Dupilumab shows long-term safety and efficacy in patients with moderate to severe atopic dermatitis enrolled in a phase 3 open-label extension study

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Supported by Sanofi and Regeneron Pharmaceuticals, Inc. Medical writing and editorial assistance were funded by Sanofi and Regeneron Pharmaceuticals.

Disclosure: Dr Deleuran provides research support, has consulting/advisory board agreements, and/or has received honoraria for lecturing from AbbVie, Eli Lilly, Galapagos, LEO Pharma, Meda, Pfizer, Pierre Fabre, Regeneron Pharmaceuticals, and Sanofi Genzyme. Dr Thaçi has received honoraria for participation on ad boards, as a speaker, and for consultancy from AbbVie, Almirall, Amgen, Boehringer Ingelheim, Celgene, Dignity, Eli Lilly, Galapagos, GlaxoSmithKline, Janssen, LEO Pharma, Morphosis, Merck Sharp & Dohme, Novartis, Pfizer, Sandoz-Hexal, Pfizer, Regeneron Pharmaceuticals, Sanofi, and UCB and has received research grants from Celgene and Novartis. Dr Beck serves as a consultant/advisory board member for AbbVie, Boehringer Ingelheim, Eli Lilly, Menlo Therapeutics, Novan, Realm Therapeutics, Regeneron Pharmaceuticals, and Sanofi Genzyme and is a clinical study investigator for AbbVie, Regeneron Pharmaceuticals, and Realm Therapeutics. Dr de Bruin-Weller is a principal investigator and advisory board member for AbbVie; is an advisory board member for Eli Lilly; is a principal investigator for LEO Pharma; is a principal investigator and advisory board member for Pfizer; is a principal investigator, provides research support, has received honoraria for lecturing, and is an advisory board member and consultant for Regeneron Pharmaceuticals and Sanofi Genzyme; and is an advisory board member for UCB. Dr Blauvelt is a scientific advisor and clinical study investigator for AbbVie, Aclaris, Akros, Allergan, Almirall, Amgen, Arena, Boehringer Ingelheim, Bristol-Myers Squibb, Celgene, Dermavant, Dermira, Eli Lilly, Galderma, Genentech/Roche, GlaxoSmithKline, Janssen, LEO Pharma, Meiji, Merck Sharp & Dohme, Novartis, Pfizer, Purdue Pharma, Regeneron Pharmaceuticals, Revance, Sandoz, Sanofi Genzyme, Sienna Biopharmaceuticals, Sun Pharma, UCB, Valeant, and Vidac and is a paid speaker for Janssen, Regeneron Pharmaceuticals, and Sanofi Genzyme. Dr Forman has received consulting fees from AbbVie, Cellceutix, Galderma, and Psoria-Light; lecture fees from AbbVie and Novartis; and grant support from AstraZeneca, Eli Lilly, Incyte, Janssen, Novartis, Promius, Regeneron Pharmaceuticals, Pfizer, and Valeant. Dr Bissonnette is a consultant for and/or has received grants/research support from AbbVie, Aquinox Pharma, Arcutis Antiobix, Asana, Astellas, Boehringer Ingelheim, Brickell Biotech, Dermavant, Dermira, Dignity Sciences, Eli Lilly, Galderma, Glenmark, GlaxoSmithKline-Stiefel, Hoffman-La Roche, Kiniksa, Incyte, LEO Pharma, Neokera, Pfizer, Ralexar, Regeneron Pharmaceuticals, Sanofi Genzyme, and Vitae and is a shareholder of Innovaderm Research. Dr Reich is an advisor and/or paid speaker and/or investigator for AbbVie, Affibody, Almirall, Amgen, Biogen, Boehringer Ingelheim, Celgene, Centocor, Covagen, Forward Pharma, Fresenius Medical Care, GlaxoSmithKline, Janssen-Cilag, Kyowa Kirin, LEO Pharma, Eli Lilly, Medac, Merck Sharp & Dohme, Novartis, Miltenyi Biotec, Ocean Pharma, Pfizer, Regeneron Pharmaceuticals,

Background: Significant unmet need exists for long-term treatment of moderate to severe atopic dermatitis (AD).

Objective: To assess the long-term safety and efficacy of dupilumab in patients with AD.

Methods: This ongoing, multicenter, open-label extension study (NCT01949311) evaluated long-term dupilumab treatment in adults who had previously participated in phase 1 through 3 clinical trials of dupilumab for AD. This analysis examined patients given 300 mg dupilumab weekly for up to 76 weeks at data cutoff (April 2016). Safety was the primary outcome; efficacy was also evaluated.

Results: Of 1491 enrolled patients (1042.9 patient-years), 92.9% were receiving treatment at cutoff. The safety profile was consistent with previously reported trials (420.4 adverse events/100 patient-years and 8.5 serious adverse events/100 patient-years), with no new safety signals; common adverse events included nasopharyngitis, conjunctivitis, and injection-site reactions. Sustained improvement was seen up to 76 weeks in all efficacy outcomes, including measures of skin inflammation, pruritus, and quality of life.

Limitations: Lack of control arm, limited number of patients with 76 weeks or longer of treatment (median follow-up, 24 weeks), and patients not receiving the approved dose regimen of 300 mg every 2 weeks.

Conclusion: The safety and efficacy profile from this study supports the role of dupilumab as continuous long-term treatment for patients with moderate to severe AD. (J Am Acad Dermatol 2020;82:377-88.)

Key words: atopic dermatitis; biologic therapy; dupilumab; IL-4; IL-13; long-term; open label; monoclonal antibody; efficacy; quality of life; safety.

Samsung Bioepis, Sanofi, Takeda, UCB, Valeant, and XenoPort. Dr Soong has received research funding from 3M, Aimmune, AstraZeneca, Circassia, Genentech, Galderma, Glenmark, LEO Pharma, Menlo Therapeutics, Novartis, Optinose, Pfizer, Regeneron Pharmaceuticals, Ralexar, Roche, Sanofi, Stallergenes, and Teva; has received speaking fees from AstraZeneca, Circassia, Optinose, Roche-Genentech, GlaxoSmithKline, Sanofi, Regeneron Pharmaceuticals, and Teva; and has received consulting fees from AbbVie, ALK, AstraZeneca, Regeneron Pharmaceuticals, Stallergenes, and Teva. Dr Hussain is an investigator for Regeneron Pharmaceuticals and Shire. Dr Foley has received honoraria and/or research grants and/or has served as an investigator and/or advisory board member for AbbVie, Amgen, BMS, Boehringer Ingelheim, Celgene, Celtaxsys, Cutanea, Dermira, Eli Lilly, Galderma, Genentech, GlaxoSmithKline, Janssen, LEO Pharma, Merck, Novartis, Pfizer, Regeneron Pharmaceuticals, Roche, Sanofi, Sun Pharma, UCB Pharma, and Valeant. Dr Hide has received research funding, consulting fees, and/or speaking fees from GlaxoSmithKline, Kaken Pharmaceutical, Kyowa Hakko Kirin, Mitsubishi-Tanabe, Merck Sharp & Dohme, Taiho Pharmaceutical, Teikoku Seiyaku, and Sanofi. Dr Bouaziz has received speaking fees from Novartis; consulting fees from Eli Lilly and Neovacs; a research grant from Therakos; and a travel grant from AbbVie, Janssen, and Sanofi. Dr Gelfand has received consulting fees/honoraria from AbbVie, Coherus, Janssen Biologics (formerly Centocor), Merck, Novartis, Valeant, and Pfizer; receives research grants (to the Trustees of the University of Pennsylvania) from AbbVie, Eli Lilly, Janssen, Novartis, Regeneron Pharmaceuticals, Sanofi, and Pfizer; has done continuing medical education work related to Lilly and AbbVie; and is a co-patent holder of resiquimod for treatment of cutaneous T-cell lymphoma. Dr Sher serves on the advisory board of and as speaker for Aimmune, Optinose, Regeneron Pharmaceuticals, and Sanofi and does research for Aimmune, DBV, Galderma, GlaxoSmithKline, Optinose, Pfizer, Regeneron Pharmaceuticals, Sanofi, Teva, and Watson. Dr Schuttelaar has received honoraria for participation on advisory boards for Sanofi Genzyme and has participated in clinical trials with AbbVie, Novartis, and Sanofi Genzyme. Dr Akinlade, Dr Ardeleanu, Dr Chen, Dr Davis, Dr Gadkari, Dr Graham, Dr Rajadhyaksha, and Dr Wang are employees and shareholders of Regeneron Pharmaceuticals, Inc. Drs Eckert, Pirozzi, and Staudinger are employees of and may hold stock and/or stock options in Regeneron Pharmaceuticals.

Some of the data reported in this article were presented at the American Society for Clinical Pharmacology and Therapeutics 2017 Annual Meeting, Washington, DC; the American Academy of Allergy, Asthma & Immunology 2017 Annual Meeting, Atlanta, GA; the Society for Investigative Dermatology 2017 Annual Meeting, Atlanta, GA; Maui Derm for Dermatologists 2017, Maui, HI; the Society of Dermatology Physician Assistants 2017 Annual Summer Dermatology Conference, San Diego, CA; the DERM2017 Conference, Las Vegas, NV; the Maui Derm NP+PA Summer 2017 meeting, Colorado Springs, CO; and the Japanese Society for Cutaneous Immunology and Allergy 2018 Annual Meeting, Nara, Japan.

Accepted for publication July 24, 2019.

Reprints not available from the authors.

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Published online July 30, 2019.

0190-9622

https://doi.org/10.1016/j.jaad.2019.07.074

Atopic dermatitis (AD), a chronic inflammatory skin disease affecting approximately 2% to 10% of adults,[1-3] is characterized by pruritus, eczematous lesions, and upregulation of type 2 immune responses[1,4,5] and is commonly associated with other atopic/allergic diseases.[1] AD is also associated with impaired quality of life (QoL),[6] sleep deprivation,[7] impaired school/work productivity,[8] negative psychologic effects,[9] and increased health care resource use.[10] As a chronic disease, moderate to severe AD typically requires long-term treatment[1]; however, continuous, long-term use of many treatments, particularly higher-potency topical corticosteroids (TCS), oral corticosteroids, ultraviolet therapy, and systemic immunosuppressants, is not recommended because of safety risks or lack of efficacy data.[5,11-17]

CAPSULE SUMMARY

- Some topicals and nearly all conventional systemic treatments for atopic dermatitis are not recommended for continuous long-term treatment due to safety concerns; after 76 weeks, continuous dupilumab treatment showed a favorable and stable safety and efficacy profile.
- Dupilumab addresses an unmet need for patients with atopic dermatitis who require long-term treatment.

Dupilumab, a fully human VelocImmune (Regeneron, Tarrytown, NY)–derived[18,19] monoclonal antibody, blocks the shared receptor component for interleukin (IL) 4 and IL-13, key drivers of type 2 inflammation in diseases such as AD, asthma, allergic rhinitis, and food allergies, which are often associated as comorbidities,[20] thus inhibiting their signaling. Dupilumab is approved in the United States for patients 12 years and older with moderate to severe AD inadequately controlled by topical prescription treatments or when those therapies are not advisable,[21] in Japan for adult patients with AD not adequately controlled with existing therapies, and in Europe for adult patients with moderate to severe AD who are candidates for systemic therapy.[22] Dupilumab is also approved in certain patients with asthma and chronic rhinosinusitis with nasal polyps (CRSwNP) in a number of countries. In phase 1 through 3 clinical trials, dupilumab monotherapy or with concomitant TCS significantly reduced disease severity and improved QoL to 16 weeks and, in 1 trial, to 52 weeks.[23-30] The overall safety profile of dupilumab across these trials was generally similar to placebo, except for higher injection-site reaction (ISR) and conjunctivitis rates and lower skin infection and AD exacerbation rates in patients treated with dupilumab versus placebo. Dupilumab has shown efficacy in other type 2 diseases, including uncontrolled persistent asthma,[31-33] CRSwNP,[34] and eosinophilic esophagitis.[35]

This open-label extension (OLE) study evaluated the long-term safety and efficacy of dupilumab in adults previously enrolled in randomized, double-blinded, placebo-controlled dupilumab studies of moderate to severe AD. Here, we report initial safety and efficacy data collected through April 2016, the cutoff date for regulatory submissions for drug approval in AD, from a patient cohort completing up to 76 weeks of treatment.

METHODS

This ongoing, multicenter OLE (NCT01949311) evaluated long-term use of dupilumab in adults (aged ≥18 years) who previously participated in phase 1 through 3 clinical trials of dupilumab use for AD.[23-30,36] Patients were enrolled at 319 sites in 23 North American, European, and Asia-Pacific countries. The main exclusion criteria were dupilumab-related adverse events (AEs) and serious AEs (SAEs) leading to discontinuation in previous (parent) studies. The primary objective was to assess the long-term safety of dupilumab in patients with AD. Additionally, efficacy parameters and incidence and impact of immunogenicity were assessed.

Patients received subcutaneous dupilumab 300 mg weekly, including an initial loading dose of 600 mg (300 mg if the last dupilumab dose in the previous study was ≤4 weeks before OLE baseline) administered on day 1. Patients enrolled in the early stage (starting October 2013) received 200 mg weekly (400 mg loading dose). The protocol was subsequently amended on December 12, 2013, to a regimen of 300 mg weekly based on the dose regimens selected for phase 3 studies.[24] Patients could be treated for up to 3 years. Concomitant topical treatments were allowed without restriction. Only systemic treatments for AD were considered rescue treatments and required discontinuation of study treatment for the duration of rescue and an additional 5 half-lives of the rescue agent.

This study was conducted in accordance with the Declaration of Helsinki and International Conference on Harmonisation Guidelines for Good Clinical Practice. Each patient provided informed consent before study procedures were performed. For each site, the protocol, informed-consent form, and patient information were approved by an institutional review board and independent ethics committee.

Abbreviations used:

AD:	atopic dermatitis
ADA:	antidrug antibody
AE:	adverse event
BP:	baseline of parent study
DLQI:	Dermatology Life Quality Index
EASI:	Eczema Area and Severity Index
EASI-50:	>50% reduction in Eczema Area and Severity Index score
EASI-75:	>75% reduction in Eczema Area and Severity Index score
EASI-90:	>90% reduction in Eczema Area and Severity Index score
IGA:	Investigator's Global Assessment
IL:	interleukin
ISR:	injection-site reaction
MedDRA:	Medical Dictionary for Regulatory Activities
NRS:	Numerical Rating Scale
OLE:	open-label extension
POEM:	Patient-Oriented Eczema Measure
PY:	patient-years
QoL:	quality of life
SAE:	serious adverse event
TCS:	topical corticosteroids

The primary endpoint was incidence and rate (events per 100 patient-years [PY]) of AEs. Key secondary endpoints included proportion of patients achieving Investigator's Global Assessment (IGA) of 0 or 1 and improvement in the Eczema Area and Severity Index (EASI) of at least 75% (EASI-75) from baseline of the parent study (BP). Other secondary endpoints included absolute and percent change from BP in the Peak Pruritus Numerical Rating Scale (NRS), Dermatology Life Quality Index (DLQI),[37] and Patient-Oriented Eczema Measure (POEM).[38] Endpoints were analyzed descriptively using all observed data. Antidrug antibodies (ADAs) were assessed in patient sera.

All patients who received dupilumab were included in the safety analysis set. Efficacy analyses were performed in the safety analysis set and in the week 52 and week 76 cohorts (including all patients who reached the respective timepoint or would have reached that timepoint had they not discontinued earlier).

Subgroup analyses were performed for patients who had not received dupilumab in the parent study (dupilumab-naive), representing a continuous treatment paradigm since the OLE start, and patients with 13 weeks or longer between the last dupilumab injection in the parent study and the first injection in the OLE (retreatment), a discontinuous treatment paradigm. (These subsets do not account for 100% of patients; other subsets were not included.)

RESULTS

Patients

A total of 1587 patients were screened from 12 parent studies (NCT01259323: n = 8[23,29]; NCT01859988: n = 310[24]; NCT01385657: n = 13[23,29]; NCT01548404: n = 62[23]; NCT01639040: n = 17[23]; NCT02260986: n = 126[26]; NCT01979016: n = 48[30]; NCT02210780: n = 176[28]; NCT02277743: n = 359[25]; NCT02395133: n = 40 [M. Worm, unpublished data, April 2019]; NCT02277769: n = 425[25]; and NCT02647086: n = 3[36]); 1491 patients received dupilumab in this study (1042.9 PY). Most patients (1179/1491) received 300 mg weekly; 312 patients received dupilumab 200 mg weekly (mean, 18.5 doses; range, 1-52 doses) before protocol amendment to 300 mg weekly (9 patients received 200 mg weekly and discontinued before switching). Patients received a mean of 37.5 doses of dupilumab (range, 1-125 doses); 17.8% of patients had 76 or more cumulative doses. Few patients (7.1%) discontinued the study prematurely, and the majority (98.6%) were at least 80% adherent with study treatment.

Baseline characteristics are shown in Table I. Most patients (1246/1491, 84%) had associated atopic/allergic disease (Table I). As of the cutoff date for this analysis, 1385/1491 (92.9%) patients were actively receiving study treatment, with 428 (28.7%) patients in the week 52 cohort and 284 (19.0%) patients in the week 76 cohort.

Safety

Overall, 4384 AEs were reported, with exposure-adjusted rates of 420.4 events/100 PY and 8.5 SAEs/100 PY; 70.7% of patients had at least 1 AE; 5.0% had at least 1 SAE, and no individual SAE was reported in at least 1% of patients or more (Table II). Most AEs were mild to moderate; fewer than 5% of patients reported an SAE. Seven patients (0.5%) experienced 8 SAEs that were considered by the investigator to be related to the study drug: Hodgkin disease, prostate cancer, enterocolitis, serum sickness, eczema herpeticum, herpes ophthalmic, epilepsy, and eczema. No deaths were reported. The most common AEs included nasopharyngitis, upper respiratory tract infection, AD, and headache as Medical Dictionary for Regulatory Activities (MedDRA) Preferred Terms; 150 (10.1%) patients reported ISRs (36.53 events/100 PY) as a MedDRA High-Level Term (Table II), the majority of mild/moderate severity.

Additionally, 10.7% (n = 160) reported conjunctivitis with various descriptors (20.8 events/100 PY). Most conjunctivitis cases were mild to moderate; 5 of 1491 patients (0.3%) reported severe conjunctivitis

Table I. Baseline demographics and disease characteristics

Characteristics		Values (N = 1491)
Demographic characteristics at baseline		**Current study (OLE)**
Age in years, median (IQR)		39.0 (29.0-49.0)
Duration of AD in years, median (IQR)		29.0 (19.0-40.0)
Race, n (%)		
White		1051 (70.5)
Black		106 (7.1)
Asian		300 (20.1)
Other		23 (1.5)
Not reported		11 (0.7)
Sex, n (%)		
Male		894 (60.0)
Region, n (%)		
Americas		753 (50.5)
Asia Pacific		190 (12.7)
Eastern Europe		232 (15.6)
Western Europe		316 (21.2)
Body weight in kg, median (IQR)		76.0 (64.2-89.5)
BMI in kg/m^2, median (IQR)		25.7 (22.7-29.5)
Treatment in parent study		
Previously treated with dupilumab,* n		850
Dupilumab 300 mg qw, n		401
Dupilumab 300 mg q2w, n		274
Other dupilumab doses,† n		175
Dupilumab-naive subgroup, n		606
Received placebo qw in parent study, n		577
Screening failure in parent study, n		29
Treatment blinded in parent study,‡ n		35
Number of patients with current history of atopic/allergic conditions reported in parent study, n (%)		1246 (84)
Allergic rhinitis		754 (51)
Asthma		637 (43)
Food allergy		568 (38)
Allergic conjunctivitis		380 (25)
Hives		229 (15)
Chronic rhinosinusitis		93 (6)
Nasal polyps		39 (3)
Atopic keratoconjunctivitis		35 (2)
Eosinophilic esophagitis		6 (<1)
Other allergies		965 (65)
Disease characteristics at baseline	**Parent study**	**Current study (OLE)**
EASI, median (IQR)	30.5 (21.6-42.7)	17.1 (9.2-29.9)
Patients with IGA score,§‖ n (%)		
0	0	12 (0.8)
1	0	56 (3.8)
2	0	217 (14.6)
3	687 (46.1)	847 (56.8)
4	770 (51.6)	359 (24.1)
Peak Pruritus NRS score, median (IQR)	7.6 (6.0-8.7)	6.0 (4.0-7.0)
POEM total score, median (IQR)	22.0 (18.0-26.0)	17.0 (11.0-23.0)
DLQI total score, median (IQR)	15.0 (10.0-21.0)	9.0 (4.0-14.0)
EQ-5D pain/discomfort (*no problems*), n (%)	N/A	548 (36.8)

Continued

Table I. Cont'd

Disease characteristics at baseline	Parent study	Current study (OLE)
Patients with PGADS score,[¶] n (%)		
Excellent	13 (0.9)	41 (2.7)
Very good	54 (3.6)	170 (11.4)
Good	215 (14.4)	378 (25.4)

BMI, Body mass index; *DLQI*, Dermatology Life Quality Index; *EASI*, Eczema Area and Severity Index; *EQ-5D*, European Quality of Life-5 Dimensions; *IGA*, Investigator's Global Assessment; *IQR*, interquartile range; *N/A*, not applicable; *NRS*, Numerical Rating Scale; *OLE*, open-label extension; *PGADS*, Patient Global Assessment of Disease Status; *POEM*, Patient-Oriented Eczema Measure; *q2w*, every 2 weeks; *q4w*, every 4 weeks; *qw*, weekly.

*Includes patients who received any dupilumab treatment, including retreatment subgroup (n = 381) with period of longer than 13 weeks between parent dupilumab treatment and first injection, interrupted treatment subgroup (n = 409) with period of at least 6 and up to 13 weeks between parent dupilumab treatment and first injection, and continuous treatment subgroup (n = 60) with period of less than 6 weeks between parent dupilumab treatment and first injection.

[†]Includes the following dupilumab doses in the parent study: 75 mg qw, 100 mg q4w, 150 mg qw, 200 mg q2w, 200 mg qw, 300 mg q4w.

[‡]Patient has not yet been unblinded from parent study.

[§]0, clear; 1, almost clear; 2, mild disease; 3, moderate disease; 4, severe disease.

[‖]31 patients had missing IGA at baseline of parent study.

[¶]117 patients had missing PGADS at baseline of parent study.

Table II. Safety assessment

Adverse events		Total population (N = 1491)
AEs, n (events/100 PY)		4384 (420.4)
Patients with ≥1 AE, n (%)		1054 (70.7)
Patients with ≥1 SAE, n (%)[*]		74 (5.0)
Patients with AEs leading to permanent discontinuation, n (%)		27 (1.8)
Patients with ≥1 SAE, n (%)		71 (4.8)
Deaths, n		0
Most common AEs by PT (≥2% of patients by MedDRA PT)	**n (%)[*]**	**Events/100 PY[†]**
Nasopharyngitis	306 (20.5)	46.7
Upper respiratory tract infection	142 (9.5)	17.2
Dermatitis atopic	123 (8.2)	15.3
Headache	106 (7.1)	19.6
Oral herpes	64 (4.3)	11.4
Blood creatine phosphokinase increased	53 (3.6)	5.9
Bronchitis	47 (3.2)	5.3
Diarrhea	41 (2.7)	4.5
Back pain	41 (2.7)	4.4
Viral upper respiratory tract infection	38 (2.5)	4.3
Cough	34 (2.3)	3.8
Influenza	31 (2.1)	3.6
Conjunctivitis[‡]	160 (10.7)	20.8
Injection-site reactions[§]	150 (10.1)	36.5
Most common SAEs by PT (>1 patient by MedDRA PT)		
Ligament rupture	2 (0.1)	0.192
Squamous cell carcinoma of skin	3 (0.2)	0.288
Syncope	2 (0.1)	0.192
Inguinal hernia	2 (0.1)	0.192
Osteoarthritis	3 (0.2)	0.288
Depression	2 (0.1)	0.192
Chronic obstructive pulmonary disease	2 (0.1)	0.192
Dermatitis atopic	3 (0.2)	0.384
Noncardiac chest pain	2 (0.1)	0.288

AE, Adverse event; *MedDRA*, Medical Dictionary for Regulatory Activities; *PT*, MedDRA Preferred Term; *PY*, patient-years; *SAE*, serious adverse event.

*Patient who reported ≥ 2 AEs with the same PT was counted only once for that term.

[†]Total PY were calculated as the sum of study observational periods over all patients.

[‡]Conjunctivitis cluster includes conjunctivitis, allergic conjunctivitis, bacterial conjunctivitis, viral conjunctivitis, and atopic conjunctivitis.

[§]MedDRA High-Level Term.

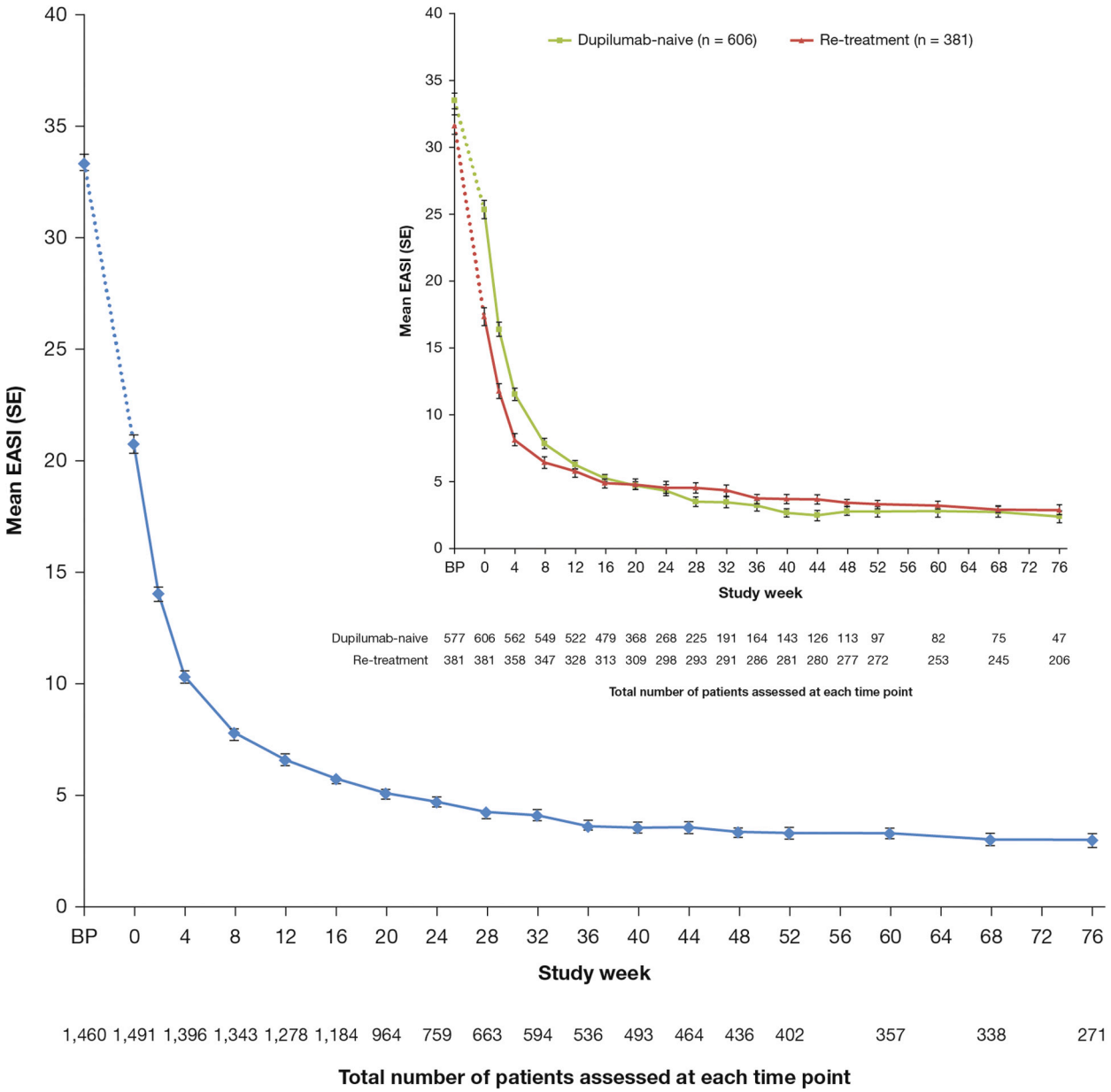

Fig 1. Mean EASI at each visit for the total population (main figure) and the dupilumab-retreatment and dupilumab-naive subgroups (inset). *BP*, Baseline of parent study; *EASI*, Eczema Area and Severity Index; *SE*, standard error.

(5/217 [2.3%] of all conjunctivitis cases). Although most conjunctivitis events resolved, 45 of 217 (20.7%) events were ongoing at cutoff. Three patients (0.2% of total) discontinued dupilumab because of conjunctivitis-related AEs (3/217, 1.4%).

New AE occurrences were assessed over 12-week treatment intervals (0-12 weeks, 12-24 weeks, etc) throughout the study period. There were numerically fewer new ISRs and conjunctivitis events over time: 126 of 1491 (8.5%) and 86 of 1491 (5.8%) patients had ISRs and conjunctivitis during weeks 0-12, and these numbers dropped to 3 of 445 (0.7%) and 8 of 445 (1.8%) during weeks 48-60.

Review of safety data for dupilumab-naive and retreated patients showed no evidence of increased risk of AEs associated with a single dupilumab retreatment (data not shown).

Efficacy in the total population (safety analysis set)

AD skin lesion severity and AD-related symptoms generally improved throughout the OLE. Mean EASI

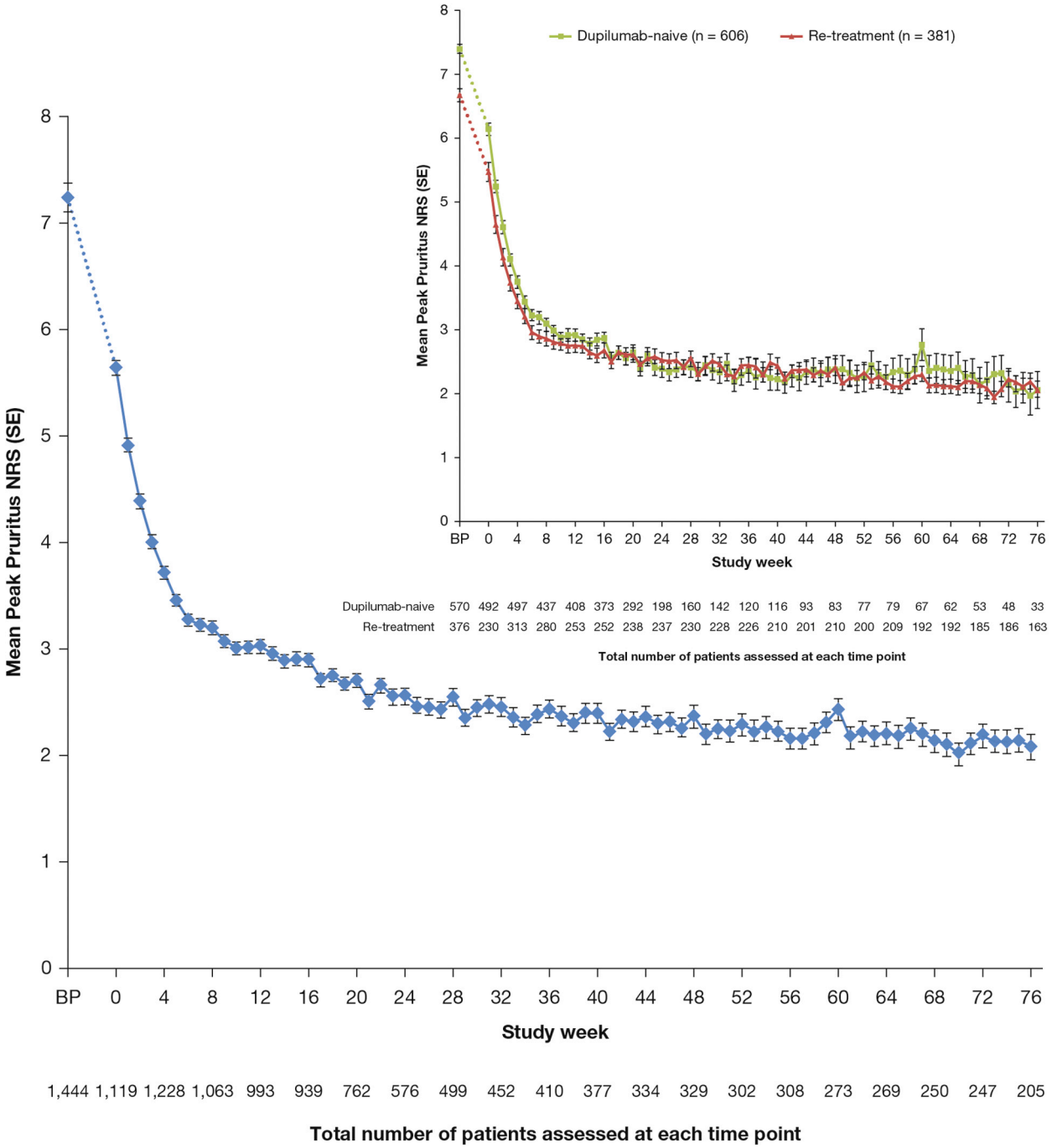

Fig 2. Mean Peak Pruritus NRS score at each visit for the total population (main figure) and dupilumab-retreatment and dupilumab-naive subgroups (inset). *BP*, Baseline of parent study; *NRS*, Numerical Rating Scale; *SE*, standard error.

(standard error) at week 76 was 3.11 (0.308) (Fig 1). Overall, there was a continuous progressive improvement in EASI from week 2 to week 24, followed by subtle incremental improvement thereafter.

Similar improvements were observed for Peak Pruritus NRS (Fig 2), DLQI, and POEM (not shown) up to 76 weeks.

Improvements consistent with the overall population were observed in dupilumab-naive and retreatment subgroups for EASI (Fig 1) and Peak Pruritus NRS (Fig 2), DLQI, and POEM (not shown). Time to first EASI improvement of 50% (EASI-50), 75% (EASI-75), and 90% (EASI-90) from BP and time to first IGA of 0 or 1 were also assessed (median days [95% confidence

Table III. Efficacy outcomes at weeks 52 and 76.

Outcomes	Week 52 (n = 428)*	Week 76 (n = 284)†
Proportion of patients who achieved IGA score of 0 or 1, n/subgroup total (%)	221/398 (55.5)	144/249 (57.8)
EASI, mean change from BP ± SD	−28.0 ± 13.38	−28.8 ± 13.49
EASI, mean % change from BP ± SD	−89.0 ± 16.08	−90.0 ± 13.48
Proportion of patients who achieved EASI-50 relative to BP, n/subgroup total (%)	385/398 (96.7)	244/249 (98.0)
Proportion of patients who achieved EASI-75 relative to BP, n/subgroup total (%)	346/398 (86.9)	220/249 (88.4)
Proportion of patients who achieved EASI-90 relative to BP, n/subgroup total (%)	265/398 (66.6)	171/249 (68.7)
Peak Pruritus NRS, mean change from BP ± SD	−4.20 ± 2.45	−4.29 ± 2.53
Peak Pruritus NRS, mean % change from BP ± SD	−62.0 ± 30.07	−63.7 ± 32.41
Proportion of patients who achieved Peak Pruritus NRS score improvement ≥ 4 points from BP, n/subgroup total (%)‡	169/262 (64.5)	106/165 (64.2)
Proportion of patients who achieved Peak Pruritus NRS score improvement ≥ 3 points from BP, n/subgroup total (%)§	206/277 (74.4)	134/176 (76.1)
Proportion of patients who achieved an IGA score ≤ 2, n/subgroup total (%)	356/398 (89.4)	224/249 (90.0)
Proportion of patients with ≥ 2-point improvement in IGA among patients with baseline IGA ≥ 2, n/subgroup total (%)	214/384 (55.7)	141/243 (58.0)
Proportion of patients with EQ-5D pain dimension (*no problems*), n/subgroup total (%)	311/398 (78.1)‖	200/248 (80.6)
DLQI, mean percent change from BP ± SD	−76.6 ± 29.13¶	−77.4 ± 27.60
Post hoc efficacy endpoints		
Proportion of patients who achieved EASI total score ≤ 10, n/subgroup total (%)	364/398 (91.5)	231/249 (92.8)
Proportion of patients who achieved Peak Pruritus NRS ≤ 3, n/subgroup total (%)	230/297 (77.4)	152/188 (80.9)
Proportion of patients who achieved 0-5 on DLQI total score, n/subgroup total (%)	334/398 (83.9)¶	202/242 (83.5)
Proportion of patients who achieved EASI total score ≤ 12, n/subgroup total (%)	375/398 (94.2)	237/249 (95.2)
Proportion of patients who achieved Peak Pruritus NRS ≤ 5, n/subgroup total (%)	278/297 (93.6)	177/188 (94.1)
Proportion of patients who achieved Peak Pruritus NRS ≤ 4, n/subgroup total (%)	263/297 (88.6)	172/188 (91.5)
Proportion of patients who achieved 0 or 1 on DLQI total score, n/subgroup total (%)	190/398 (47.7)¶	129/242 (53.3)
Proportion of patients who achieved 0 or 1 (*not relevant* or *a little*) on all 10 DLQI subdomain scores, n/subgroup total (%)	322/398 (80.9)¶	197/242 (81.4)
Sensitivity analyses		
EASI, LS mean change from BP ± SE (multiple imputation)	−27.85 ± 0.653	−28.81 ± 0.807
EASI, LS mean % change from BP ± SE (multiple imputation)	−88.6 ± 0.87	−89.4 ± 0.91
Peak Pruritus NRS, LS mean change from BP ± SE (multiple imputation)	−4.26 ± 0.124	−4.33 ± 0.158
Peak Pruritus NRS, LS mean % change from BP ± SE (multiple imputation)	−62.5 ± 1.66	−63.5 ± 2.23
Proportion of patients who achieved EASI-75 relative to BP, n (%) (nonresponder imputation)	334 (78)	214 (75)
Proportion of patients who achieved EASI-50 relative to BP, n (%) (nonresponder imputation)	373 (87)	238 (84)
Proportion of patients who achieved Peak Pruritus NRS score improvement ≥ 3 points from baseline of current study who had Peak Pruritus NRS score at baseline ≥ 3, n/subgroup total (%) (nonresponder imputation)	199/397 (50)	130/264 (49)

BP, Baseline of parent study; *DLQI*, Dermatology Life Quality Index; *EASI*, Eczema Area and Severity Index; *EASI-50*, >50% reduction in EASI score; *EASI-75*, >75% reduction in Eczema Area and Severity Index score; *EASI-90*, >90% reduction in Eczema Area and Severity Index score; *EQ-5D*, European Quality of Life-5 Dimensions; *IGA*, Investigator's Global Assessment; *LS*, least squares; *NRS*, Numerical Rating Scale; *SD*, standard deviation; *SE*, standard error.

*Efficacy at week 52 observed for week 52 cohort, which included all patients enrolled at least 53 weeks before data cutoff (accounting for ± 1-week visit window).

†Efficacy at week 76 observed for week 76 cohort, which included all patients enrolled at least 77 weeks before data cutoff (accounting for ± 1-week visit window).

‡Among patients with parent baseline Peak Pruritus NRS score ≥ 4.

§Among patients with parent baseline Peak Pruritus NRS score ≥ 3.

‖EQ-5D pain dimension score assessed at week 48.

¶DLQI assessed at week 48.

interval]): 29 [29-30], 85 [59-85], 169 [142-197], and 169 [142-197], respectively.

Efficacy in week 52 and week 76 cohorts

Improvements in percent change and absolute change from BP at week 52 and week 76 in the respective week 52 and week 76 cohorts (Table III) reflected improvements seen in the total population. At weeks 56 and 76, more than 60% of patients achieved EASI-90. At week 76, most patients achieved IGA of 0 or 1, at least 4-point improvement in Peak Pruritus NRS, and *no problems* in the pain dimension of the European QoL-5 Dimensions (Table III).

Sensitivity analyses were consistent with efficacy of all observed patients for the week 52 and week 76 cohorts (Table III), suggesting no bias on treatment outcomes due to patient withdrawal.

Additional AD treatments during the study

Overall, 50.3% of patients (750/1491) did not use additional medications for AD. Of those who did, 44.4% received TCS (662/1491) and 13.3% received topical calcineurin inhibitors (198/1491). A total of 55 (3.7%) patients required systemic therapy, considered rescue treatment in this study. Most rescued patients (52/55) received corticosteroids; 5 patients received nonsteroidal immunosuppressants (4/5 cyclosporine A). A post hoc analysis found that rescued patients had numerically higher incidences of infections (69.1% vs 48.0%) and conjunctivitis (18.2% vs 10.4%) AEs compared with the rest of the patients. However, the accuracy and relevance of these findings are limited by a small sample size for rescued patients (3.7% of the overall analysis population).

Immunogenicity

Overall, 830 patients had at least 1 ADA result after the first dose and were included in the analysis. Overall, 23 of 830 (2.8%) patients had treatment-emergent ADAs in the OLE, of whom 16 of 308 (5.2%) patients were in the retreatment subgroup, 4 of 178 (2.2%) were in the interrupted treatment group, and 3 of 305 (1.0%) patients were in the dupilumab-naive subgroup; 8 of 830 patients (1.0%) had ADA responses lasting longer than 12 weeks. In the continuous treatment population (n = 38), no patients had additional incidence of treatment-emergent ADAs. One patient with treatment-emergent ADAs permanently discontinued treatment due to AE (deemed unrelated to ADA), and none had SAEs. Functional dupilumab[36] concentrations were similar in treatment-emergent ADA-positive and ADA-negative patients. Few patients (n = 6) with moderate ADA titer levels had lower dupilumab concentrations, which attained levels similar to those in ADA-negative patients in approximately 26 weeks. No patient had high ADA titer levels during the OLE. One retreatment patient with high titer levels at OLE baseline decreased to low titer levels around week 76. In the overall population, there was no meaningful difference in efficacy between ADA-positive and ADA-negative patients.

DISCUSSION

This first-step analysis of a long-term, open-label study of dupilumab 300 mg weekly in patients who previously participated in randomized, double-blinded, placebo-controlled clinical trials of dupilumab is, to our knowledge, the longest published study with a systemic drug in adults with AD to date and the first report of dupilumab safety and efficacy beyond 52 weeks of treatment.

The safety profile of dupilumab in this study is consistent with previous studies.[23-30] The exposure-adjusted rate of AEs and SAEs was also consistent with previously reported rates of AEs and SAEs for dupilumab weekly plus TCS (476.23 AEs/100 PY and 4.98 SAEs/100 PY) and slightly lower than placebo plus TCS (532.38 AEs/100 PY and 7.85 SAEs/100 PY) at 52 weeks.[26]

Although previous long-term studies in cyclosporine and azathioprine have been limited by high discontinuation rates,[39-42] very few patients (1.8%) discontinued dupilumab in this study before data cutoff. No new safety signal associated with dupilumab use in moderate to severe AD was identified. Nasopharyngitis, upper respiratory tract infection, AD, headache, ISRs, and conjunctivitis were the only AEs that occurred in 5% of patients or more. Few patients were ADA-positive during the 76-week treatment period.

Conjunctivitis and ISR rates reported here were comparable with those of previous phase 3 trials of dupilumab in AD and occurred more frequently with dupilumab than placebo.[23-27] Very few patients had severe conjunctivitis (0.3%, 5/1491). Although there was no placebo arm, the low rate of withdrawal due to conjunctivitis (0.2%, 3/1491) and ISRs (<0.1%, 1/1491) is notable. Furthermore, the diminishing occurrence of new conjunctivitis or ISR events over time suggests that their incidence may decrease with continued dupilumab treatment. The impact of long-term dupilumab treatment on safety will be evaluated further once longer-term (up to 3 years) data from this study are available.

Dupilumab showed consistent and sustained efficacy over a 76-week treatment period, reducing AD signs and symptoms (including improving skin lesions and pruritus) and improving QoL. Mean

efficacy scores reflect early onset of action, with evident improvements at first post-baseline visit continuing steadily over 76 weeks of treatment. Efficacy was observed regardless of prior treatment received or duration of treatment gap from prior study. Improvements were seen from both current and parent study baseline in the overall population, with or without imputation for missing data, and among 52- or 76-week cohorts.

More than half of patients did not require additional treatment for AD during the treatment period. This, combined with the relatively small numbers of patients requiring systemic rescue therapy, supports the idea that dupilumab monotherapy or concomitant with topical AD medications provides long-term disease control in patients with moderate to severe AD.

Study limitations

The proportion of patients able to reach 76 weeks of treatment by the time of data cutoff for this first-step analysis was relatively low compared with the total number of patients enrolled; nevertheless, it constitutes a reasonable sample for these types of analyses. The number of patients who dropped out was very low, and 92.9% of patients were still receiving dupilumab at data cutoff. The lack of a control arm limits interpretation of study outcomes, including the ability to detect rare but serious AEs. For retreatment patients, the results of this analysis may not fully characterize the consequences of multiple retreatments (ie, on-and-off, on-demand, or other discontinuous treatment paradigms). Subsequent analyses will provide further details on the benefits and risks of long-term dupilumab treatment. Finally, the regimen of dupilumab 300 mg weekly in this study is higher than the regimen of 300 mg every 2 weeks approved in most countries. However, safety and efficacy were similar between the 2 dose regimens in multiple phase 3 trials, suggesting they are clinically equivalent. The 300-mg week dose was chosen for this study to increase the likelihood of identifying any safety signals and to generate safety data that could adequately support dosage regimens of both 300 mg weekly and every 2 weeks.

CONCLUSIONS

Treatment for up to 76 weeks with dupilumab 300 mg was well tolerated, with a safety profile consistent with those of previous clinical trials of shorter durations (16-52 weeks).[23-30] The most common AEs (conjunctivitis and ISRs) were seen more often at the beginning of dupilumab treatment and diminished over time. Dupilumab-naive patients experienced improvements in AD signs and symptoms comparable to those shown by dupilumab-treated patients in parent studies. Patients with dupilumab treatment before the OLE study showed additional clinical benefits that were sustained through the end of the observation period. Irrespective of dupilumab treatment history, by week 52, most patients attained AD severity scores consistent with no or low disease activity. No meaningful impact on efficacy or safety in the few ADA-positive patients was observed.

The favorable benefit-risk profile in this study supports the long-term role of dupilumab treatment for patients with moderate to severe AD and shows that blocking IL-4 and IL-13 signaling can achieve sustained control of AD signs and symptoms with an acceptable safety profile in patients with significant disease burden and for whom conventional topical treatments are inadequate.

We would like to thank the patients and their families; the investigators; Kim Robinson of the Alabama Allergy & Asthma Center, Birmingham; Miriam Kore, Tatiana Constant, Catherine Stanford, Mbole Ekaney, and Linda Williams of Regeneron Pharmaceuticals, Inc; Dianne Barry and El-Bdaoui Haddad of Sanofi Genzyme for their contributions; Qin Zhang, formerly of Regeneron Pharmaceuticals, Inc, for statistical analyses; and Ravi Subramanian, PhD, Ferdinando Giacco, PhD, and Mihai Surducan, PhD, of Excerpta Medica for medical writing, editorial, and submission support.

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Title:
Dupilumab shows long-term safety and efficacy in patients with moderate to severe atopic dermatitis enrolled in a phase 3 open-label extension study

Date:
2020-02

Citation:
Deleuran, M., Thaci, D., Beck, L. A., de Bruin-Weller, M., Blauvelt, A., Forman, S., Bissonnette, R., Reich, K., Soong, W., Hussain, I., Foley, P., Hide, M., Bouaziz, J. - D., Gelfand, J. M., Sher, L., Schuttelaar, M. L. A., Wang, C., Chen, Z., Akinlade, B. ,... Ardeleanu, M. (2020). Dupilumab shows long-term safety and efficacy in patients with moderate to severe atopic dermatitis enrolled in a phase 3 open-label extension study. JOURNAL OF THE AMERICAN ACADEMY OF DERMATOLOGY, 82 (2), pp.377-388. https://doi.org/10.1016/j.jaad.2019.07.074.