

# Journal Pre-proof

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

Mette Deleuran, MD, DMSc, Diamant Thaçi, MD, Lisa A. Beck, MD, Marjolein de Bruin-Weller, MD, PhD, Andrew Blauvelt, MD, MBA, Seth Forman, MD, Robert Bissonnette, MD, Kristian Reich, MD, Weily Soong, MD, Iftikhar Hussain, MD, Peter Foley, MD, Michihiro Hide, MD, PhD, Jean-David Bouaziz, MD, PhD, Joel M. Gelfand, MD, MSCE, Lawrence Sher, MD, Marie L.A. Schuttelaar, MD, PhD, Chen Wang, PhD, Zhen Chen, PhD, MS, MA, Bolanle Akinlade, MD, Abhijit Gadkari, PhD, Laurent Eckert, PhD, John D. Davis, PhD, Manoj Rajadhyaksha, PhD, Heribert Staudinger, MD, PhD, Neil M.H. Graham, MD, Gianluca Pirozzi, MD, PhD, Marius Ardeleanu, MD



PII: S0190-9622(19)32465-X

DOI: <https://doi.org/10.1016/j.jaad.2019.07.074>

Reference: YMJD 13683

To appear in: *Journal of the American Academy of Dermatology*

Received Date: 29 June 2018

Revised Date: 19 July 2019

Accepted Date: 24 July 2019

Please cite this article as: Deleuran M, Thaçi D, Beck LA, de Bruin-Weller M, Blauvelt A, Forman S, Bissonnette R, Reich K, Soong W, Hussain I, Foley P, Hide M, Bouaziz J-D, Gelfand JM, Sher L, Schuttelaar MLA, Wang C, Chen Z, Akinlade B, Gadkari A, Eckert L, Davis JD, Rajadhyaksha M, Staudinger H, Graham NMH, Pirozzi G, Ardeleanu M, Dupilumab shows long-term safety and efficacy in moderate-to-severe atopic dermatitis patients enrolled in a phase 3 open-label extension study, *Journal of the American Academy of Dermatology* (2019), doi: <https://doi.org/10.1016/j.jaad.2019.07.074>.

This is a PDF file of an article that has undergone enhancements after acceptance, such as the addition of a cover page and metadata, and formatting for readability, but it is not yet the definitive version of record. This version will undergo additional copyediting, typesetting and review before it is published in its final form, but we are providing this version to give early visibility of the article. Please note that, during the production process, errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.



**Article type:** Original article

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

Mette Deleuran, MD, DMSc<sup>1</sup>, Diamant Thaçi, MD<sup>2</sup>, Lisa A. Beck, MD<sup>3</sup>, Marjolein de Bruin-Weller, MD, PhD<sup>4</sup>, Andrew Blauvelt, MD, MBA<sup>5</sup>, Seth Forman, MD<sup>6</sup>, Robert Bissonnette, MD<sup>7</sup>, Kristian Reich, MD<sup>8</sup>, Weily Soong, MD<sup>9</sup>, Iftikhar Hussain, MD<sup>10</sup>, Peter Foley, MD<sup>11</sup>, Michihiro Hide, MD, PhD<sup>12</sup>, Jean-David Bouaziz, MD, PhD<sup>13</sup>, Joel M. Gelfand, MD, MSCE<sup>14</sup>, Lawrence Sher, MD<sup>15</sup>, Marie L.A. Schuttelaar, MD, PhD<sup>16</sup>, Chen Wang, PhD<sup>17</sup>, Zhen Chen, PhD, MS, MA<sup>18</sup>, Bolanle Akinlade, MD<sup>18</sup>, Abhijit Gadkari, PhD<sup>18</sup>, Laurent Eckert, PhD<sup>19</sup>, John D. Davis, PhD<sup>18</sup>, Manoj Rajadhyaksha, PhD<sup>18</sup>, Heribert Staudinger, MD, PhD<sup>20</sup>, Neil M.H. Graham, MD<sup>18</sup>, Gianluca Pirozzi, MD, PhD<sup>20</sup>, and Marius Ardeleanu, MD<sup>18</sup>

<sup>1</sup>Aarhus University Hospital, Aarhus, Denmark; <sup>2</sup>University of Lübeck, Lübeck, Germany; <sup>3</sup>University of Rochester Medical Center, Rochester, NY, USA; <sup>4</sup>University Medical Centre Utrecht, Utrecht, Netherlands; <sup>5</sup>Oregon Medical Research, Portland, OR, USA; <sup>6</sup>Forman Dermatology and Skin Cancer Institute, Tampa, FL, USA; <sup>7</sup>Innovaderm Research, Montreal, Canada; <sup>8</sup>Center for Translational Research in Inflammatory Skin Diseases, Institute for Health Services Research in Dermatology and Nursing, University Medical Center Hamburg-Eppendorf, Skinflammation® Center, Hamburg, Germany, and Dermatologikum Berlin, Berlin, Germany; <sup>9</sup>Alabama Allergy & Asthma Center, Birmingham, AL, USA; <sup>10</sup>Vital Prospects Clinical Research Institute, PC, Tulsa, OK, USA; <sup>11</sup>University of Melbourne, Skin & Cancer Foundation Inc., Carlton, Australia; <sup>12</sup>Hiroshima University, Hiroshima, Japan; <sup>13</sup>Saint-Louis Hospital, Paris, France; <sup>14</sup>University of Pennsylvania, Philadelphia, PA, USA; <sup>15</sup>Peninsula Research Associates, Rolling Hills Estates, CA, USA; <sup>16</sup>University of Groningen, University Medical Centre Groningen, Groningen, Netherlands; <sup>17</sup>Regeneron Pharmaceuticals, Inc., Basking Ridge, NJ, USA; <sup>18</sup>Regeneron Pharmaceuticals, Tarrytown, NY, USA; <sup>19</sup>Sanofi, Chilly-Mazarin, France; <sup>20</sup>Sanofi, Bridgewater, NJ, USA

**Corresponding author:** Mette Deleuran, MD, DMSc, Department of Dermatology, Aarhus University Hospital, Palle Juul Jensens Boulevard 67, 8200 Aarhus N, Denmark

Phone: +45 7846 1851; Fax: +45 7846 1850; E-mail: [mettdele@rm.dk](mailto:mettdele@rm.dk)

**Funding sources:** Research sponsored by Sanofi and Regeneron Pharmaceuticals, Inc. ClinicalTrials.gov Identifier: NCT01949311. Medical writing and editorial assistance were funded by Sanofi and Regeneron Pharmaceuticals, Inc.

**Conflicts of interest:**

**M Deleuran:** AbbVie, Eli Lilly, Galapagos, LEO Pharma, Meda, Pfizer, Pierre Fabre, Regeneron Pharmaceuticals, Inc., Sanofi Genzyme – research support, consulting/advisory board agreements, and/or honoraria for lecturing.

**D Thaçi:** 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, Inc., Sanofi, UCB – honoraria for participation on ad boards, as a speaker and for consultancy; Celgene and Novartis – research grants.

**LA Beck:** AbbVie, Boehringer Ingelheim, Eli Lilly, Menlo Therapeutics, Novan, Realm Therapeutics, Regeneron Pharmaceuticals, Inc., Sanofi Genzyme – consultant/advisory board member; AbbVie, Regeneron Pharmaceuticals, Inc., Realm Therapeutics – clinical study investigator.

**M de Bruin-Weller:** AbbVie – principal investigator, advisory board member; Eli Lilly – advisory board member; LEO Pharma – principal investigator; Pfizer – principal investigator, advisory board member; Regeneron Pharmaceuticals, Inc., Sanofi Genzyme – principal investigator, research support, honoraria for lecturing, advisory board member, and consultant; UCB – advisory board member.

45 **A Blauvelt:** AbbVie, Aclaris, Akros, Allergan, Almirall, Amgen, Arena, Boehringer Ingelheim, Bristol-Myers  
46 Squibb, Celgene, Dermavant, Dermira, Eli Lilly, Galderma, Genentech/Roche, GlaxoSmithKline, Janssen,  
47 LEO Pharma, Meiji, Merck Sharp & Dohme, Novartis, Pfizer, Purdue Pharma, Regeneron  
48 Pharmaceuticals, Inc., Revance, Sandoz, Sanofi Genzyme, Sienna Pharmaceuticals, Sun Pharma, UCB,  
49 Valeant, Vidac – scientific adviser and clinical study investigator; Janssen, Regeneron Pharmaceuticals,  
50 Inc., Sanofi Genzyme – paid speaker.

51 **S Forman:** AbbVie, Cellceutix, Galderma, Psoria-Ligh – consulting fees; AbbVie, Novartis – lecture fees;  
52 AstraZeneca, Eli Lilly, Incyte, Janssen, Novartis, Promius, Regeneron Pharmaceuticals, Inc., Pfizer,  
53 Valeant – grant support.

54 **R Bissonnette:** AbbVie, Aquinox Pharma, Arcutis Antibio, Asana, Astellas, Boehringer Ingelheim, Brickell  
55 Biotech, Dermavant, Dermira, Dignity Sciences, Eli-Lilly, Galderma, Glenmark, GlaxoSmithKline -Stiefel,  
56 Hoffman-LaRoche Ltd, Kiniksa, Incyte, LEO Pharma, Neokera, Pfizer, Ralexar, Regeneron  
57 Pharmaceuticals, Inc., Sanofi Genzyme, Vitae – consultant and/or grants/research support; Innovaderm  
58 Research – shareholder.

59 **K Reich:** AbbVie, Affibody, Almirall, Amgen, Biogen, Boehringer Ingelheim, Celgene, Centocor, Covagen,  
60 Forward Pharma, Fresenius Medical Care, GlaxoSmithKline, Janssen-Cilag, Kyowa Kirin, LEO Pharma, Eli  
61 Lilly, Medac, Merck Sharp & Dohme, Novartis, Miltenyi Biotec, Ocean Pharma, Pfizer, Regeneron  
62 Pharmaceuticals, Inc., Samsung Bioepis, Sanofi, Takeda, UCB, Valeant, Xenoport – advisor and/or paid  
63 speaker for and/or investigator.

64 **W Soong:** 3M, Aimmune, AstraZeneca, Circassia, Genentech, Galderma, Glenmark, LEO Pharma, Menlo  
65 Therapeutics, Novartis, Optinose, Pfizer, Regeneron Pharmaceuticals, Inc., Relaxar, Roche, Sanofi,  
66 Stallergens, Teva – research funding; AstraZeneca, Circassia, Optinose, Roche-Genentech,

67 GlaxoSmithKline, Sanofi, Regeneron Pharmaceuticals, Inc., Teva – speaking fees; AbbVie, ALK,  
68 AstraZeneca, Regeneron Pharmaceuticals, Inc., Stallergens, Teva – consulting fees.

69 **I Hussain:** Regeneron Pharmaceuticals, Inc., Shire – investigator.

70 **P Foley:** AbbVie, Amgen, BMS, Boehringer Ingelheim, Celgene, Celtaxsys, Cutanea, Dermira, Eli Lilly,  
71 Galderma, Genentech, GlaxoSmithKline, Janssen, LEO Pharma, Merck, Novartis, Pfizer, Regeneron  
72 Pharmaceuticals, Inc., Roche, Sanofi, Sun Pharma, UCB Pharma, Valeant – has received honoraria and/or  
73 research grants and/or served as an investigator and/or advisory board member.

74 **M Hide:** GlaxoSmithKline, KAKEN Pharmaceutical, Kyowahakko-Kirin, Mitsubishi-Tanabe, Merck Sharp  
75 and Dohme, TAIHO Pharmaceutical, TEIKOKU SEIYAKU, Sanofi – research funding, consulting fees,  
76 and/or speaking fees.

77 **J-D Bouaziz:** Novartis – speaking fees; Eli Lilly, Neovacs – consulting fees; Therakos – research grant;  
78 AbbVie, Janssen, Sanofi – travel grant.

79 **J Gelfand:** AbbVie, Coherus, Janssen Biologics (formerly Centocor), Merck, Novartis Corp, Valeant, Pfizer  
80 Inc. – consultant/honoraria; AbbVie, Eli Lilly, Janssen, Novartis, Regeneron Pharmaceuticals, Inc., Sanofi,  
81 and Pfizer Inc. – receives research grants (to the Trustees of the University of Pennsylvania); related to  
82 Lilly, AbbVie – continuing medical education work. Dr. Gelfand is a co-patent holder of resiquimod for  
83 treatment of cutaneous T cell lymphoma.

84 **L Sher:** Aimmune, Optinose, Regeneron Pharmaceuticals, Inc., Sanofi – advisory board, speaker;  
85 Aimmune, DBV, Galderma, GlaxoSmithKline, Optinose, Pfizer, Regeneron Pharmaceuticals, Inc., Sanofi,  
86 Teva, Watson – research.

87 **MLA Schuttelaar:** Sanofi Genzyme – received honoraria for participation on advisory boards; AbbVie,  
88 Novartis, Sanofi Genzyme – participated in clinical trials.

**B Akinlade, M Ardeleanu, Z Chen, JD Davis, A Gadkari, NMH Graham, M Rajadhyaksha, C Wang:**

Regeneron Pharmaceuticals, Inc. – employees and shareholders.

**L Eckert, G Pirozzi, H Staudinger:** employee, may hold stock and/or stock options in the company.

**IRB status statement:** Prior to study initiation, approval of the protocol, informed consent form, and patient information were obtained from an institutional review board.

**Statement of prior presentation:** Some of the data reported in this manuscript have been presented at: the American Society for Clinical Pharmacology and Therapeutics 2017 Annual Meeting, the American Academy of Allergy, Asthma & Immunology 2017 Annual Meeting, the Society for Investigative Dermatology 2017 Annual Meeting, Maui Derm for Dermatologists 2017, the Society of Dermatology Physician Assistants 2017 Annual Summer Dermatology Conference, the DERM2017 Conference, Maui Derm NP+PA Summer 2017 meeting, and the Japanese Society for Cutaneous Immunology and Allergy 2018 Annual Meeting.

**ClinicalTrials.gov Identifier:** NCT01949311

**Manuscript word count:** 2,527

**Abstract word count:** 200

**Capsule summary word count:** 49

**References:** 42

**Figures:** 2

**Tables:** 3

**Attachments:** CONSORT checklist, protocol, statistical analysis plan

109 **Keywords:** atopic dermatitis, biologic therapy, dupilumab, IL-4, IL-13, long-term, open label, monoclonal  
110 antibody, efficacy, quality of life, safety



111 **Abstract (200/200 words)**

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

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

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

119 **Results:** Of 1,491 enrolled patients (1,042.9 patient-years), 92.9% remained on treatment at cutoff. The  
120 safety profile was consistent with previously reported trials (420.4 adverse events [AEs]/100 patient-  
121 years [100PY] and 8.5 serious AEs/100PY), with no new safety signals; common AEs included  
122 nasopharyngitis, conjunctivitis, and injection-site reactions. Sustained improvement was seen up to 76  
123 weeks in all efficacy outcomes, including measures of skin inflammation, pruritus, and quality of life.

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

126 **Conclusion:** The safety and efficacy profile from this study supports the role of dupilumab as continuous  
127 long-term treatment for patients with moderate-to-severe AD.

128 **Capsule summary (49/50 words)**

- 129       • Some topicals and nearly all conventional systemic treatments for atopic dermatitis are not  
130       recommended for continuous long-term treatment due to safety concerns; after 76 weeks,  
131       continuous dupilumab treatment demonstrated a favorable and stable safety and efficacy  
132       profile.
- 133       • Dupilumab addresses an unmet need for atopic dermatitis patients requiring long-term  
134       treatment.

## INTRODUCTION

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

Dupilumab, a fully human *VelocImmune*<sup>®</sup>-derived<sup>18,19</sup> monoclonal antibody, blocks the shared receptor component for interleukin (IL)-4 and IL-13, key drivers of type 2 diseases such as AD, asthma, allergic rhinitis, and food allergies, which are often associated as comorbidities,<sup>20</sup> thus inhibiting their signaling. Dupilumab is approved for patients aged ≥12 years in the USA with moderate-to-severe AD inadequately controlled by topical prescription treatments or when those therapies are not advisable,<sup>21</sup> adult AD patients in Japan not adequately controlled with existing therapies, and moderate-to-severe adult AD patients in Europe who are candidates for systemic therapy.<sup>22</sup> In phase 1-3 clinical trials, dupilumab monotherapy or with concomitant TCS significantly reduced disease severity and improved QoL to 16 weeks and, in one trial, to 52 weeks.<sup>23-30</sup> 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 dupilumab- vs placebo-treated patients. Dupilumab has demonstrated efficacy in other type 2 diseases, including uncontrolled persistent asthma,<sup>31-33</sup> chronic sinusitis with nasal polyposis,<sup>34</sup> and eosinophilic esophagitis.<sup>35</sup>

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

**METHODS**

This ongoing, multicenter OLE (NCT01949311) evaluated long-term use of dupilumab in adults (aged  $\geq 18$  years) who previously participated in phase 1–3 clinical trials of dupilumab in AD.<sup>23–30,36</sup> Patients were enrolled at 319 sites (23 North American, European, and Asia-Pacific countries). 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 long-term safety of dupilumab in AD patients. Additionally, efficacy parameters and incidence and impact of immunogenicity were assessed. Patients received subcutaneous 300mg dupilumab weekly (qw), including an initial loading dose of 600mg (300mg if the last dupilumab dose in previous study was  $\leq 4$  weeks prior to OLE baseline) administered on Day 1. Patients enrolled in the early stage (starting October 2013) received 200mg qw (400mg loading dose). The protocol was subsequently amended on December 12, 2013 to the 300mg qw regimen based on the dose regimens selected for phase 3 studies.<sup>24</sup> Patients could be treated for up to 3 years. Concomitant topical treatments were allowed without restriction. Only systemic treatments for AD were considered rescue 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 Harmonization Guidelines for Good Clinical Practice. Each patient provided informed consent prior to performing any study procedures. For each site the protocol, informed-consent form, and patient information were approved by an institutional review board and independent ethics committee.

The primary endpoint was incidence and rate (events per 100 patient-years [100PY]) of AEs. Key secondary endpoints included proportion of patients achieving Investigator's Global Assessment (IGA) of 0–1 and  $\geq 75\%$  improvement in Eczema Area and Severity Index (EASI-75) from baseline of parent study (BP). Other secondary endpoints included absolute and percent change from BP in Peak Pruritus

186 Numerical Rating Scale (NRS), Dermatology Life Quality Index (DLQI),<sup>37</sup> and Patient-Oriented Eczema  
187 Measure (POEM).<sup>38</sup> Endpoints were analyzed descriptively using all observed data. Antidrug antibodies  
188 (ADAs) were assessed in patient sera.

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

192 Subgroup analyses were performed on patients who had not received dupilumab in the parent study  
193 (dupilumab-naïve), representing a continuous treatment paradigm since the OLE start, and patients with  
194  $\geq 13$  weeks between the last dupilumab injection in the parent study and the first injection in the OLE  
195 (re-treatment), a discontinuous treatment paradigm (these subsets do not account for 100% of patients;  
196 other subsets were not included).

## RESULTS

### *Patients*

1,587 patients were screened from 12 parent studies (NCT01259323/n=8<sup>23,29</sup>; NCT01859988/n=310<sup>24</sup>; NCT01385657/n=13<sup>23,29</sup>; NCT01548404/n=62<sup>23</sup>; NCT01639040/n=17<sup>23</sup>; NCT02260986/n=126<sup>26</sup>; NCT01979016/n=48<sup>30</sup>; NCT02210780/n=176<sup>28</sup>; NCT02277743/n=359<sup>25</sup>; NCT02395133/n=40 [Worm M, unpublished data April 2019]; NCT02277769/n=425<sup>25</sup>; NCT02647086/n=3<sup>36</sup>); 1,491 patients received dupilumab in this study (1,042.9 PY). Most patients (1,179/1,491) received 300mg qw; 312 patients received dupilumab 200mg qw (mean 18.5 doses [range 1–52]) before protocol amendment to 300mg qw (9 patients received 200mg qw and discontinued before switching). Patients received a mean of 37.5 doses of dupilumab (range 1–125); 17.8% of patients had  $\geq 76$  cumulative doses. Few patients (7.1%) discontinued the study prematurely, and the majority (98.6%) were  $\geq 80\%$  adherent with study treatment.

Baseline characteristics are shown in **Table 1**. Most (1,246/1,491) patients (84%) had associated atopic/allergic disease (**Table 1**). As of cutoff date for this analysis, 1,385/1,491 (92.9%) patients were actively receiving study treatment, with 428 patients (28.7%) in the Week 52 cohort and 284 patients (19.0%) in the Week 76 cohort.

### *Safety*

Overall, 4,384 AEs were reported, with exposure-adjusted rates of 420.4 events/100PY and 8.5 SAEs/100PY; 70.7% of patients had  $\geq 1$  AE and 5.0% had  $\geq 1$  SAE; no SAE was reported in  $\geq 1\%$  of patients (**Table 2**). Most AEs were mild-to-moderate;  $<5\%$  of patients reported an SAE. Seven patients (0.5%) experienced 8 SAEs that were considered related to study drug by the investigator: Hodgkin's 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 (PTs); 150 patients (10.1%) reported ISRs (36.53 events/100PY) as MedDRA High Level Term (**Table 2**), the majority of mild/moderate severity.

Additionally, 10.7% reported conjunctivitis with various descriptors (20.8 events/100PY). Most conjunctivitis cases were mild-to-moderate; 5/1,491 patients (0.3%) reported severe conjunctivitis (5/217 [2.3%] of all conjunctivitis cases). Although most conjunctivitis events resolved, 45/217 events (20.7%) were ongoing at cutoff. Three patients (0.2% of total) discontinued dupilumab due to 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: 126/1491 (8.5%) and 86/1491 (5.8%) had ISRs and conjunctivitis during Weeks 0–12, while these numbers dropped to 3/445 (0.7%) and 8/445 (1.8%) during Weeks 48–60.

Review of safety data for dupilumab-naïve and re-treated patients found no evidence of increased risk of AEs associated with a single dupilumab re-treatment (data not shown).

#### *Efficacy in the total population (SAF)*

AD skin lesion severity and AD-related symptoms generally improved throughout the OLE. Mean EASI (standard error) at Week 76 was 3.11 (0.308) (**Figure 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 (**Figure 2**), DLQI, and POEM (not shown) up to 76 weeks.

Improvements consistent with the overall population were observed in dupilumab-naïve and re-treatment subgroups for EASI (**Figure 1**) and Peak Pruritus NRS (**Figure 2**), DLQI, and POEM (not shown).



Time to first  $\geq 50\%/75\%/90\%$  EASI improvement from BP (EASI-50/EASI-75/EASI-90) and time to first IGA 0 or 1 were also assessed (median days [95% confidence interval]): 29 (29–30)/85 (59–85)/169 (142–197) and 169 (142–197), respectively.

#### *Efficacy in the 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 3**) reflected improvements seen in the total population. At Week 56 and 76,  $>60\%$  of patients achieved EASI-90. At Week 76, most patients achieved IGA 0–1,  $\geq 4$ -point improvement in Peak Pruritus NRS, and “no problems” in the pain dimension of European QoL-5 Dimensions (**Table 3**).

Sensitivity analyses were consistent with efficacy of all observed patients for the Week 52 and Week 76 cohorts (**Table 3**), suggesting no bias on treatment outcomes due to patient withdrawal.

#### *Additional AD treatments during the study*

Overall, 50.3% of patients did not use additional medications for AD. Of those who did, 44.4% received TCS and 13.3% received topical calcineurin inhibitors. A total of 55 patients (3.7%) required systemic therapy, considered rescue in this study. Most rescued patients (52/55) received corticosteroids; 5 patients received non-steroidal 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 to 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).

262 *Immunogenicity*

263 830 patients had  $\geq 1$  ADA result post-first dose and were included in the analysis. Overall, 23/830  
264 patients (2.8%) had treatment-emergent ADAs in the OLE, of whom 16/308 patients (5.2%) were in the  
265 re-treatment subgroup, 4/178 (2.2%) in the interrupted treatment group, and 3/305 patients (1.0%) in  
266 the dupilumab-naïve subgroup; 8/830 patients (1.0%) had ADA responses lasting  $>12$  weeks. In the  
267 continuous treatment population ( $n=38$ ), no patients had additional incidence of treatment-emergent  
268 ADAs. One patient with treatment-emergent ADAs permanently discontinued treatment due to AE  
269 (deemed unrelated to ADA) and none had SAEs. Functional dupilumab<sup>36</sup> concentrations were similar in  
270 treatment-emergent ADA-positive and ADA-negative patients. Few patients ( $n=6$ ) with moderate ADA  
271 titer levels had lower dupilumab concentrations, which attained levels similar to those in ADA-negative  
272 patients in approximately 26 weeks. No patient had high ADA titers during the OLE. One re-treatment  
273 patient with high-titers at OLE baseline decreased to low titers around Week 76. In the overall  
274 population, there was no meaningful difference in efficacy between ADA-positive and ADA-negative  
275 patients.

**DISCUSSION**

This first-step analysis of a long-term open-label study of 300mg qw dupilumab in patients who previously participated in randomized, double-blinded, placebo-controlled clinical trials of dupilumab is 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.<sup>23-30</sup> The exposure-adjusted rate of AEs and SAEs was also consistent with previously reported rates of AEs and SAEs for dupilumab qw+TCS (476.23 AEs/100PY and 4.98 SAEs/100PY) and slightly lower than placebo+TCS (532.38 AEs/100PY and 7.85 SAEs/100PY) at 52 weeks.<sup>26</sup>

While previous long-term studies in cyclosporine and azathioprine have been limited by high discontinuation rates,<sup>39-42</sup> 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 in  $\geq 5\%$  of patients. Few patients were ADA-positive during the 76-week treatment period.

Conjunctivitis and ISR rates reported here were comparable to previous phase 3 trials of dupilumab in AD, which occurred more frequently with dupilumab than placebo.<sup>23-27</sup> Very few patients had severe conjunctivitis (0.3%). Despite no placebo arm, the low rate of withdrawal due to conjunctivitis (0.2%) and ISRs (<0.1%) 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 that dupilumab monotherapy or concomitant with topical AD medications provides long-term disease control in moderate-to-severe AD patients.

#### *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 to the total number of patients enrolled; nevertheless, it constitutes a reasonable sample for these types of analyses. The number of drop-outs 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 ability to detect rare but serious AEs. For re-treatment patients, the results of this analysis may not fully characterize the consequences of multiple retreatments (i.e. 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 300mg qw regimen in this study is higher than the 300mg every 2 weeks (q2w) regimen approved in most countries. However, safety and efficacy were similar between the two dose regimens in multiple phase 3 trials suggesting they are clinically equivalent. The 300mg qw dose was chosen for this study to increase the likelihood of identifying any safety signals and to generate safety data that could adequately support both 300mg qw and q2w dose regimens.

322

323 **CONCLUSIONS**

324 Treatment for up to 76 weeks with dupilumab 300mg was well-tolerated, with a safety profile consistent  
325 with previous clinical trials of shorter durations (16-52 Weeks).<sup>23-30</sup> The most common AEs (conjunctivitis  
326 and ISRs) were seen more often at the beginning of dupilumab treatment and diminished over time.

327 Dupilumab-naïve patients experienced improvements in AD signs and symptoms comparable to those  
328 demonstrated by dupilumab-treated patients in parent studies. Patients with dupilumab treatment prior  
329 to the OLE study showed additional clinical benefits that were sustained through the end of the  
330 observation period. Irrespective of dupilumab treatment history, by Week 52 most patients attained AD  
331 severity scores consistent with no or low disease activity. No meaningful impact on efficacy or safety in  
332 the few ADA-positive patients was observed.

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

**337 ACKNOWLEDGMENTS**

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

**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

EQ-5D: European Quality of Life-5 Dimensions

IGA: Investigator's Global Assessment

IL: interleukin

IL-4R: interleukin-4 receptor

IQR: interquartile range

ISR: injection-site reaction

MedDRA: Medical Dictionary for Regulatory Activities

NRS: Numerical Rating Scale

OLE: open-label extension

PGADS: Patient Global Assessment of Disease Status

POEM: Patient-Oriented Eczema Measure

PT: Preferred Term

PY: patient-years

QoL: quality of life

- 368   qw: weekly
- 369   q2w: every 2 weeks
- 370   q4w: every 4 weeks
- 371   SAE: serious adverse event
- 372   SAF: safety analysis set
- 373   SD: standard deviation
- 374   SE: standard error
- 375   TCS: topical corticosteroids



## REFERENCES

1. Weidinger S, Novak N. Atopic dermatitis. *Lancet*. 2016;387(10023):1109-1122.
2. Silverberg JI, Hanifin JM. Adult eczema prevalence and associations with asthma and other health and demographic factors: a US population-based study. *J Allergy Clin Immunol*. 2013;132(5):1132-1138.
3. Silverberg JI, Nelson DB, Yosipovitch G. Addressing treatment challenges in atopic dermatitis with novel topical therapies. *J Dermatolog Treat*. 2016;27(6):568-576.
4. Gittler JK, Shemer A, Suárez-Fariñas M, et al. Progressive activation of T(H)2/T(H)22 cytokines and selective epidermal proteins characterizes acute and chronic atopic dermatitis. *J Allergy Clin Immunol*. 2012;130(6):1344-1354.
5. Boguniewicz M, Alexis AF, Beck LA, et al. Expert perspectives on management of moderate-to-severe atopic dermatitis: a multidisciplinary consensus addressing current and emerging therapies. *J Allergy Clin Immunol Pract*. 2017;5(6):1519-1531.
6. Sánchez-Pérez J, Daudén-Tello E, Mora AM, et al. Impact of atopic dermatitis on health-related quality of life in Spanish children and adults: the PSEDA study. *Actas Dermosifiliogr*. 2013;104(1):44-52.
7. Silverberg JI, Garg NK, Paller AS, et al. Sleep disturbances in adults with eczema are associated with impaired overall health: a US population-based study. *J Invest Dermatol*. 2015;135(1):56-66.
8. Murota H, Kitaba S, Tani M, et al. Impact of sedative and non-sedative antihistamines on the impaired productivity and quality of life in patients with pruritic skin diseases. *Allergol Int*. 2010;59(4):345-354.

9. Simpson EL, Bieber T, Eckert L, et al. Patient burden of moderate to severe atopic dermatitis (AD): insights from a phase 2b clinical trial of dupilumab in adults. *J Am Acad Dermatol*. 2016;74(3):491-498.
10. Eckert L, Gupta S, Amand C, et al. The burden of atopic dermatitis in US adults: Health care resource utilization data from the 2013 National Health and Wellness Survey. [published online October 7, 2017]. *J Am Acad Dermatol*. doi: 10.1016/j.jaad.2017.08.002.
11. Ring J, Alomar A, Bieber T, et al. Guidelines for treatment of atopic eczema (atopic dermatitis) Part I. *J Eur Acad Dermatol Venereol*. 2012;26(8):1045-1060.
12. Ring J, Alomar A, Bieber T, et al. Guidelines for treatment of atopic eczema (atopic dermatitis) Part II. *J Eur Acad Dermatol Venereol*. 2012;26(9):1176-1193.
13. Sidbury R, Davis DM, Cohen DE, et al. Guidelines of care for the management of atopic dermatitis: section 3. Management and treatment with phototherapy and systemic agents. *J Am Acad Dermatol*. 2014;71(2):327-349.
14. Sidbury R, Davis DM, Cohen DE, et al. Guidelines of care for the management of atopic dermatitis: section 4. Prevention of disease flares and use of adjunctive therapies and approaches. *J Am Acad Dermatol*. 2014;71(6):1218-1233.
15. Eichenfield LF, Tom WL, Berger TG, et al. Guidelines of care for the management of atopic dermatitis: section 2. Management and treatment of atopic dermatitis with topical therapies. *J Am Acad Dermatol*. 2014;71(1):116-132.
16. Katayama I, Aihara M, Ohya Y, et al; Japanese Society of Allergology. Japanese guidelines for atopic dermatitis 2017. *Allergol Int*. 2017;66(2):230-247.

17. Garritsen FM, Brouwer MW, Limpens J, et al. Photo(chemo)therapy in the management of atopic dermatitis: an updated systematic review with implications for practice and research. *Br J Dermatol.* 2014;170(3):501-513.
18. MacDonald LE, Karow M, Stevens S, et al. Precise and in situ genetic humanization of 6 Mb of mouse immunoglobulin genes. *Proc Natl Acad Sci U S A.* 2014;111(14):5147-5152.
19. Murphy AJ, Macdonald LE, Stevens S, et al. Mice with megabase humanization of their immunoglobulin genes generate antibodies as efficiently as normal mice. *Proc Natl Acad Sci U S A.* 2014;111(14):5153-5158.
20. Gandhi NA, Bennett BL, Graham NMH, et al. Targeting key proximal drivers of type 2 inflammation in disease. *Nat Rev Drug Discov.* 2016;15(1):35-50.
21. Dupixent [package insert]. Tarrytown, NY: Regeneron Pharmaceuticals, Inc.; 2017.
22. European Medicines Agency. Committee for Medicinal Products for Human Use. Summary of opinion (initial authorisation). Dupixent (dupilumab).  
[https://www.ema.europa.eu/documents/smop-initial/chmp-summary-positive-opinion-dupixent\\_en.pdf](https://www.ema.europa.eu/documents/smop-initial/chmp-summary-positive-opinion-dupixent_en.pdf). Accessed April 4, 2019.
23. Beck LA, Thaçi D, Hamilton JD, et al. Dupilumab treatment in adults with moderate-to-severe atopic dermatitis. *N Engl J Med.* 2014;371(2):130-139.
24. Thaçi D, Simpson EL, Beck LA, et al. Efficacy and safety of dupilumab in adults with moderate-to-severe atopic dermatitis inadequately controlled by topical treatments: a randomised, placebo-controlled, dose-ranging phase 2b trial. *Lancet.* 2016;387(10013):40-52.

25. Simpson EL, Bieber T, Guttman-Yassky E, et al. Two phase 3 trials of dupilumab versus placebo in atopic dermatitis. *N Engl J Med*. 2016;375(24):2335-2348.
26. Blauvelt A, de Bruin-Weller M, Gooderham M, et al. Long-term management of moderate-to-severe atopic dermatitis with dupilumab and concomitant topical corticosteroids (LIBERTY AD CHRONOS): a 1-year, randomised, double-blinded, placebo-controlled, phase 3 trial. *Lancet*. 2017;389(10086):2287-2303.
27. de Bruin-Weller M, Thaçi D, Smith CH, et al. Dupilumab with concomitant topical corticosteroids in adult patients with atopic dermatitis who are not adequately controlled with or are intolerant to ciclosporin A, or when this treatment is medically inadvisable: a placebo-controlled, randomized phase 3 clinical trial (LIBERTY AD CAFÉ). *Br J Dermatol*. 2018;178(5):1083-1101.
28. Blauvelt A, Simpson EL, Tying SK. Dupilumab does not affect correlates of vaccine-induced immunity: A randomized, placebo-controlled trial in adults with moderate-to-severe atopic dermatitis. *J Am Acad Dermatol*. 2019;80(1):158-167.e1
29. Hamilton JD, Suárez-Fariñas M, Dhingra N, et al. Dupilumab improves the molecular signature in skin of patients with moderate-to-severe atopic dermatitis. *J Allergy Clin Immunol*. 2014;134(6):1293-1300.
30. Guttman-Yassky E, Bissonnette R, Ungar B, et al. Dupilumab progressively improves systemic and cutaneous abnormalities in patients with atopic dermatitis. *J Allergy Clin Immunol*. 2019;143(1):155-172.
31. Wenzel S, Ford L, Pearlman D, et al. Dupilumab in persistent asthma with elevated eosinophil levels. *N Engl J Med*. 2013;368(26):2455-2466.

32. Wenzel S, Castro M, Corren J, et al. Dupilumab efficacy and safety in adults with uncontrolled persistent asthma despite use of medium-to-high-dose inhaled corticosteroids plus a long-acting  $\beta_2$  agonist: a randomised double-blind placebo-controlled pivotal phase 2b dose-ranging trial. *Lancet*. 2016;388(10039):31-44.
33. Castro M, Corren J, Pavord ID, et al. Dupilumab efficacy and safety in moderate-to-severe uncontrolled asthma. *N Engl J Med*. 2018;378(26):2486-2496.
34. Bachert C, Mannent L, Naclerio RM, et al. Effect of subcutaneous dupilumab on nasal polyp burden in patients with chronic sinusitis and nasal polyposis: a randomized clinical trial. *JAMA*. 2016;315(5):469-479.
35. Hirano I, Dellon ES, Hamilton JD, et al. Dupilumab efficacy and safety in adult patients with active eosinophilic esophagitis: a randomized double-blind placebo-controlled phase 2 trial. Orlando, FL, USA: World Congress of Gastroenterology at ACG; 2017. Oct 13–18, 2017.
36. Davis JD, Bansal A, Hassman D, et al. Evaluation of potential disease-mediated drug-drug interaction in patients with moderate-to-severe atopic dermatitis receiving dupilumab. *Clin Pharmacol Ther*. 2018 Dec;104(6):1146-1154.
37. Basra MK, Salek MS, Camilleri L, et al. Determining the minimal clinically important difference and responsiveness of the Dermatology Life Quality Index (DLQI): further data. *Dermatology*. 2015;230(1):27-33.
38. Schram ME, Spuls PI, et al. EASI, (objective) SCORAD and POEM for atopic eczema: responsiveness and minimal clinically important difference. *Allergy*. 2012;67(1):99-106.
39. van der Schaft J, Politiek K, van den Reek JM, et al. Drug survival for ciclosporin A in a long-term daily practice cohort of adult patients with atopic dermatitis. *Br J Dermatol*. 2015;172(6):1621-1627.

- 481 40. Berth-Jones J, Takwale A, Tan E, et al. Azathioprine in severe adult atopic dermatitis: a double-blind,  
482 placebo-controlled, crossover trial. *Br J Dermatol.* 2002;147(2):324-330.
- 483 41. Berth-Jones J, Graham-Brown RA, Marks R, et al. Long-term efficacy and safety of cyclosporin in  
484 severe adult atopic dermatitis. *Br J Dermatol.* 1997;136(1):76-81.
- 485 42. van der Schaft J, Politiek K, van den Reek JM, et al. Drug survival for azathioprine and enteric-coated  
486 mycophenolate sodium in a long-term daily practice cohort of adult patients with atopic dermatitis.  
487 *Br J Dermatol.* 2016;175(1):199-202.

488 **Table 1.** Baseline demographics and disease characteristics.

	Patient values (N = 1,491)
Demographic characteristics at baseline:	Current study (OLE)
Age, median (IQR), years	39.0 (29.0–49.0)
Duration of AD, median (IQR), years	29.0 (19.0–40.0)
Race, n (%)	
White	1,051 (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, median (IQR), kg	76.0 (64.2–89.5)
BMI, median (IQR), kg/m <sup>2</sup>	25.7 (22.7–29.5)
Treatment in parent study:	
Previously treated with dupilumab, <sup>a</sup> n	850
Dupilumab 300mg qw, n	401
Dupilumab 300mg q2w, n	274
Other dupilumab doses, <sup>b</sup> n	175
Dupilumab-naïve subgroup, n	606
Received placebo qw in parent study, n	577
Screen failure in parent study, n	29
Treatment blinded in parent study, <sup>c</sup> n	35
Number of patients with current history of atopic/allergic conditions reported in parent study, n (%)	1,246 (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 of:	Parent study	Current study (OLE)
EASI, median (IQR)	30.5 (21.6–42.7)	17.1 (9.2–29.9)
Patients with IGA score, <sup>d,e</sup> 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)
Patients with PGADS score, <sup>f</sup> 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.

<sup>a</sup>Includes patients who received any dupilumab treatment, including re-treatment subgroup (n = 381) with period of >13 weeks between parent dupilumab treatment and first injection, interrupted treatment subgroup (n = 409) with period of ≥6 and ≤13 weeks between parent dupilumab treatment and first injection, and continuous treatment subgroup (n = 60) with period of <6 weeks between parent dupilumab treatment and first injection. <sup>b</sup>Includes the following dupilumab doses in parent study: 75 mg *qw*, 100 mg *q4w*, 150 mg *qw*, 200 mg *q2w*, 200 mg *qw*, 300 mg *q4w*. <sup>c</sup>Patient has not yet been unblinded from parent study. <sup>d</sup>0 = clear; 1 = almost clear; 2 = mild disease; 3 = moderate disease; 4 = severe disease. <sup>e</sup>31 patients had missing IGA at baseline of parent study. <sup>f</sup>117 patients had missing PGADS at baseline of parent study.



**Table 2.** Safety assessment.

	<b>Total population (N = 1,491)</b>	
AEs, n (events/100PY)	4,384 (420.4)	
Patients with $\geq 1$ AE, n (%)	1,054 (70.7)	
Patients with $\geq 1$ SAE, n (%) <sup>a</sup>	74 (5.0)	
Patients with AEs leading to permanent discontinuation, n (%)	27 (1.8)	
Patients with $\geq 1$ severe AE, n (%)	71 (4.8)	
Deaths, n	0	
<b>Most common AEs by PT (<math>\geq 2\%</math> of patients by MedDRA PT)</b>	<b>n (%)<sup>a</sup></b>	<b>Events/100PY<sup>b</sup></b>
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 <sup>c</sup>	160 (10.7)	20.8
Injection-site reactions <sup>d</sup>	150 (10.1)	36.5
<b>Most common SAEs by PT (<math>&gt;1</math> patient by MedDRA PT)</b>		
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
Non-cardiac chest pain	2 (0.1)	0.288

100PY, 100 patient-years; AE, adverse event; MedDRA, Medical Dictionary for Regulatory Activities; PT, MedDRA Preferred Term; SAE, serious adverse event.

<sup>a</sup>Patient who reported  $\geq 2$  AEs with the same PT was counted only once for that term. <sup>b</sup>Total patient-years were calculated as the sum of study observational periods over all patients. <sup>c</sup>Conjunctivitis cluster includes conjunctivitis, allergic conjunctivitis, bacterial conjunctivitis, viral conjunctivitis, and atopic conjunctivitis. <sup>d</sup>MedDRA High Level Term.

510 **Table 3.** Efficacy outcomes at Week 52 and Week 76.

	<b>Week 52 (n = 428)<sup>a</sup></b>	<b>Week 76 (n = 284)<sup>b</sup></b>
Proportion of patients who achieved IGA score of 0 or 1, n/N (%)	221/398 (55.5)	144/249 (57.8)
EASI, mean change from baseline of parent study $\pm$ SD	-28.0 $\pm$ 13.38	-28.8 $\pm$ 13.49
EASI, mean % change from baseline of parent study $\pm$ SD	-89.0 $\pm$ 16.08	-90.0 $\pm$ 13.48
Proportion of patients who achieved EASI-50 relative to baseline of parent study, n/N (%)	385/398 (96.7)	244/249 (98.0)
Proportion of patients who achieved EASI-75 relative to baseline of parent study, n/N (%)	346/398 (86.9)	220/249 (88.4)
Proportion of patients who achieved EASI-90 relative to baseline of parent study, n/N (%)	265/398 (66.6)	171/249 (68.7)
Peak Pruritus NRS, mean change from baseline of parent study $\pm$ SD	-4.20 $\pm$ 2.45	-4.29 $\pm$ 2.53
Peak Pruritus NRS, mean % change from baseline of parent study $\pm$ SD	-62.0 $\pm$ 30.07	-63.7 $\pm$ 32.41
Proportion of patients who achieved Peak Pruritus NRS score improvement $\geq$ 4 points from baseline of parent study, n/N (%) <sup>c</sup>	169/262 (64.5)	106/165 (64.2)
Proportion of patients who achieved Peak Pruritus NRS score improvement $\geq$ 3 points from baseline of parent study, n/N (%) <sup>d</sup>	206/277 (74.4)	134/176 (76.1)
Proportion of patients who achieved an IGA score $\leq$ 2, n/N (%)	356/398 (89.4)	224/249 (90.0)
Proportion of patients with $\geq$ 2-point improvement in IGA among patients with baseline IGA $\geq$ 2, n/N (%)	214/384 (55.7)	141/243 (58.0)
Proportion of patients with EQ-5D pain dimension (no problems), n/N (%)	311/398 (78.1) <sup>e</sup>	200/248 (80.6)
DLQI, mean percent change from baseline of parent study $\pm$ SD	-76.6 $\pm$ 29.13 <sup>f</sup>	-77.4 $\pm$ 27.60
<b>Post-hoc efficacy endpoints</b>		
Proportion of patients who achieved EASI total score $\leq$ 10, n/N (%)	364/398 (91.5)	231/249 (92.8)
Proportion of patients who achieved Peak Pruritus NRS $\leq$ 3, n/N (%)	230/297 (77.4)	152/188 (80.9)
Proportion of patients achieving 0–5 on DLQI total score, n/N (%)	334/398 (83.9) <sup>f</sup>	202/242 (83.5)
Proportion of patients who achieved EASI total score $\leq$ 12, n/N (%)	375/398 (94.2)	237/249 (95.2)

Proportion of patients who achieved Peak Pruritus NRS $\leq 5$ , n/N (%)	278/297 (93.6)	177/188 (94.1)
Proportion of patients who achieved Peak Pruritus NRS $\leq 4$ , n/N (%)	263/297 (88.6)	172/188 (91.5)
Proportion of patients achieving 0 or 1 on DLQI total score, n/N (%)	190/398 (47.7) <sup>f</sup>	129/242 (53.3)
Proportion of patients achieving 0 or 1 (not relevant or a little) on all 10 DLQI subdomain scores, n/N (%)	322/398 (80.9) <sup>f</sup>	197/242 (81.4)
<b>Sensitivity analyses</b>		
EASI, LS mean change from baseline of parent study $\pm$ SE (multiple imputation)	-27.85 $\pm$ 0.653	-28.81 $\pm$ 0.807
EASI, LS mean % change from baseline of parent study $\pm$ SE (multiple imputation)	-88.6 $\pm$ 0.87	-89.4 $\pm$ 0.91
Peak Pruritus NRS, LS mean change from baseline of parent study $\pm$ SE (multiple imputation)	-4.26 $\pm$ 0.124	-4.33 $\pm$ 0.158
Peak Pruritus NRS, LS mean % change from baseline of parent study $\pm$ SE (multiple imputation)	-62.5 $\pm$ 1.66	-63.5 $\pm$ 2.23
Proportion of patients who achieved EASI-75 relative to baseline of parent study, n (%) (non-responder imputation)	334 (78)	214 (75)
Proportion of patients who achieved EASI-50 relative to baseline of parent study, n (%) (non-responder imputation)	373 (87)	238 (84)
Proportion of patients who achieved Peak Pruritus NRS score improvement $\geq 3$ points from baseline of current study who had Peak Pruritus NRS score at baseline $\geq 3$ , n/N (%) (non-responder imputation)	199/397 (50)	130/264 (49)

DLQI, Dermatology Life Quality Index; EASI, Eczema Area and Severity Index; EQ-5D, European Quality of Life-5 Dimensions; IGA, Investigator's Global Assessment; NRS, Numerical Rating Scale; SD, standard deviation; SE, standard error.

<sup>a</sup>Efficacy at Week 52 observed for Week 52 cohort, which included all patients enrolled at least 53 weeks prior to data cutoff (accounting for +/- 1 week visit window). <sup>b</sup>Efficacy at Week 76 observed for Week 76 cohort, which included all patients enrolled at least 77 weeks prior to data cutoff (accounting for +/- 1 week visit window). <sup>c</sup>Among patients with parent baseline Peak Pruritus NRS score  $\geq 4$ . <sup>d</sup>Among patients with parent baseline Peak Pruritus NRS score  $\geq 3$ . <sup>e</sup>EQ-5D pain dimension score assessed at Week 48. <sup>f</sup>DLQI assessed at Week 48.

520 **Figure legends**

521 **Fig 1.** Mean EASI at each visit for the total population (main figure) and dupilumab re-treatment and  
522 dupilumab-naïve subgroups (inset).

523 *BP*, baseline of parent study; *EASI*, Eczema Area and Severity Index.

524

525 **Fig 2.** Mean Peak Pruritus NRS score at each visit for the total population (main figure) and dupilumab  
526 re-treatment and dupilumab-naïve subgroups (inset).

527 *BP*, baseline of parent study; *NRS*, Numerical Rating Scale; *SE*, standard error.



