 (0.382)	−10.41 (0.365)	<0.0001
Dupilumab qw vs Placebo	−5.42 (0.382)	−10.56 (0.335)	<0.0001
Asian			
Dupilumab q2w vs Placebo	−3.58 (0.734)	−8.08 (0.732)	<0.0001
Dupilumab qw vs Placebo	−3.58 (0.734)	−8.24 (0.661)	<0.0001
Black/African American			
Dupilumab q2w vs Placebo	−6.09 (0.742)	−9.34 (1.070)	0.0120
Dupilumab qw vs Placebo	−6.09 (0.742)	−8.63 (0.739)	0.0148



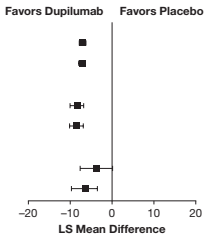
(F)

Subgroup	Placebo % Change (SE)	Dupilumab % Change (SE)	*P* Value
White			
Dupilumab q2w vs Placebo	−28.1 (3.62)	−68.0 (3.73)	<0.0001
Dupilumab qw vs Placebo	−28.1 (3.62)	−67.9 (3.21)	<0.0001
Asian			
Dupilumab q2w vs Placebo	−22.4 (7.44)	−55.6 (6.34)	<0.0001
Dupilumab qw vs Placebo	−22.4 (7.44)	−59.5 (5.89)	<0.0001
Black/African American			
Dupilumab q2w vs Placebo	−43.2 (10.94)	−68.8 (13.39)	0.1430
Dupilumab qw vs Placebo	−43.2 (10.94)	−69.3 (8.89)	0.0821



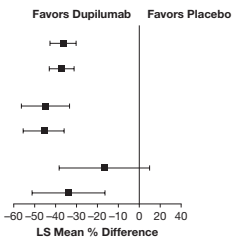
(G)

Subgroup	Placebo Change (SE)	Dupilumab Change (SE)	*P* Value
White			
Dupilumab q2w vs Placebo	−5.75 (0.466)	−12.70 (0.444)	<0.0001
Dupilumab qw vs Placebo	−5.75 (0.466)	−12.88 (0.427)	<0.0001
Asian			
Dupilumab q2w vs Placebo	−1.66 (0.927)	−9.97 (0.856)	<0.0001
Dupilumab qw vs Placebo	−1.66 (0.927)	−10.01 (0.764)	<0.0001
Black/African American			
Dupilumab q2w vs Placebo	−6.37 (1.162)	−10.12 (1.571)	0.0575
Dupilumab qw vs Placebo	−6.37 (1.162)	−12.85 (1.139)	<0.0001



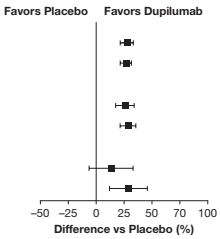
(H)

Subgroup	Placebo % Change (SE)	Dupilumab % Change (SE)	*P* Value
White			
Dupilumab q2w vs Placebo	−24.2 (2.81)	−60.5 (2.85)	<0.0001
Dupilumab qw vs Placebo	−24.2 (2.81)	−61.1 (2.68)	<0.0001
Asian			
Dupilumab q2w vs Placebo	−6.0 (5.58)	−50.7 (5.58)	<0.0001
Dupilumab qw vs Placebo	−6.0 (5.58)	−51.6 (4.65)	<0.0001
Black/African American			
Dupilumab q2w vs Placebo	−32.1 (6.42)	−48.6 (8.90)	0.1346
Dupilumab qw vs Placebo	−32.1 (6.42)	−65.8 (6.57)	0.0002



(I)

Subgroup	Placebo Rate n/N (%)	Dupilumab Rate n/N (%)	*P* Value
White			
Dupilumab q2w vs Placebo	67/510 (13.1)	160/394 (40.6)	<0.0001
Dupilumab qw vs Placebo	67/510 (13.1)	209/525 (39.8)	<0.0001
Asian			
Dupilumab q2w vs Placebo	5/189 (2.6)	36/127 (28.3)	<0.0001
Dupilumab qw vs Placebo	5/189 (2.6)	57/185 (30.8)	<0.0001
Black/African American			
Dupilumab q2w vs Placebo	8/55 (14.5)	7/25 (28.0)	0.0524
Dupilumab qw vs Placebo	8/55 (14.5)	21/48 (43.8)	0.0026



(J)

Subgroup	Placebo Rate n/N1 (%)	Dupilumab Rate n/N1 (%)	*P* Value
White			
Dupilumab q2w vs Placebo	70/400 (17.5)	149/319 (46.7)	<0.0001
Dupilumab qw vs Placebo	70/400 (17.5)	203/441 (46.0)	<0.0001
Asian			
Dupilumab q2w vs Placebo	30/158 (19.0)	50/107 (46.7)	<0.0001
Dupilumab qw vs Placebo	30/158 (19.0)	78/145 (53.8)	<0.0001
Black/African American			
Dupilumab q2w vs Placebo	11/36 (30.6)	9/19 (47.4)	0.1671
Dupilumab qw vs Placebo	11/36 (30.6)	14/29 (48.3)	0.1734

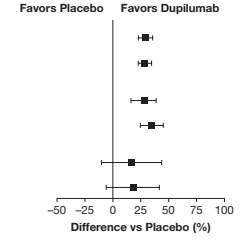
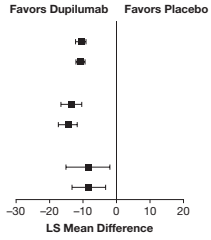


FIGURE 2. Forest plot of change from baseline to week 16 (weight-adjusted): (A) LS mean change in EASI; (B) LS mean percent change in EASI; (C) LS mean change in average of weekly Peak Pruritus NRS; (D) LS mean percent change in average of weekly Peak Pruritus NRS; (E) LS mean change in DLQI; (F) LS mean percent change in DLQI; (G) LS mean change in POEM; (H) LS mean percent change in POEM. DLQI, Dermatology Life Quality Index; EASI, Eczema Area and Severity Index; LS, least squares; NRS, Numerical Rating Scale; POEM, Patient-Oriented Eczema Measure; qw, weekly; q2w, every 2 weeks; SE, standard error. Solid squares represent difference vs placebo in dupilumab q2w and qw dose groups; error bars show 95% confidence interval; *P* values are for difference vs placebo in dupilumab q2w and qw dose groups.

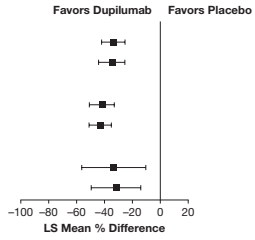
(A)

Subgroup	Placebo Change (SE)	Dupilumab Change (SE)	*P* Value
White			
Dupilumab q2w vs Placebo	−14.90 (0.738)	−25.39 (0.709)	<0.0001
Dupilumab qw vs Placebo	−14.90 (0.738)	−25.48 (0.648)	<0.0001
Asian			
Dupilumab q2w vs Placebo	−11.04 (1.757)	−24.47 (1.681)	<0.0001
Dupilumab qw vs Placebo	−11.04 (1.757)	−25.57 (1.487)	<0.0001
Black/African American			
Dupilumab q2w vs Placebo	−11.89 (1.904)	−20.31 (2.633)	0.0118
Dupilumab qw vs Placebo	−11.89 (1.904)	−20.15 (1.884)	0.0011



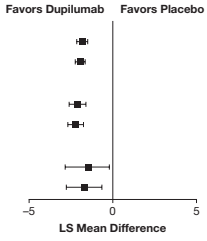
(B)

Subgroup	Placebo % Change (SE)	Dupilumab % Change (SE)	*P* Value
White			
Dupilumab q2w vs Placebo	−44.0 (3.77)	−77.7 (3.73)	<0.0001
Dupilumab qw vs Placebo	−44.0 (3.77)	−78.7 (4.09)	<0.0001
Asian			
Dupilumab q2w vs Placebo	−33.0 (5.28)	−74.6 (5.21)	<0.0001
Dupilumab qw vs Placebo	−33.0 (5.28)	−76.0 (4.64)	<0.0001
Black/African American			
Dupilumab q2w vs Placebo	−38.6 (7.17)	−71.9 (8.82)	0.0047
Dupilumab qw vs Placebo	−38.6 (7.17)	−70.3 (6.47)	0.0006



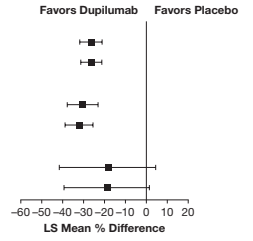
(C)

Subgroup	Placebo Change (SE)	Dupilumab Change (SE)	*P* Value
White			
Dupilumab q2w vs Placebo	−2.28 (0.150)	−4.13 (0.149)	<0.0001
Dupilumab qw vs Placebo	−2.28 (0.150)	−4.23 (0.137)	<0.0001
Asian			
Dupilumab q2w vs Placebo	−1.43 (0.280)	−3.57 (0.281)	<0.0001
Dupilumab qw vs Placebo	−1.43 (0.280)	−3.66 (0.247)	<0.0001
Black/African American			
Dupilumab q2w vs Placebo	−2.20 (0.375)	−3.74 (0.538)	0.0224
Dupilumab qw vs Placebo	−2.20 (0.375)	−3.95 (0.402)	0.0013



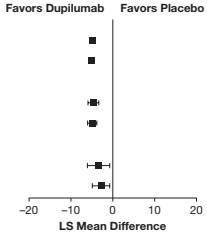
(D)

Subgroup	Placebo % Change (SE)	Dupilumab % Change (SE)	*P* Value
White			
Dupilumab q2w vs Placebo	−28.7 (2.35)	−55.1 (2.32)	<0.0001
Dupilumab qw vs Placebo	−28.7 (2.35)	−55.0 (2.16)	<0.0001
Asian			
Dupilumab q2w vs Placebo	−18.7 (3.98)	−49.3 (4.00)	<0.0001
Dupilumab qw vs Placebo	−18.7 (3.98)	−50.9 (3.50)	<0.0001
Black/African American			
Dupilumab q2w vs Placebo	−31.0 (7.55)	−49.5 (9.72)	0.1135
Dupilumab qw vs Placebo	−31.0 (7.55)	−50.0 (6.86)	0.0695



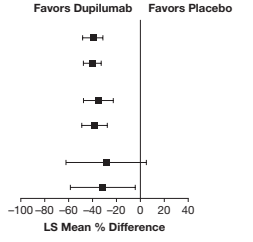
(E)

Subgroup	Placebo Change (SE)	Dupilumab Change (SE)	*P* Value
White			
Dupilumab q2w vs Placebo	−5.33 (0.362)	−10.36 (0.361)	<0.0001
Dupilumab qw vs Placebo	−5.33 (0.362)	−10.54 (0.348)	<0.0001
Asian			
Dupilumab q2w vs Placebo	−3.59 (0.765)	−8.22 (0.748)	<0.0001
Dupilumab qw vs Placebo	−3.59 (0.765)	−8.33 (0.662)	<0.0001
Black/African American			
Dupilumab q2w vs Placebo	−5.97 (0.793)	−9.36 (1.086)	0.0127
Dupilumab qw vs Placebo	−5.97 (0.793)	−8.70 (0.759)	0.0117



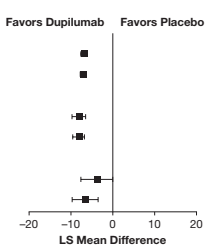
(F)

Subgroup	Placebo % Change (SE)	Dupilumab % Change (SE)	*P* Value
White			
Dupilumab q2w vs Placebo	−27.4 (3.68)	−67.1 (3.64)	<0.0001
Dupilumab qw vs Placebo	−27.4 (3.68)	−67.6 (3.42)	<0.0001
Asian			
Dupilumab q2w vs Placebo	−21.8 (6.63)	−56.8 (6.17)	<0.0001
Dupilumab qw vs Placebo	−21.8 (6.63)	−59.9 (5.39)	<0.0001
Black/African American			
Dupilumab q2w vs Placebo	−40.5 (10.69)	−68.9 (12.46)	0.0967
Dupilumab qw vs Placebo	−40.5 (10.69)	−71.5 (8.44)	0.0248



(G)

Subgroup	Placebo Change (SE)	Dupilumab Change (SE)	*P* Value
White			
Dupilumab q2w vs Placebo	−5.79 (0.484)	−12.70 (0.458)	<0.0001
Dupilumab qw vs Placebo	−5.79 (0.484)	−12.85 (0.415)	<0.0001
Asian			
Dupilumab q2w vs Placebo	−1.68 (0.872)	−9.79 (0.861)	<0.0001
Dupilumab qw vs Placebo	−1.68 (0.872)	−9.89 (0.773)	<0.0001
Black/African American			
Dupilumab q2w vs Placebo	−6.23 (1.149)	−10.09 (1.589)	0.0467
Dupilumab qw vs Placebo	−6.23 (1.149)	−12.77 (1.172)	<0.0001



(H)

Subgroup	Placebo % Change (SE)	Dupilumab % Change (SE)	*P* Value
White			
Dupilumab q2w vs Placebo	−24.2 (2.90)	−60.4 (2.91)	<0.0001
Dupilumab qw vs Placebo	−24.2 (2.90)	−60.9 (2.63)	<0.0001
Asian			
Dupilumab q2w vs Placebo	−6.1 (5.46)	−49.9 (6.04)	<0.0001
Dupilumab qw vs Placebo	−6.1 (5.46)	−50.9 (4.75)	<0.0001
Black/African American			
Dupilumab q2w vs Placebo	−31.7 (6.37)	−48.7 (8.99)	0.1190
Dupilumab qw vs Placebo	−31.7 (6.37)	−65.5 (6.87)	0.0003

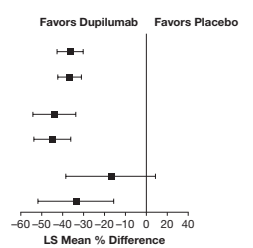


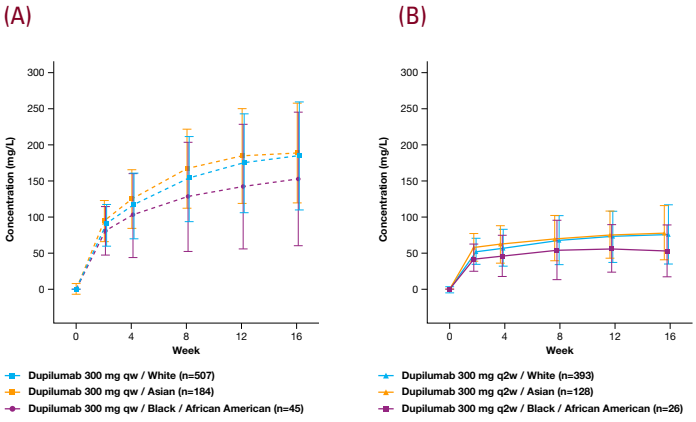
TABLE 2.

Adverse Events Reported Between Baseline and Week 16

	White			Asian			Black/African American		
Patients with	Placebo (n=509)	Dupilumab 300 mg q2w (n=402)	Dupilumab 300 mg qw (n=517)	Placebo (n=188)	Dupilumab 300 mg q2w (n=128)	Dupilumab 300 mg qw (n=184)	Placebo (n=53)	Dupilumab 300 mg q2w (n=27)	Dupilumab 300 mg qw (n=47)
≥1 TEAE,[a] n (%)	362 (71.1)	292 (72.6)	372 (72.0)	128 (68.1)	83 (64.8)	121 (65.8)	24 (45.3)	12 (44.4)	26 (55.3)
≥1 TE-SAE,[a] n (%)	22 (4.3)	11 (2.7)	13 (2.5)	7 (3.7)	1 (0.8)	1 (0.5)	0	1 (3.7)	0
≥1 TEAE Causing Discontinuation of Study Drug Permanently, n (%)	12 (2.4)	6 (1.5)	12 (2.3)	7 (3.7)	0	3 (1.6)	1 (1.9)	0	0
Death, n (%)[b]	0	0	1 (0.2)	0	0	0	0	0	0
Conjunctivitis[c]	29 (5.7)	45 (11.2)	80 (15.5)	6 (3.2)	13 (10.2)	15 (8.2)	1 (1.9)	1 (3.7)	3 (6.4)

[a]Adverse events reported at the level of MedDRA PT. [b]Detailed description of the event is given previously.[19] [c]The generic term of conjunctivitis was used to summarize a cluster of MedDRA PTs that include: conjunctivitis (of undetermined etiology), allergic conjunctivitis, viral conjunctivitis, bacterial conjunctivitis, and atopic keratoconjunctivitis. MedDRA, Medical Dictionary for Regulatory Activities; PT, Preferred Term; qw, weekly; q2w, every two weeks; TEAE, treatment-emergent adverse event; TE-SAE, treatment-emergent serious adverse event.

FIGURE 3. Mean (±SD) functional dupilumab concentration vs time by racial subgroup: (A) Dupilumab 300 mg qw; (B) Dupilumab 300 mg q2w; qw, weekly; q2w, every 2 weeks; SD, standard deviation.



In all treatment groups within each racial subset, 44-73% of patients reported ≥1 TEAE (Table 2). TE-SAEs and discontinuation of study drug generally occurred more often in patients receiving placebo (Table 2). One death was reported in a 31-year-old White male receiving dupilumab 300 mg qw in SOLO 2, but was not considered to be treatment related.[21] Conjunctivitis was the only common TEAE of clinical concern attributable to dupilumab (Table 2).

Pharmacokinetics

In all three trials and among all racial and treatment groups, dupilumab PK steady state was achieved by week 16 (Figure 3). The mean trough concentrations were comparable between White and Asian patients, with slightly lower levels noted in Black/African American patients.

DISCUSSION

Dupilumab with or without concomitant TCS significantly improved AD signs, symptoms, and QoL across all racial subgroups studied in this analysis, with efficacy generally consistent with the data reported for the overall populations in SOLO 1 and 2[21] and CHRONOS.[22]

Although the original trial publications also presented categorical efficacy endpoints,[21,22] this analysis focuses on continuous outcomes, which are the most sensitive and best suited for subset analyses, particularly with relatively small patient subsets. The reported endpoints in the present analysis provide a comprehensive racial subgroup analysis by assessing all major domains that define AD severity and response to treatment, including objective signs, subjective symptoms, and QoL.

Efficacy outcomes in White and Asian patients were similar to those in the overall populations of the trial.[21,22] While numeric trends always favored dupilumab vs placebo in the Black/African American subset, statistical significance in efficacy outcomes was not achieved consistently in either dupilumab group due primarily to the low numbers of Black/African American patients. Various other factors, including biologic, may have played a role in the observed inconsistencies between Black/African American patients and White and Asian patients.

Slightly lower mean trough concentrations were noted in Black/African American patients compared with White and Asian patients, which could be due, at least in part, to the higher average body weight of Black/African American patients in this analysis. Body weight was assessed as a potential confounding factor of this analysis, but weight-adjusted and weight-unadjusted

analyses were generally consistent. For example, significant clinical improvements were reported more consistently with the 300 mg qw regimen than q2w in both weight-adjusted and unadjusted analyses. Of note, a separate population PK analysis based on a larger dataset (Kovalenko P et al., manuscript in preparation) found no meaningful effect of racial subgroup on dupilumab PK after correction for body weight.

Differential mutations in skin barrier and innate/adaptive immunity genes may impact the nature of AD in racial subgroups. Filaggrin loss-of-function mutations, which lead to deficiency of the structural protein filaggrin and resulting skin barrier defects, have been identified as a major predisposing factor for the development of AD in Europeans and Asians.[6] In contrast, in individuals of African descent, the association between filaggrin mutations and AD is less clear; overall, evidence suggests these mutations occur less frequently in African Americans compared with European Americans. Loss-of-function mutations in the closely related filaggrin-2 protein were associated with African, but not European, American patients with AD. However, filaggrin as well as lipid alterations may also be influenced by cytokines, rather than by genetics.[27,28] Other potential genetic factors include variants of the tight junction gene claudin and the immune-related genes *TLSP* and *IRF2*, which have been noted in patients of African descent with AD.[6] Race-specific alterations in epidermal structure may contribute to molecular and histologic differences observed between White, Asian, and Black/African American individuals and may account for some differences in transepidermal water loss observed between European and African Americans.[6] Racial and ethnic variations in epidermal and dermal structure and function[29] may explain why the presentation of AD in individuals of African descent often differs from that in other racial subgroups, with notable extensor involvement and more frequent perifollicular accentuation and scattered distinct papules on the extensors and trunk, xerosis, Dennie–Morgan lines, hyperlinearity of the palms, periorbital dark circles, lichenification, prurigo nodularis, and post-inflammatory dyspigmentation.[6] Similar differences in AD characteristics have also been observed in patients participating in studies conducted in Africa compared with other regions.[7] Collectively, these differences may impact the course of AD in Black/African American patients. However, the limited current data on AD in Black/African American patients have restricted understanding of the disease and outcomes in this patient subset. For example, a recent systematic review and meta-analysis of studies evaluating the clinical features of AD in various populations found that only 4% reported the inclusion of Black/African American patients;[7] while another review of US studies of systemic AD therapy found that none presented a stratification of results by racial subgroup.[30]

The safety data among racial subgroups were consistent with those reported in the overall populations.[21,22]

Although data on racial differences are not available for other systemic therapies, the efficacy and safety observations here are generally consistent with studies of topical therapies such as pimecrolimus (Whites, Asians, Blacks, and Hispanics)[31] and tacrolimus (Asians vs Caucasians),[32] which showed no differences in treatment outcomes among racial subgroups.

The analysis had several limitations. First, only data from a short 16-week treatment duration were presented, as the small number of patients in some racial subgroups of the CHRONOS trial at week 52 prevented robust statistical analyses. Second, the analysis did not directly compare dupilumab dose regimens. Finally, only a small number of Black/African American patients were available for analysis; therefore, differences between dupilumab and placebo did not always reach the level of nominal statistical significance ($P<0.05$), particularly for the q2w dose regimen.

CONCLUSIONS

Irrespective of racial subgroup, dupilumab results in significant clinical improvement and a favorable benefit-risk profile in patients with moderate-to-severe AD inadequately controlled with topical medications. Trends in this analysis suggest that dupilumab 300 mg qw may provide incremental benefits over the q2w regimen in Black/African American patients; however, interpretation is limited by the small sample size of the Black/African American cohort and variations in mean body weight between racial subgroups. Overall, these results support the relevance of moderating type 2 inflammation by blocking IL-4 and IL-13 signaling for treatment of AD among all racial subgroups.

ACKNOWLEDGMENTS

The authors thank Thomas Hultsch for his contributions.

FUNDING STATEMENT

Research sponsored by Sanofi and Regeneron Pharmaceuticals, Inc. ClinicalTrials.gov Identifiers: NCT02277743; NCT02277769, NCT02260986. Medical writing/editorial assistance provided by Carolyn Ellenberger, PhD, of Excerpta Medica, funded by Sanofi Genzyme and Regeneron Pharmaceuticals, Inc.

DISCLOSURES

Andrew F. Alexis is an advisory board member/consultant for Almirall, Beiersdorf, BioPharmX, Celgene, Cipla, Dermavant, Dermira, Galderma, LEO Pharma, Menlo Therapeutics, Novartis, Pfizer, Regeneron Pharmaceuticals, Inc., Sanofi, Trevi Therapeutics, Unilever, Valeant; investigator for Almirall, Bristol-Myers Squibb, Celgene, Galderma, LEO Pharma, Menlo Therapeutics, Novartis, RxL. Marta Rendon is an investigator for Regeneron Pharmaceuticals, Inc. Jonathan I. Silverberg is an investigator for AbbVie, Celgene, Eli Lilly & Co., GlaxoSmithKline, Incyte, LEO Pharma, Realm, Regeneron Pharmaceuticals, Inc., Roche; consultant for AbbVie, Anacor Pharmaceuticals, Eli Lilly &

Co., Galderma, GSK, Incyte, Kiniksa, LEO Pharma, MedImmune (AstraZeneca), Menlo Therapeutics, Pfizer, Procter & Gamble, Realm, Regeneron Pharmaceuticals, Inc.; speaker for Regeneron Pharmaceuticals, Inc. David M. Pariser is a consultant, received honoraria from Bickel Biotechnology, Biofrontera, Celgene, Dermira, DUSA Pharmaceuticals, LEO Pharma, Novartis, Promius Pharma, Regeneron Pharmaceuticals, Inc., Sanofi, TheraVida, Inc., Valeant; principal investigator, received grants, research funding from Abbott Laboratories, Amgen, Asana BioSciences, Bickel Biotechnology, Celgene, Dermavant Sciences, Eli Lilly & Co., LEO Pharma, Merck & Co., Novartis, Novo Nordisk, Ortho Dermatologics, Peplin, Pfizer, Photocure ASA, Promius Pharma, Regeneron Pharmaceuticals, Inc., Stiefel/GSK, Valeant; advisory board member, received honoraria from Pfizer; principal investigator, received honoraria from LEO Pharma, Pfizer; investigator, received grants, research funding from Promius Pharma. Benjamin Lockshin received honoraria and/or research grants from AbbVie, Celgene, Dermira, Eli Lilly & Co., Franklin Bioscience, Galderma, Janssen, LEO Pharma, Novartis, Pfizer, Regeneron Pharmaceuticals, Inc., Sanofi, Sun Pharmaceutical Industries. Christopher E.M. Griffiths received honoraria and/or research grants from AbbVie, Almirall, Eli Lilly & Co., Janssen, LEO Pharma, Merck & Co., Novartis, Pfizer, Regeneron Pharmaceuticals, Inc., Roche, Sandoz, Sanofi, Sun Pharmaceutical Industries, Ltd., UCB Pharma. Jamie Weisman received research grants from AbbVie, Allergan, Amgen, Boehringer Ingelheim, Celgene, Dermira, Eli Lilly & Co., Galderma, GSK, Janssen, LEO Pharma, Merck & Co., Novartis, Pfizer, Regeneron Pharmaceuticals, Inc., UCB; advisory board member or speakers' bureau for AbbVie, Eli Lilly & Co., Janssen, Regeneron Pharmaceuticals, Inc., UCB. Andreas Wollenberg is an advisor, speaker, or investigator for ALK Abelló, Almirall, Anacor, Astellas, Beiersdorf AG, Bencard, Bioderma, Chugai, Eli Lilly & Co., Galderma, GSK, Hans Karrer, LEO Pharma, L'Oreal, Maruho, MedImmune, Novartis, Pfizer, Pierre Fabre, Sanofi, Regeneron Pharmaceuticals, Inc. Zhen Chen, John D. Davis, Abhijit Gadkari, Brad Shumel, Neil M.H. Graham, Marius Ardeleanu are employees and shareholders of Regeneron Pharmaceuticals, Inc. Meng Li, Laurent Eckert, Ana B. Rossi are employees of Sanofi, and may hold stock and/or stock options in the company. Ana B. Rossi ORCID: 0000-0001-5345-678X

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