



# The Safety Data of Dupilumab for the Treatment of Moderate-to-Severe Atopic Dermatitis in Infants, Children, Adolescents, and Adults

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## Abstract

**Background** Atopic dermatitis (AD) significantly affects quality of life in patients of all ages and requires long-term treatment. Dupilumab is approved for uncontrolled moderate-to-severe AD in patients aged  $\geq 6$  months and in other type 2 inflammatory diseases. Data from placebo-controlled, randomized clinical trials (RCTs) and long-term open-label extensions (OLEs) enable comprehensive assessment of dupilumab's safety profile for up to 5 years.

**Objective** To integrate short- and long-term dupilumab safety data in patients with moderate-to-severe AD.

**Methods** We describe safety from eight phase 3 trials with  $> 7000$  patient-years of dupilumab use: five 16-week RCTs in children (6 months–11 years, with concomitant topical corticosteroids [TCS]) and adolescents and adults ( $\geq 12$  years, without TCS); one 52-week RCT in adults (with TCS); and two OLEs in children and adolescents (6–11- and 12–18-year cohorts,  $\pm$  TCS, duration  $\leq 1$  year) and adults ( $\pm$  TCS, duration  $\leq 5$  years).

**Results** The proportion of patients experiencing  $\geq 1$  treatment-emergent adverse event (TEAE) in RCTs was lower with dupilumab versus placebo in children/infants and was similar with dupilumab versus placebo in adults/adolescents. Exposure-adjusted incidence rates with longer-term treatment in OLEs were similar to the RCTs. Most TEAEs reported in RCT and OLE studies were mild to moderate and not related to study drug (per investigators). Fewer patients in the dupilumab versus placebo treatment arms experienced serious TEAEs (16-week RCTs: infants/children 0.8% vs 3.0%; adults/adolescents 2.2% vs 4.6%; 52-week RCT: 3.2–3.6% vs 5.1%). Common TEAEs that had higher incidence rates with dupilumab compared with placebo in RCTs included injection-site reactions (Medical Dictionary for Regulatory Activities High Level Term) and conjunctivitis (clustered term). Serious infections and non-herpetic skin infections were more frequent with placebo.

**Conclusions** In the most comprehensive dupilumab safety assessment to date, safety was consistent with the known dupilumab safety profile. [Graphical abstract and video abstract available.]

**Trial Registration** ClinicalTrials.gov Identifiers: NCT03346434; NCT03345914; NCT03054428; NCT02277743; NCT02277769; NCT02260986; NCT01949311; NCT02612454. EudraCT: 2016-000955-28; 2016-004997-16; 2015-004458-16; 2014-001198-15; 2014-002619-40; 2013-003254-24; 2013-001449-15; 2015-001396-40.

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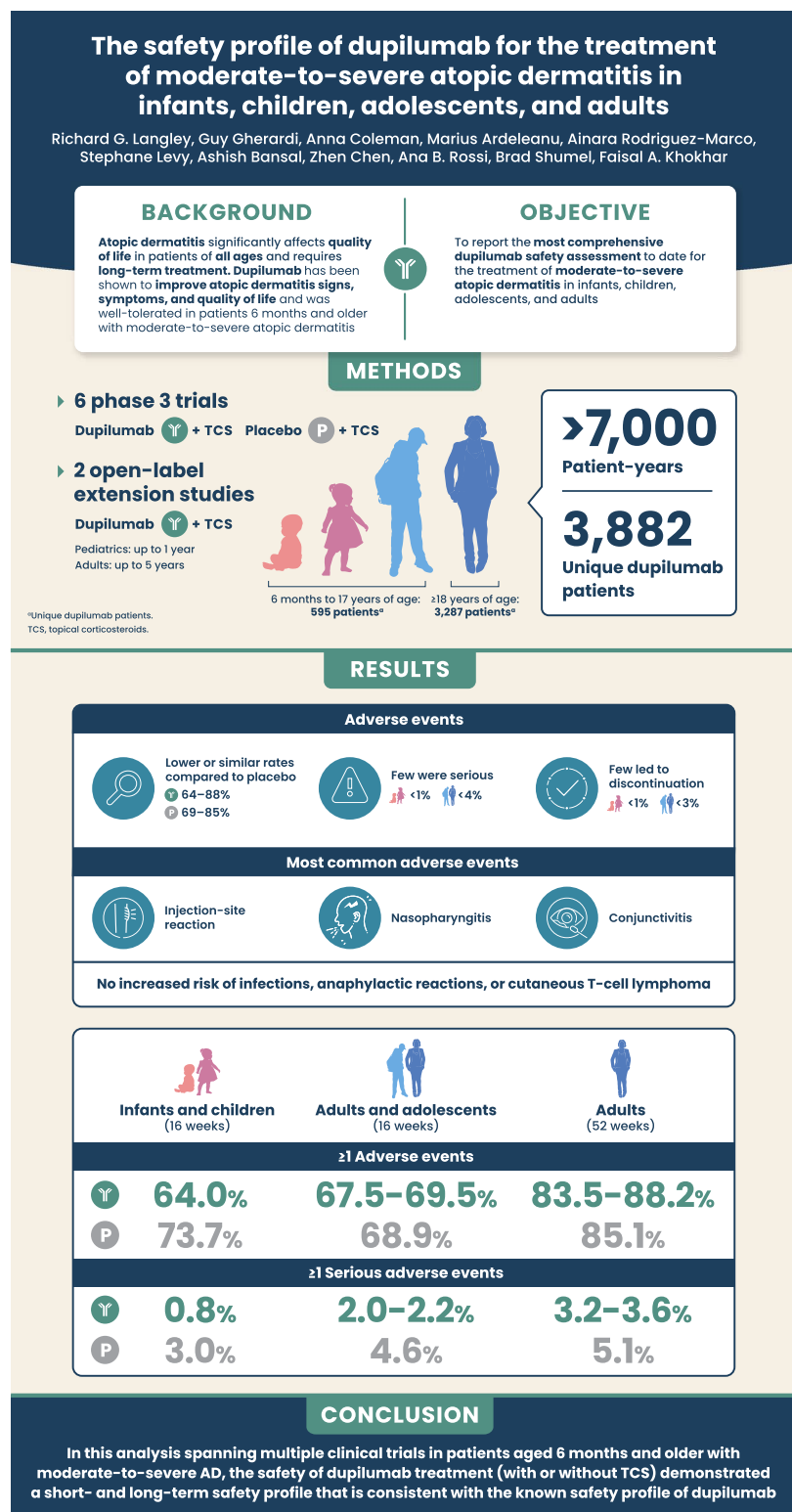
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Atopic dermatitis is a chronic skin disease that affects people of all ages. Since patients with atopic dermatitis require continuous, life-long treatment, doctors and patients must understand the risks and benefits of treatment options before choosing one medication over another. This study reviews the safety of the drug dupilumab, which is used to treat infants, children, adolescents, and adults who have moderate-to-severe atopic dermatitis that is not well controlled with topical corticosteroids. We looked at side effects and safety data from more than 4000 patients who received either dupilumab or placebo treatment for up to 5 years in **B, O, I, S** trials. This study is the largest safety analysis of dupilumab to date. We found that children 6 months to **A, O, S** receiving dupilumab had fewer side effects than **R** patients in the placebo group. Adolescents and adults (12 years and older) taking dupilumab and placebo had similar **S**es of side effects. Serious side effects were more frequent in the placebo than in the dupilumab group in all age groups. **B**est side effects in patients who received dupilumab were mild or moderate, were not caused by dupilumab, and did not stop patients from taking dupilumab. The most common side effects that occurred more frequently in dupilumab-treated patients were pain or swelling around the injection location, common colds, and conjunctivitis. In conclusion, the safety of dupilumab in over 3000 patients in this study is consistent with the known dupilumab safety profile for infants, children, adolescents, and adults.

### Key Points

**R** Treatment-emergent adverse event rates in pediatric and adult patients with atopic dermatitis (AD) treated with dupilumab were similar or lower than in those receiving placebo—most were mild or moderate and few led to treatment discontinuation.

Consistent with previous reports, this analysis confirms that there is no labeling requirement for routine laboratory monitoring of adverse events for patients treated with dupilumab.

This comprehensive review of patients with moderate-to-severe AD treated with dupilumab for  $\leq 5$  years confirms that overall safety of dupilumab was consistent with the known dupilumab safety profile across age groups.

Atopic dermatitis (AD) is a type 2 inflammatory skin disease that affects patients of all ages and can have a profound impact on the quality of life of patients and their families [1–3]. The high burden and chronic systemic nature of type 2 inflammation in moderate-to-severe AD support the need for well-tolerated, long-term systemic treatment. Although nontargeted systemic therapies, including systemic corticosteroids and nonsteroidal immunosuppressants, have been used for moderate-to-severe AD, many are recommended only for short-term treatment in specific populations owing to safety considerations and require routine laboratory testing [4–9]. For children in particular, many nontargeted systemic therapies are often used off-label and may be associated with impacts on bone mineralization, adrenal suppression, increased risk of infections, and subsequent hospitalizations [10, 11]. Thus, there is a critical need for efficacious systemic treatments that have demonstrated long-term safety profiles.

Dupilumab is a fully human monoclonal antibody that targets the shared receptor component for interleukin (IL)-4 and IL-13, inhibiting signaling of both IL-4 and IL-13, two of the key and central drivers of type 2 inflammation in multiple diseases [12–14]. Dupilumab is currently approved in AD, asthma, chronic rhinosinusitis with nasal polyposis (CRSwNP), eosinophilic esophagitis, and prurigo nodularis in the USA, and in one or more of these indications in Europe, Japan, and more than 60 countries worldwide [12, 15]. In multiple, phase 3, placebo-controlled, randomized clinical trials (RCTs), dupilumab with or without topical corticosteroids (TCS) versus placebo significantly improved AD signs, symptoms, and quality of life and was well tolerated in infants, adolescents, and adults with uncontrolled moderate-to-severe AD, and in children with severe AD [12, 15–21]. Improvements in response to dupilumab were sustained up to 5 years of continued treatment in open-label extension (OLE) trials in adults and up to 2 years in adolescents, children, and infants [16, 22–25].

This paper provides the most comprehensive analysis of safety data to date from phase 3 RCTs and OLEs of dupilumab for patients aged  $\geq 6$  months with moderate-to-severe or severe AD. This in-depth overview of the safety profile of dupilumab is based on data from  $> 6000$  patients and  $> 7000$  total patient-years of exposure for multiple dose regimens, including the currently approved regimens [12, 15]. A comprehensive understanding of dupilumab's safety profile is key to appropriate benefit–risk assessments by clinicians and patients.

## 2.1 Study Design and Patients

This analysis includes data from six phase 3 RCTs of dupilumab for treatment of uncontrolled moderate-to-severe AD in patients aged from 6 months through to adults and two phase 3 OLE trials (Fig. 1 of the Electronic Supplementary Material [ESM]) [17, 19, 20, 23, 24, 26–28]. Detailed methodology, baseline characteristics, efficacy, and safety results were reported previously; dose regimens and sample sizes are shown in Fig. 1 of the ESM.

Two OLEs were included in this analysis (Fig. 1 of the ESM). LIBERTY AD OLE (NCT01949311) enrolled adults (aged  $\geq 18$  years) from all phase 1–3 trials of dupilumab for AD who had adequately completed the required parent study assessments or were screened for phase 3 studies but were not randomized owing to randomization closure. The present analyses included patients who participated for up to approximately 5 years of treatment (data cutoff: 27 June 2022) [25]. LIBERTY AD PED-OLE (NCT02612454) included pediatric patients who had participated in a prior dupilumab study for AD. The present analyses included two cohorts who participated up to approximately 1 year: adolescents (aged 12–17 years) who had previously participated in R668-AD-1607 (NCT03050151), R668-AD-1412 (NCT02407756), or LIBERTY AD ADOL (NCT03054428) [23] (PED-OLE data cutoff: 15 December 2018); and children (aged 6–11 years) who had previously participated in LIBERTY AD PEDS (NCT03345914) (PED-OLE data cutoff: 1 July 2020) [24].

All trials were conducted in accordance with the Declaration of Helsinki, the International Conference on Harmonisation Good Clinical Practice guideline, and applicable regulatory requirements. Independent data and safety monitoring committees conducted blinded monitoring of patient safety data. The local institutional review boards or ethics committees at each study center oversaw trial conduct and documentation. For each trial, all patients or their parents/guardians provided written informed consent before participating in the trial. Written informed consent was obtained from all patients and the patients' parents/guardians prior to commencement of any study treatment.

## 2.2 Analysis Datasets

Patients who received  $\geq 1$  dose of dupilumab or placebo, either as monotherapy or with concomitant TCS, were included. Data from the 16-week monotherapy RCTs in adults (aged  $\geq 18$  years; LIBERTY

AD [NCT02211709]) and adolescents were pooled into dupilumab 200/300 mg every 2 weeks (q2w), dupilumab 300 mg once weekly (qw), and placebo cohorts (Fig. 1 of the ESM). The adult 52-week RCT + TCS (LIBERTY AD CHRONOS; NCT02260986) is reported separately (Fig. 1 of the ESM). Data from two 16-week RCTs + TCS in children and infants (LIBERTY AD PEDS [NCT03345914], aged 6–11 years; and LIBERTY AD PRESCHOOL Part B [NCT03346434], aged 0.5–5 years) were pooled into dupilumab (200/300 mg every 4 weeks [q4w] or 200 mg q2w) + TCS and placebo + TCS cohorts (Fig. 1 of the ESM). Exposure-adjusted incidence rates (EAIRs) were calculated as the number of patients per 100 patient-years (nP/100PY) in adult OLE and for each of the cohorts (adolescents and children) in PED-OLE.

## 2.3 Adverse Event Collection and Coding

Treatment-emergent adverse events (TEAEs) and treatment-emergent serious adverse events (TE-SAEs) were coded using the Medical Dictionary for Regulatory Activities (MedDRA). TE-SAEs were defined as any untoward medical occurrence that was fatal or life-threatening, required hospitalization or prolonged existing hospitalization, caused persistent or significant disability/incapacity, was a congenital anomaly/birth defect, or was deemed an important medical event by the investigator [29]. Severity was investigator-assessed as mild, moderate, or severe. TEAEs were graded as severe by investigators if they produced significant impairment of functioning or incapacitation and were a definite hazard to the patient's health; treatment for symptoms may have been given and/or the patient may have been hospitalized.

Prespecified clusters of MedDRA Preferred Terms (PTs) used in this analysis (conjunctivitis cluster, keratitis cluster, **I**minthic infections MedDRA High Level Group Term [HLGT], anaphylactic reactions cluster, and upper respiratory tract infections cluster) are summarized in Table 1 of the ESM.

## 2.4 Statistical Analysis

All analyses were performed using the safety dataset from each study, which included all patients receiving  $\geq 1$  dose of study drug, as treated. All values were reported using descriptive statistics, and analyses were performed using SAS<sup>®</sup> version 9.4 or higher. Events were reported either as the number and percent of patients reporting  $\geq 1$  event or as the nP with  $\geq 1$  event per 100 PY to account for differences in exposure between trials.



### 3.1 Patient Exposure and Demographics

This analysis includes 3882 dupilumab-treated patients (including patients enrolled in the OLEs who had been previously treated with placebo in the parent RCT), with an overall total exposure of > 7000 patient-years. Baseline characteristics and demographics were balanced across study treatment groups and the pooled analysis cohorts (Tables 1 and 2; Table 2 of the ESM). The longest recorded exposure was 1938 days, which was achieved by one patient in the adult OLE.

### 3.2 Overall Safety Profile

The proportions of patients with  $\geq 1$  TEAE were similar or lower in dupilumab-treated patients than in patients receiving placebo (Table 3). In the 16-week RCTs, 67.5% (dupilumab 300 mg qw), 69.5% (dupilumab 200/300 mg q2w), and 68.9% (placebo) of adults/adolescents experienced  $\geq 1$  TEAE; among children/infants, 64.0% (dupilumab + TCS) and 73.7% (placebo + TCS) experienced  $\geq 1$  TEAE. In the 52-week RCT in adults (CHRONOS), 83.5% (dupilumab 300 mg qw + TCS), 88.2% (dupilumab 300 mg q2w + TCS), and 85.1% (placebo + TCS) of patients experienced  $\geq 1$  TEAE (Table 3). In the adult OLE, 166.0 nP/100PY experienced  $\geq 1$  TEAE during up to 5 years of treatment, which was numerically lower than EAIRs observed in the 52-week RCT (325.1, 322.4, and 378.5 nP/100PY for placebo + TCS, dupilumab 300 mg qw + TCS, and dupilumab 300 mg q2w + TCS groups, respectively; Table 4), suggesting that longer exposure to dupilumab does not increase the incidence of TEAEs. In the PED-OLE, the overall incidence of TEAEs was similar to those reported in the respective parent studies (Tables 3 and 4 of the ESM).

TEAEs leading to discontinuation of study drug were infrequent and occurred at similar rates among the dupilumab and placebo groups in the 16-week trials (< 2% of patients). In the 52-week RCT, TEAEs leading to treatment discontinuation were more frequent in the placebo (7.9%) vs dupilumab groups (qw, 2.9%; q2w, 1.8%; Table 3). In the adult OLE, the EAIR of TEAEs that led to treatment discontinuation (1.7 nP/100PY) was lower than EAIRs in the 52-week RCT (8.3, 2.6, and 2.5 nP/100PY for placebo + TCS, dupilumab 300 mg + TCS, and dupilumab 300 mg q2w + TCS groups, respectively; Table 4). In the PED-OLE, the EAIRs of TEAEs leading to treatment discontinuation were 0.7 and 0.7 nP/100PY in children and adolescents, respectively (Tables 3 and 4 of the ESM).

In all six RCTs, TE-SAEs occurred in a higher proportion of patients receiving placebo than dupilumab, including 4.6% of adults/adolescents receiving placebo vs 2.0–2.2% dupilumab-treated adults/adolescents and 0.8% of infants/children treated with dupilumab + TCS vs 3.0% of those in the placebo + TCS arm (Table 3). In the 16-week RCTs, no TE-SAEs were reported in  $\geq 2$  dupilumab-treated patients. TE-SAEs occurring in  $\geq 2$  patients receiving placebo were reported only in the adult/adolescent 16-week RCT (0.4–0.7%; Table 5 of the ESM). In the 52-week RCT, TE-SAEs were more frequent with placebo + TCS (5.1%) than dupilumab + TCS (3.2–3.6%), and no TE-SAE PTs in the dupilumab arm were reported in > 1 patient (Table 3; Table 5 of the ESM).

In the adult OLE, EAIRs of TE-SAEs at 5 years were similar to those in the 52-week RCT (Table 4). In the PED-OLE, EAIRs of TE-SAEs were 3.7 and 1.7 nP/100PY in children and adolescents, respectively (Table 4 of the ESM). In both the adult OLE and the PED-OLE, there was no discernable pattern to the TE-SAE PTs (data not shown).

One patient in OLE who had received placebo in the parent studies had a TE-SAE of serum sickness after two doses of dupilumab 300 mg qw, which was considered related (Table 4). Symptoms included joint pain, fever, tachycardia, headache, hives, and weakness; signs included sinus tachycardia, rash, trace edema in the lower extremities, and swelling of the joints of the fingers, hands, and wrists. This patient had high titers of anti-dupilumab antibodies and discontinued dupilumab after this event.

No anaphylactic reactions (narrow Standardized MedDRA Query [SMQ]) were reported in the RCTs (Table 3). Seven cases (0.1 nP/100PY) of anaphylactic reactions were reported in the adult OLE, seven cases were reported in children, and none were reported in adolescents (Table 4; Tables 3 and 4 of the ESM). None of the cases of anaphylactic reaction in the adult or pediatric OLEs were considered related to dupilumab; most were considered related to food allergies.

Two cases of cutaneous T-cell lymphoma (CTCL) were reported throughout all studies: one patient receiving placebo + TCS during the adult 52-week RCT and one patient receiving dupilumab 300 mg qw in the adult OLE, which were considered unrelated to study drug (Tables 3 and 4; Supplementary Material: Patient Narratives of the ESM).

Five deaths were reported throughout all studies: one patient receiving dupilumab 300 mg qw during LIBERTY AD SOLO 2 (an event of suicide 8 days after the most recent dose of study drug), one patient receiving dupilumab 300 mg qw + TCS in the 52-week RCT (motor vehicle accident), and three patients receiving dupilumab 300 mg qw in the adult OLE (one due to natural causes and two due to

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|                                                  | Adults (SOLO 1 and 2) and adolescents (ADOL; 12 years and over), 16-week RCTs |                                       |                                            | Adults (CHRONOS), 52-week RCT   |                                             |                                              | B O I S<br>Infants and children (PEDS, PRE-SCHOOL; 6 months to 11 years), 16-week RCTs |                                                                   |
|--------------------------------------------------|-------------------------------------------------------------------------------|---------------------------------------|--------------------------------------------|---------------------------------|---------------------------------------------|----------------------------------------------|----------------------------------------------------------------------------------------|-------------------------------------------------------------------|
|                                                  | Placebo ( <i>n</i> = 541)                                                     | Dupilumab 300 mg qw ( <i>n</i> = 455) | Dupilumab 200/300 mg q2w ( <i>n</i> = 547) | Placebo + TCS ( <i>n</i> = 315) | Dupilumab 300 mg qw + TCS ( <i>n</i> = 315) | Dupilumab 300 mg q2w + TCS ( <i>n</i> = 110) | Placebo + TCS ( <i>n</i> = 198)                                                        | Dupilumab 200/300 q4w + TCS or 200 mg q2w + TCS ( <i>n</i> = 261) |
| Age, years, mean (SD)                            | 34.6 (15.6)                                                                   | 38.2 (14.5)                           | 34.8 (15.8)                                | 36.6 (13.0)                     | 36.9 (13.7)                                 | 39.4 (14.0)                                  | 6.6 (2.7)                                                                              | 7.3 (2.8)                                                         |
| Age group, <i>n</i> (%)                          |                                                                               |                                       |                                            |                                 |                                             |                                              |                                                                                        |                                                                   |
| 6 months–11 years                                | n/a                                                                           | n/a                                   | n/a                                        | n/a                             | n/a                                         | n/a                                          | 198 (100)                                                                              | 261 (100)                                                         |
| 12–17 years                                      | 85 (15.7)                                                                     | n/a                                   | 82 (15.0)                                  | n/a                             | n/a                                         | n/a                                          | n/a                                                                                    | n/a                                                               |
| 18–59 years                                      | 424 (78.4)                                                                    | 417 (91.6)                            | 425 (77.7)                                 | 297 (94.3)                      | 290 (92.1)                                  | 99 (90.0)                                    | n/a                                                                                    | n/a                                                               |
| ≥ 60 years                                       | 32 (5.9)                                                                      | 38 (8.4)                              | 40 (7.3)                                   | 18 (5.7)                        | 25 (7.9)                                    | 11 (10.0)                                    | n/a                                                                                    | n/a                                                               |
| Duration of AD, years, mean (SD)                 | 26.2 (14.6)                                                                   | 27.7 (15.4)                           | 25.5 (15.1)                                | 27.5 (14.3)                     | 27.8 (14.5)                                 | 30.2 (15.4)                                  | 5.7 (2.6)                                                                              | 6.2 (2.9)                                                         |
| Sex, male, <i>n</i> (%)                          | 302 (55.8)                                                                    | 275 (60.4)                            | 316 (57.8)                                 | 193 (61.3)                      | 190 (60.3)                                  | 63 (57.3)                                    | 114 (57.6)                                                                             | 132 (50.6)                                                        |
| Race, <i>n</i> (%)                               |                                                                               |                                       |                                            |                                 |                                             |                                              |                                                                                        |                                                                   |
| White                                            | 349 (64.5)                                                                    | 312 (68.6)                            | 379 (69.3)                                 | 208 (66.0)                      | 205 (65.1)                                  | 77 (70.0)                                    | 127 (64.1)                                                                             | 189 (72.4)                                                        |
| Black or African American                        | 49 (9.1)                                                                      | 34 (7.5)                              | 32 (5.9)                                   | 19 (6.0)                        | 13 (4.1)                                    | 2 (1.8)                                      | 38 (19.2)                                                                              | 41 (15.7)                                                         |
| Asian                                            | 118 (21.8)                                                                    | 95 (20.9)                             | 111 (20.3)                                 | 83 (26.3)                       | 89 (28.3)                                   | 29 (26.4)                                    | 17 (8.6)                                                                               | 15 (5.7)                                                          |
| Other/not reported                               | 25 (4.6)                                                                      | 14 (3.1)                              | 25 (4.6)                                   | 5 (1.6)                         | 8 (2.5)                                     | 2 (1.8)                                      | 16 (8.1)                                                                               | 16 (6.1)                                                          |
| Weight, kg, mean (SD)                            | 74.3 (19.3)                                                                   | 77.5 (18.9)                           | 75.3 (19.8)                                | 75.0 (18.6)                     | 74.5 (17.7)                                 | 73.0 (17.5)                                  | 25.6 (11.3)                                                                            | 28.6 (12.0)                                                       |
| EASI (range 0–72), mean (SD)                     | 34.4 (14.3)                                                                   | 32.6 (13.3)                           | 32.6 (13.5)                                | 32.6 (12.9)                     | 32.1 (12.7)                                 | 33.5 (13.4)                                  | 36.7 (12.3)                                                                            | 36.5 (12.7)                                                       |
| IGA (range 0–4), <i>n</i> (%)                    |                                                                               |                                       |                                            |                                 |                                             |                                              |                                                                                        |                                                                   |
| 2                                                | 0                                                                             | 0                                     | 0                                          | 0                               | 1 (0.3)                                     | 0                                            | 0                                                                                      | 0                                                                 |
| 3                                                | 270 (49.9)                                                                    | 239 (52.5)                            | 280 (51.2)                                 | 168 (53.3)                      | 168 (53.3)                                  | 56 (50.9)                                    | 17 (8.6)                                                                               | 21 (8.0)                                                          |
| 4                                                | 271 (50.1)                                                                    | 216 (47.5)                            | 267 (48.8)                                 | 147 (46.7)                      | 146 (46.3)                                  | 54 (49.1)                                    | 181 (91.4)                                                                             | 240 (92.0)                                                        |
| SCORAD score (range 0–103), mean (SD)            | 69.1 (14.2)                                                                   | 67.6 (13.3)                           | 67.5 (13.8)                                | 66.0 (13.5)                     | 65.9 (13.6)                                 | 69.0 (15.2)                                  | 72.9 (11.7)                                                                            | 73.7 (12.1)                                                       |
| Peak weekly Pruritus NRS (range 0–10), mean (SD) | 7.5 (1.8)                                                                     | 7.3 (1.9)                             | 7.4 (1.7)                                  | 7.3 (1.8)                       | 7.1 (1.9)                                   | 7.5 (1.7)                                    | 7.7 (1.5)                                                                              | 7.7 (1.4)                                                         |
| POEM (range 0–28), mean (SD)                     | 20.7 (5.8)                                                                    | 20.6 (5.9)                            | 20.4 (5.8)                                 | 20.0 (6.0)                      | 20.1 (6.1)                                  | 20.4 (5.6)                                   | 21.8 (5.1)                                                                             | 21.6 (5.3)                                                        |
| DLQI/CDLQI (range 0–30), mean (SD)               | 14.8 (7.4)                                                                    | 15.1 (7.5)                            | 14.4 (7.1)                                 | 14.7 (7.4)                      | 14.4 (7.2)                                  | 14.7 (7.3)                                   | 15.5 (7.2)                                                                             | 15.6 (7.1)                                                        |

AD atopic dermatitis, *CDLQI* Children’s Dermatology Life Quality Index, *DLQI* Dermatology Life Quality Index, *EASI* Eczema Area and Severity Index, *IGA* Investigator’s Global Assessment, *n/a* not applicable, *NRS* Numeric Rating Scale, *POEM* Patient-Oriented Eczema Measure, *q2w* every 2 weeks, *q4w* every 4 weeks, *qw* once weekly, *RCT* randomized clinical trial, *SCORAD* SCORing Atopic Dermatitis, *SD* standard deviation, *TCS* topical corticosteroids

|                                                                              | Total patient-years | Median duration (days) | Longest exposure (days) <sup>a</sup> |
|------------------------------------------------------------------------------|---------------------|------------------------|--------------------------------------|
| RCTs                                                                         |                     |                        |                                      |
| Adults (SOLO 1 and 2) and adolescents (ADOL; 12 to < 18 years), 16-week RCTs |                     |                        |                                      |
| Placebo ( <i>n</i> = 541)                                                    | 150.5               | 112                    | 146                                  |
| Dupilumab 300 mg qw ( <i>n</i> = 455)                                        | 132.5               | 112                    | 126                                  |
| Dupilumab 200/300 mg q2w ( <i>n</i> = 547)                                   | 162.5               | 112                    | 154                                  |
| Adults (CHRONOS), 52-week RCT                                                |                     |                        |                                      |
| Placebo + TCS ( <i>n</i> = 315)                                              | 260.3               | 364                    | 370                                  |
| Dupilumab 300 mg qw + TCS ( <i>n</i> = 315)                                  | 290.1               | 364                    | 371                                  |
| Dupilumab 300 mg q2w + TCS ( <i>n</i> = 110)                                 | 98.9                | 364                    | 378                                  |
| Infants and children (PEDS, PRESCHOOL; 6 months to 11 years), 16-week RCTs   |                     |                        |                                      |
| Placebo + TCS ( <i>n</i> = 198)                                              | 59.3                | 112                    | 126                                  |
| Dupilumab 200/300 q4w + TCS or 200 mg q2w + TCS ( <i>n</i> = 261)            | 79.8                | 112                    | 134                                  |
| Total dupilumab exposure                                                     | 764.0               | 112                    | 378                                  |
| OLEs                                                                         |                     |                        |                                      |
| Adult OLE (up to 5 years) ( <i>n</i> = 2677)                                 |                     |                        |                                      |
| Total dupilumab exposure                                                     | 5389.1              | 651                    | 1938                                 |
| PED-OLE (up to 1 year)                                                       |                     |                        |                                      |
| Aged 6–11 years <sup>b</sup> ( <i>n</i> = 321)                               | 393.9               | 448                    | 743                                  |
| Aged 12–17 years <sup>c</sup> ( <i>n</i> = 294)                              | 295.4               | 308                    | 1078                                 |
| Total dupilumab exposure                                                     | 689.3               | 366                    | 1078                                 |

<sup>a</sup>For the RCTs, the longest exposure includes patients who may have had early or late visits (but still within the protocol study window) during the study treatment period. For the adult OLE, the longest exposure includes patients who received dupilumab in the parent trial, and/or may have had early or late visits during the study treatment period, and/or enrolled earlier than 4 years prior to the analysis cutoff date of 19 March 2021. For the patients aged 12–17 years enrolled in PED-OLE, the longest exposure includes patients who received dupilumab in the parent trial, and/or may have had early or late visits during the study treatment period, and/or enrolled earlier than 1 year prior to the analysis cutoff date of 15 December 2018. For the patients aged 6–11 years enrolled in PED-OLE, the longest exposure includes patients who received dupilumab in the parent trial, and/or may have had early or late visits during the study treatment period, and/or enrolled earlier than 1 year prior to the analysis cutoff date of 1 July 2020

<sup>b</sup>Parent study was PEDS

<sup>c</sup>Parent studies were R668-AD-1412 (NCT02407756), R668-AD-1607 (NCT03050151), and ADOL. Five patients with solely weight-based dosing regimens in R668-AD-1412 were excluded from this analysis

OLE open-label extension, q2w every 2 weeks, q4w every 4 weeks, qw once weekly, RCT randomized clinical trial, TCS topical corticosteroids

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unknown causes) [20, 28]. All five deaths were considered unrelated to the study drug (Tables 3 and 4; Supplementary Material: Patient Narratives of the ESM).

### 3.4 Common Adverse Events

TEAEs occurring in ≥ 5% of patients in any patient group are presented in Table 3. After 16 or 52 weeks of treatment, injection site reactions (MedDRA High Level Term [HLT]) and conjunctivitis (clustered PTs, see below) occurred more frequently in all dupilumab versus placebo recipients. Nasopharyngitis was also reported slightly more frequently at 16 weeks in dupilumab-treated patients (8.2–9.9%) vs patients receiving placebo (7.6–7.9%), but overall rates of upper respiratory tract infections (cluster term) were comparable

between treatment groups across all cohorts. Headache was reported more frequently in dupilumab-treated adolescents/ R i A than patients B eiving placebo but was less frequent in infants/children. The most common TEAEs did not lead to treatment discontinuation and were mild to moderate in severity; severe TEAEs were infrequent (Tables 6 and 7 of the ESM).

Worsening of AD was the most common TEAE in the placebo group and was more frequent than in the corresponding dupilumab groups in the 16-week RCTs (adolescents/adults: 31.2% placebo vs 13.0–14.1% dupilumab; infants/children: 21.2% placebo vs 8.0% dupilumab) and the 52-week RCT (adults: 46.7% placebo + TCS vs 17.5–20.0% dupilumab + TCS; Table 3). Adjudicated non-herpetic skin infections were also more frequent in patients receiving placebo vs

Note: For optimal accuracy, use this together with the separately extracted evidence PDFs. Highlighting may not work in some PDFs due to differences in text formatting.

| n (%)                                                     | Adults (SOLO 1 and 2) and adolescents (ADOL; aged ≥ 12 years) pooled, 16-week RCTs |                               |                                    | Adults (CHRONOS), 52-week RCT |                                     |                                      | B, O, I, Sren (PEDS, PRESCHOOL; aged 6 months to 11 years) pooled, 16-week RCTs |                                                           |
|-----------------------------------------------------------|------------------------------------------------------------------------------------|-------------------------------|------------------------------------|-------------------------------|-------------------------------------|--------------------------------------|---------------------------------------------------------------------------------|-----------------------------------------------------------|
|                                                           | Placebo (n = 541)                                                                  | Dupilumab 300 mg qw (n = 455) | Dupilumab 200/300 mg q2w (n = 547) | Placebo + TCS (n = 315)       | Dupilumab 300 mg qw + TCS (n = 315) | Dupilumab 300 mg q2w + TCS (n = 110) | Placebo + TCS (n = 198)                                                         | Dupilumab 200/300 q4w + TCS or 200 mg q2w + TCS (n = 261) |
| Overall summary                                           |                                                                                    |                               |                                    |                               |                                     |                                      |                                                                                 |                                                           |
| TEAE                                                      | 373 (68.9)                                                                         | 307 (67.5)                    | 380 (69.5)                         | 268 (85.1)                    | 263 (83.5)                          | 97 (88.2)                            | 146 (73.7)                                                                      | 167 (64.0)                                                |
| Serious TEAE                                              | 25 (4.6)                                                                           | 10 (2.2)                      | 11 (2.0)                           | 16 (5.1)                      | 10 (3.2)                            | 4 (3.6)                              | 6 (3.0)                                                                         | 2 (0.8)                                                   |
| TEAE leading to discontinuation                           | 8 (1.5)                                                                            | 7 (1.5)                       | 6 (1.1)                            | 25 (7.9)                      | 9 (2.9)                             | 2 (1.8)                              | 3 (1.5)                                                                         | 2 (0.8)                                                   |
| Severe TEAE                                               | 37 (6.8)                                                                           | 20 (4.4)                      | 20 (3.7)                           | 28 (8.9)                      | 17 (5.4)                            | 9 (8.2)                              | 17 (8.6)                                                                        | 3 (1.1)                                                   |
| TEAE leading to death                                     | 0                                                                                  | 1 (0.2) <sup>a</sup>          | 0                                  | 0                             | 1 (0.3) <sup>b</sup>                | 0                                    | 0                                                                               | 0                                                         |
| Most frequent TEAEs by PT (≥ 5% of patients in any group) |                                                                                    |                               |                                    |                               |                                     |                                      |                                                                                 |                                                           |
| Atopic dermatitis                                         | 169 (31.2)                                                                         | 59 (13.0)                     | 77 (14.1)                          | 147 (46.7)                    | 55 (17.5)                           | 22 (20.0)                            | 42 (21.2)                                                                       | 21 (8.0)                                                  |
| Injection-site reaction                                   | 29 (5.4)                                                                           | 72 (15.8)                     | 51 (9.3)                           | 25 (7.9)                      | 61 (19.4)                           | 16 (14.5)                            | 0                                                                               | 0                                                         |
| Nasopharyngitis                                           | 43 (7.9)                                                                           | 45 (9.9)                      | 45 (8.2)                           | 62 (19.7)                     | 62 (19.7)                           | 25 (22.7)                            | 15 (7.6)                                                                        | 24 (9.2)                                                  |
| Headache                                                  | 34 (6.3)                                                                           | 33 (7.3)                      | 49 (9.0)                           | 19 (6.0)                      | 25 (7.9)                            | 5 (4.5)                              | 11 (5.6)                                                                        | 13 (5.0)                                                  |
| Upper respiratory tract infection                         | 25 (4.6)                                                                           | 20 (4.4)                      | 23 (4.2)                           | 32 (10.2)                     | 43 (13.7)                           | 11 (10.0)                            | 18 (9.1)                                                                        | 23 (8.8)                                                  |
| Influenza                                                 | 6 (1.1)                                                                            | 3 (0.7)                       | 6 (1.1)                            | 16 (5.1)                      | 9 (2.9)                             | 4 (3.6)                              | 4 (2.0)                                                                         | 1 (0.4)                                                   |
| Sinusitis                                                 | 7 (1.3)                                                                            | 1 (0.2)                       | 2 (0.4)                            | 9 (2.9)                       | 18 (5.7)                            | 2 (1.8)                              | 0                                                                               | 1 (0.4)                                                   |
| Conjunctivitis allergic                                   | 7 (1.3)                                                                            | 10 (2.2)                      | 17 (3.1)                           | 15 (4.8)                      | 47 (14.9)                           | 12 (10.9)                            | 1 (0.5)                                                                         | 5 (1.9)                                                   |
| Asthma                                                    | 8 (1.5)                                                                            | 1 (0.2)                       | 9 (1.6)                            | 19 (6.0)                      | 2 (0.6)                             | 5 (4.5)                              | 17 (8.6)                                                                        | 5 (1.9)                                                   |
| Impetigo                                                  | 11 (2.0)                                                                           | 2 (0.4)                       | 5 (0.9)                            | 10 (3.2)                      | 4 (1.3)                             | 1 (0.9)                              | 11 (5.6)                                                                        | 5 (1.9)                                                   |
| Vomiting                                                  | 3 (0.6)                                                                            | 0                             | 5 (0.9)                            | 6 (1.9)                       | 4 (1.3)                             | 3 (2.7)                              | 10 (5.1)                                                                        | 10 (3.8)                                                  |
| Pyrexia                                                   | 8 (1.5)                                                                            | 5 (1.1)                       | 7 (1.3)                            | 7 (2.2)                       | 7 (2.2)                             | 4 (3.6)                              | 11 (5.6)                                                                        | 6 (2.3)                                                   |
| Cough                                                     | 7 (1.3)                                                                            | 4 (0.9)                       | 7 (1.3)                            | 8 (2.5)                       | 10 (3.2)                            | 3 (2.7)                              | 14 (7.1)                                                                        | 6 (2.3)                                                   |
| CR: A TEAEs of interest                                   |                                                                                    |                               |                                    |                               |                                     |                                      |                                                                                 |                                                           |
| Infections and infestations (SOC)                         | 176 (32.5)                                                                         | 142 (31.2)                    | 179 (32.7)                         | 182 (57.8)                    | 167 (53.0)                          | 64 (58.2)                            | 101 (51.0)                                                                      | 108 (41.4)                                                |
| Serious or severe infections                              | 11 (2.0)                                                                           | 3 (0.7)                       | 4 (0.7)                            | 6 (1.9)                       | 1 (0.3)                             | 1 (0.9)                              | 8 (4.0)                                                                         | 2 (0.8)                                                   |
| Adjudicated non-herpetic skin infections                  | 58 (10.7)                                                                          | 25 (5.5)                      | 30 (5.5)                           | 32 (10.2)                     | 12 (3.8)                            | 6 (5.5)                              | 35 (17.7)                                                                       | 22 (8.4)                                                  |

Note: For optimal accuracy, use this together with the separately extracted evidence PDFs. Highlighting may not work in some PDFs due to differences in text formatting.

| <i>n</i> (%)                                           | Adults (SOLO 1 and 2) and adolescents (ADOL; aged ≥ 12 years) pooled, 16-week RCTs |                                       |                                            | Adults (CHRONOS), 52-week RCT   |                                             |                                              | Infants and children (PEDS, PRESCHOOL; aged 6 months to 11 years) pooled, 16-week RCTs |                                                                   |
|--------------------------------------------------------|------------------------------------------------------------------------------------|---------------------------------------|--------------------------------------------|---------------------------------|---------------------------------------------|----------------------------------------------|----------------------------------------------------------------------------------------|-------------------------------------------------------------------|
|                                                        | Placebo ( <i>n</i> = 541)                                                          | Dupilumab 300 mg qw ( <i>n</i> = 455) | Dupilumab 200/300 mg q2w ( <i>n</i> = 547) | Placebo + TCS ( <i>n</i> = 315) | Dupilumab 300 mg qw + TCS ( <i>n</i> = 315) | Dupilumab 300 mg q2w + TCS ( <i>n</i> = 110) | Placebo + TCS ( <i>n</i> = 198)                                                        | Dupilumab 200/300 q4w + TCS or 200 mg q2w + TCS ( <i>n</i> = 261) |
| Molluscum contagiosum                                  | 2 (0.4)                                                                            | 3 (0.7)                               | 1 (0.2)                                    | 1 (0.3)                         | 5 (1.6)                                     | 1 (0.9)                                      | 3 (1.5)                                                                                | 8 (3.1)                                                           |
| Herpes viral infections (HLT)                          | 20 (3.7)                                                                           | 21 (4.6)                              | 26 (4.8)                                   | 25 (7.9)                        | 22 (7.0)                                    | 8 (7.3)                                      | 10 (5.1)                                                                               | 8 (3.1)                                                           |
| Eczema herpeticum (PT)                                 | 4 (0.7)                                                                            | 1 (0.2)                               | 3 (0.5)                                    | 6 (1.9)                         | 0                                           | 1 (0.9)                                      | 1 (0.5)                                                                                | 1 (0.4)                                                           |
| Herpes zoster (PT)                                     | 2 (0.4)                                                                            | 0                                     | 1 (0.2)                                    | 5 (1.6)                         | 1 (0.3)                                     | 1 (0.9)                                      | 0                                                                                      | 1 (0.4)                                                           |
| Helminthic infections (HLGT) <sup>c</sup>              | 0                                                                                  | 0                                     | 0                                          | 0                               | 0                                           | 0                                            | 1 (0.5)                                                                                | 1 (0.4)                                                           |
| Upper respiratory tract infection cluster <sup>d</sup> | 78 (14.4)                                                                          | 68 (14.9)                             | 80 (14.6)                                  | 108 (34.3)                      | 118 (37.5)                                  | 39 (35.5)                                    | 44 (22.2)                                                                              | 51 (19.5)                                                         |
| Injection-site reactions (HLT)                         | 36 (6.7)                                                                           | 76 (16.7)                             | 64 (11.7)                                  | 25 (7.9)                        | 63 (20.0)                                   | 18 (16.4)                                    | 9 (4.5)                                                                                | 22 (8.4)                                                          |
| Ocular TEAEs <sup>e</sup>                              |                                                                                    |                                       |                                            |                                 |                                             |                                              |                                                                                        |                                                                   |
| Conjunctivitis cluster <sup>f</sup>                    | 14 (2.6)                                                                           | 33 (7.3)                              | 53 (9.7)                                   | 25 (7.9)                        | 63 (20.0)                                   | 15 (13.6)                                    | 5 (2.5)                                                                                | 17 (6.5)                                                          |
| Keratitis cluster <sup>g</sup>                         | 0                                                                                  | 4 (0.9)                               | 0                                          | 4 (1.3)                         | 6 (1.9)                                     | 4 (3.6)                                      | 0                                                                                      | 1 (0.4)                                                           |
| Blepharitis (PT)                                       | 1 (0.2)                                                                            | 4 (0.9)                               | 2 (0.4)                                    | 3 (1.0)                         | 11 (3.5)                                    | 6 (5.5)                                      | 2 (1.0)                                                                                | 2 (0.8)                                                           |
| Eye pruritus (PT)                                      | 1 (0.2)                                                                            | 2 (0.4)                               | 3 (0.5)                                    | 4 (1.3)                         | 14 (4.4)                                    | 4 (3.6)                                      | 1 (0.5)                                                                                | 2 (0.8)                                                           |
| Dry eye (PT)                                           | 0                                                                                  | 4 (0.9)                               | 1 (0.2)                                    | 4 (1.3)                         | 6 (1.9)                                     | 3 (2.7)                                      | 1 (0.5)                                                                                | 1 (0.4)                                                           |
| Ectropion (PT)                                         | 1 (0.2)                                                                            | 0                                     | 0                                          | 0                               | 2 (0.6)                                     | 1 (0.9)                                      | 0                                                                                      | 0                                                                 |
| Entropion (PT)                                         | 0                                                                                  | 0                                     | 0                                          | 0                               | 0                                           | 0                                            | 0                                                                                      | 0                                                                 |
| Pharyngitis (PT)                                       | 9 (1.7)                                                                            | 3 (0.7)                               | 13 (2.4)                                   | 15 (4.8)                        | 10 (3.2)                                    | 5 (4.5)                                      | 0                                                                                      | 1 (0.4)                                                           |
| Anaphylactic reaction (narrow SMQ) <sup>h</sup>        | 0                                                                                  | 0                                     | 0                                          | 0                               | 0                                           | 0                                            | 0                                                                                      | 0                                                                 |





Note: For optimal accuracy, use this together with the separately extracted evidence PDFs. Highlighting may not work in some PDFs due to differences in text formatting.

| n (%)                                            | Adults (SOLO 1 and 2) and adolescents (ADOL; aged ≥ 12 years) pooled, 16-week RCTs |                               |                                    | Adults (CHRONOS), 52-week RCT |                                     |                                      | B O I S ren (PEDS, PRESCHOOL; aged 6 months to 11 years) pooled, 16-week RCTs |                                                           |
|--------------------------------------------------|------------------------------------------------------------------------------------|-------------------------------|------------------------------------|-------------------------------|-------------------------------------|--------------------------------------|-------------------------------------------------------------------------------|-----------------------------------------------------------|
|                                                  | Placebo (n = 541)                                                                  | Dupilumab 300 mg qw (n = 455) | Dupilumab 200/300 mg q2w (n = 547) | Placebo + TCS (n = 315)       | Dupilumab 300 mg qw + TCS (n = 315) | Dupilumab 300 mg q2w + TCS (n = 110) | Placebo + TCS (n = 198)                                                       | Dupilumab 200/300 q4w + TCS or 200 mg q2w + TCS (n = 261) |
| Anaphylactic reaction (related) <sup>i</sup>     | 0                                                                                  | 0                             | 0                                  | 0                             | 0                                   | 0                                    | 0                                                                             | 0                                                         |
| Serum sickness/serum sickness-like reaction (PT) | 0                                                                                  | 0                             | 0                                  | 0                             | 0                                   | 0                                    | 0                                                                             | 0                                                         |
| CTCL                                             | 0                                                                                  | 0                             | 0                                  | 1 (0.3)                       | 0                                   | 0                                    | 0                                                                             | 0                                                         |

The following MedDRA versions were used for each study: 18.0 (SOLO 1 and 2, CHRONOS); 20.1 (ADOL); 22.0 (PEDS); and 23.1 (PRESCHOOL)

CTCL cutaneous T-cell lymphoma, HLGHT MedDRA High Level Group Term, HLT MedDRA High Level Term, MedDRA Medical Dictionary for Regulatory Activities, NEC not elsewhere classified, PT MedDRA Preferred Term, q2w every 2 weeks, q4w every 4 weeks, qw once weekly, RCT randomized clinical trial, SMQ Standardized MedDRA Query, SOC MedDRA System Organ Class, TCS topical corticosteroids, TEAE treatment-emergent adverse event

<sup>a</sup>Death was due to suicide 8 days after the most recent dose of dupilumab 300 mg qw. The event occurred on study day 93 and the most recent prior dose was on study day 85; at that time, the patient had received 13 doses. This event was deemed by the investigator to be unrelated to study drug (Supplementary Material: Patient Narratives of the ESM)

<sup>b</sup>Death was due to a motor vehicle accident and was deemed by the investigator to be unrelated to study drug (Supplementary Material: Patient Narratives of the ESM)

<sup>c</sup>Includes all PTs under four MedDRA HLTs: cestode infections; helminthic infections NEC; nematode infections; and trematode infections

<sup>d</sup>Upper respiratory tract infection cluster includes the MedDRA PTs: upper respiratory tract infection; nasopharyngitis; pharyngitis streptococcal; viral upper respiratory tract infection; rhinitis; and sinusitis

<sup>e</sup>Ocular TEAEs include selected clusters and PTs of interest

<sup>f</sup>Conjunctivitis cluster includes all MedDRA PTs that include the term “conjunctivitis,” including conjunctivitis, allergic conjunctivitis, bacterial conjunctivitis, viral conjunctivitis, giant papillary conjunctivitis, adenoviral conjunctivitis, chlamydial conjunctivitis, non-infective conjunctivitis, B O al keratoconjunctivitis, and atopic keratoconjunctivitis

<sup>g</sup>Keratitis cluster includes all MedDRA PTs that include the term “keratitis,” including keratitis, ulcerative keratitis, allergic keratitis, viral keratitis, punctate keratitis, bacterial keratitis, and acanthamoeba keratitis

<sup>h</sup>Anaphylactic reaction narrow SMQ includes the PTs: anaphylactic reaction; anaphylactic shock; anaphylactic transfusion reaction; anaphylactoid reaction; anaphylactoid shock; circulatory collapse; dialysis membrane reaction; Kounis syndrome; procedural shock; shock; shock symptoms; and type 1 hypersensitivity

<sup>i</sup>Assessed as causally related to treatment by investigator

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dupilumab in the RCTs (Table 3). In addition, asthma as a TEAE was more common in infants/children receiving placebo versus dupilumab (8.6% placebo + TCS vs 1.9% Dupilumab + TCS), whereas the incidence of asthma TEAEs was similar for adults in placebo vs dupilumab groups (Table 3).

infants/children in placebo + TCS groups (51.0%) than dupilumab + TCS groups (41.4%), while the proportions in adolescents/adults were similar across treatment groups (Table 3). The EAIR of infections and infestations (70.7 nP/100PY) was numerically lower in the adult OLE than that in the 52-week RCT (placebo + TCS: 107.0 nP/100PY; dupilumab qw + TCS: 93.7 nP/100PY; dupilumab q2w + TCS: 102.8 nP/100PY; Table 4). In the PED-OLE, the EAIR of infections and infestations was similar in the child and adolescent cohorts (75.5 and 83.4 nP/100PY, respectively; Table 4 of the ESM). Serious and severe infections were infrequent in all age groups in the

3.5 Infections and Skin Infections

The proportion of patients in the RCTs with a TEAE in the MedDRA System Organ Class (SOC) category “Infections and Infestations” was numerically greater among

Note: For optimal accuracy, use this together with the separately extracted evidence PDFs. Highlighting may not work in some PDFs due to differences in text formatting.

| Exposure adjusted event rates, nP/100PY                | Overall Summary (n = 2677) | CHRONOS, 52-week RCT    |                                     |                                      |
|--------------------------------------------------------|----------------------------|-------------------------|-------------------------------------|--------------------------------------|
|                                                        |                            | Placebo + TCS (n = 315) | Dupilumab 300 mg qw + TCS (n = 315) | Dupilumab 300 mg q2w + TCS (n = 110) |
| Overall summary                                        |                            |                         |                                     |                                      |
| Serious TEAE                                           | 166.0                      | 325.1                   | 322.4                               | 378.5                                |
| TEAE leading to discontinuation                        | 5.2                        | 5.8                     | 3.4                                 | 4.0                                  |
| Severe TEAE                                            | 1.7                        | 8.3                     | 2.6                                 | 2.5                                  |
| TEAE leading to death                                  | 5.0                        | 10.3                    | 5.9                                 | 9.2                                  |
| Other TEAEs of interest                                | 0.05 <sup>b</sup>          | 0                       | 0.3 <sup>c</sup>                    | 0                                    |
| Infections and infestations (SOC)                      | 70.7                       | 107.0                   | 93.7                                | 102.8                                |
| Serious or severe infections                           | 1.4                        | 2.1                     | 0.3                                 | 1.0                                  |
| Adjudicated non-herpetic skin infections               | 4.6                        | 12.0                    | 4.1                                 | 6.1                                  |
| Molluscum contagiosum                                  | 0                          | 0.4                     | 1.7                                 | 1.0                                  |
| Herpes viral infections (HLT)                          | 6.6                        | 9.2                     | 7.7                                 | 8.2                                  |
| Eczema herpeticum (PT)                                 | 0.2                        | 2.1                     | 0                                   | 1.0                                  |
| Herpes zoster (PT)                                     | 1.0                        | 1.8                     | 0.3                                 | 1.0                                  |
| Helminthic infections (HLGT) <sup>d</sup>              | 0.02                       | 0                       | 0                                   | 0                                    |
| Upper respiratory tract infection cluster <sup>e</sup> | 33.4                       | 48.5                    | 54.3                                | 50.7                                 |
| Injection-site reactions (HLT)                         | 4.9                        | 9.4                     | 25.5                                | 20.1                                 |
| Ocular TEAEs <sup>f</sup>                              |                            |                         |                                     |                                      |
| Conjunctivitis cluster <sup>g</sup>                    | 11.4                       | 9.2                     | 24.3                                | 16.1                                 |
| Keratitis cluster <sup>h</sup>                         | 1.0                        | 1.4                     | 2.0                                 | 4.0                                  |
| Blepharitis (PT)                                       | 1.6                        | 1.1                     | 3.8                                 | 6.1                                  |
| Eye pruritus (PT)                                      | 0.6                        | 1.4                     | 4.9                                 | 4.0                                  |
| Dry eye (PT)                                           | 1.3                        | 1.4                     | 2.0                                 | 3.0                                  |
| Ectropion                                              | 0.2                        | 0                       | 0.7                                 | 1.0                                  |
| Entropion                                              | 0.04                       | 0                       | 0                                   | 0                                    |
| Arthralgia (PT)                                        | 1.6                        | 5.4                     | 3.4                                 | 5.0                                  |
| Anaphylactic reaction (narrow SMQ) <sup>i</sup>        | 0.1                        | 0                       | 0                                   | 0                                    |
| Anaphylactic reaction (related) <sup>j</sup>           | 0.02                       | 0                       | 0                                   | 0                                    |
| Serum sickness/serum sickness-like reaction (PT)       | 0.02                       | 0                       | 0                                   | 0                                    |
| CTCL                                                   | 0.02                       | 0.4                     | 0                                   | 0                                    |

MedDRA version 18.0 was used for the adult OLE and CHRONOS studies

R A utaneous T-cell lymphoma, *HLGT* MedDRA High Level Group Term, *HLT* MedDRA High Level Term, *MedDRA* Medical Dictionary for Regulatory Activities, *NEC* not elsewhere classified, *nP* number of patients, *OLE* open-label extension, *PT* MedDRA Preferred Term, *PY* Patient-years, *q2w* every 2 weeks, *qw* once weekly, *RCT* randomized clinical trial, *SMQ* Standardized MedDRA Query, *SOC* MedDRA System Organ Class, *TCS* topical corticosteroids, *TEAE* treatment-emergent adverse event

<sup>a</sup>This dataset includes nine patients who received dupilumab 200 mg qw early in the study and withdrew before the protocol was amended to the 300 mg qw regimen

<sup>b</sup>Three patients died in OLE over the 5-year period included in this analysis. One death was due to natural causes in an 88-year-old female, one was due to unknown causes in a 58-year-old female approximately 5 months after the final dose of study drug, and one was due to unknown causes in a 42-year-old male (Supplementary Material: Patient Narratives of the ESM)

<sup>c</sup>One patient died in CHRONOS. This death was due to a motor vehicle accident and was deemed by the investigator to be unrelated to study drug (Supplementary Material: Patient Narratives of the ESM)

<sup>d</sup>The helminthic infections HLGT includes all MedDRA PTs under four MedDRA HLTs: cestode infections; helminthic infections NEC; nematode infections; and trematode infections

<sup>e</sup>The upper respiratory tract infection cluster includes the MedDRA PTs: upper respiratory tract infection; nasopharyngitis; pharyngitis streptococcal; viral upper respiratory tract infection; rhinitis; and sinusitis

<sup>f</sup>Ocular TEAEs included selected clusters and PTs of interest

<sup>g</sup>Conjunctivitis cluster includes all MedDRA PTs that include the term “conjunctivitis,” including conjunctivitis, allergic conjunctivitis, bacterial conjunctivitis, viral conjunctivitis, giant papillary conjunctivitis, adenoviral conjunctivitis, chlamydial conjunctivitis, non-infective conjunctivi-

tis, vernal keratoconjunctivitis, and atopic keratoconjunctivitis

**I** keratitis cluster includes all MedDRA PTs that include the term “keratitis,” including keratitis, ulcerative keratitis, allergic keratitis, viral keratitis, punctate keratitis, bacterial keratitis and acanthamoeba keratitis

<sup>i</sup> Anaphylactic reaction narrow SMQ includes the PTs: anaphylactic reaction; anaphylactic shock; anaphylactic transfusion reaction; anaphylactoid reaction; anaphylactoid shock; circulatory collapse; dialysis membrane reaction; Kounis syndrome; procedural shock; shock; shock symptoms; and type 1 hypersensitivity

<sup>j</sup> Assessed as causally related to treatment by investigator

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RCTs and OLEs (Tables 3 and 4; Tables 3 and 4 of the ESM). EAIRs of serious/severe infections were similar in the adult OLE and the 52-week RCT (Table 4).

Adjudicated non-herpetic skin infections occurred in a higher proportion of patients receiving placebo than dupilumab in all age groups (Table 3). EAIRs of adjudicated non-herpetic skin infections were similar in the adult OLE and in dupilumab-treated patients in the 52-week RCT (4.6 and 4.1–6.1 nP/100PY, respectively; Table 4), while EAIRs in the PED-OLE for the child and adolescent cohorts were 10.9 and 8.5 nP/100PY, respectively (Table 4 of the ESM).

In the 16-week RCTs, the incidence of herpes viral infections (MedDRA HLT) was slightly lower in infants/children in dupilumab versus placebo groups, but rates in adolescents were slightly higher in dupilumab versus placebo groups (Table 3). In contrast, herpes viral infections in the 52-week RCT occurred at similar rates across treatment groups. In the adult OLE, the EAIR of herpes viral infections at 5 years was lower than in dupilumab-treated patients in the 52-week RCT (6.6 vs 7.7–8.2 nP/100PY; Table 4). The MedDRA PTs eczema herpeticum and herpes zoster each occurred in < 1% of patients in the 16-week RCTs and were less frequent in dupilumab-treated patients than in patients receiving placebo across all ages (Table 3). In the 16-week RCT, these infections were more frequent in the placebo + TCS group (1.9% and 1.6% of patients, respectively) than in the dupilumab + TCS groups (< 1%; Table 3). In the adult OLE and PED-OLE, eczema herpeticum rates were low and similar to the respective age groups in the comparable RCTs, while herpes zoster EAIRs were higher in the adult OLE than in the 52-week RCT (Table 4; Tables 3 and 4 of the ESM). In the few dupilumab-treated patients who developed eczema herpeticum, these events resolved during treatment and did not lead to treatment discontinuation or hospitalization.

Helminthic infections were infrequent overall and were more frequent in children than adults; no events were severe or serious (Table 3). Among infants and children, one case of ascariasis in the dupilumab group and one case of enterobiasis (pinworm) in the placebo group were reported in the infant/child 16-week RCTs; none were reported in the adult RCTs (Table 3). In PED-OLE, EAIRs of helminthic infections were 1.7 and 0.3 nP/100PY in children and

adolescents, respectively (Table 4 of the ESM). In the adult OLE, one case (ascariasis: 0.02 nP/100PY) was reported (Table 4).

### 3.6 Ocular TEAEs

In the 16- and 52-week RCTs, events in the conjunctivitis cluster (i.e., the cluster of MedDRA PTs with the word “conjunctivitis” in the term; Table 1 of the ESM) occurred at a higher rate with dupilumab treatment than placebo in all age groups (Tables 3 and 4; Table 8 of the ESM; Fig. 1). Most cases of conjunctivitis were mild or moderate in severity and resolved or were resolving by the end of the treatment period. In the RCTs, no severe conjunctivitis was reported in dupilumab-treated infants/children; among adolescents/adults, severe conjunctivitis was reported in ≤ 0.6% of dupilumab-treated patients and ≤ 0.3% of patients receiving placebo (Fig. 1). Two cases of conjunctivitis led to treatment discontinuation: one case of allergic conjunctivitis in an adult in the 300-mg qw group in SOLO 1 and one case of bacterial conjunctivitis in a child in the dupilumab q2w + TCS group in PEDS.

The EAIRs for the conjunctivitis cluster in the adult OLE were numerically lower than those in the 52-week RCT (Table 4). In the adult OLE, most conjunctivitis cases were mild or moderate, did not lead to discontinuation, and were resolved or resolving by the end of treatment; 27 of 541 (5.40%) cases were severe. In PED-OLE, EAIRs for conjunctivitis cluster events were 13.1 and 10.7 nP/100PY in children and adolescents, respectively (Table 4 of the ESM). Two cases of conjunctivitis in PED-OLE led to treatment discontinuation: one adolescent (0.7%) with the PT conjunctivitis and one child (0.3%) with the PT conjunctivitis bacterial.

Keratitis cluster events (defined in Table 1 of the ESM) were infrequent, occurring in < 1% of dupilumab-treated patients in the 16-week trials and in ≤ 3.6% of dupilumab-treated patients in the 52-week RCT (Tables 3 and 4). Most cases were nonserious, mild or moderate, and resolved or were resolving by the end of treatment (Table 8 of the ESM; Fig. 1). EAIRs in the adult OLE were lower than those in the 16-week RCT (Table 4). One case (0.3%) in a dupilumab + TCS-treated patient in the 52-week RCT and two (0.1%) in the adult OLE led to treatment discontinuation. No events

**at 16 weeks**

**Patients with conjunctivitis (%)**

| Treatment                | Mild | Moderate | Severe | Total |
|--------------------------|------|----------|--------|-------|
| Placebo                  | 1.1  | 0.9      | 0.6    | 2.6   |
| Dupilumab 200/300 mg q2w | 5.5  | 3.7      | 0.5    | 9.7   |
| Dupilumab 300 mg qw      | 3.3  | 3.5      | 0.4    | 7.2   |

**Patients with keratitis (%)**

| Treatment                | Mild | Moderate | Severe | Total |
|--------------------------|------|----------|--------|-------|
| Placebo                  | 0    | 0        | 0      | 0     |
| Dupilumab 200/300 mg q2w | 0    | 0        | 0      | 0     |
| Dupilumab 300 mg qw      | 0.7  | 0.2      | 0      | 0.9   |

**at 32 weeks**

**Patients with conjunctivitis (%)**

| Treatment                  | Mild | Moderate | Severe | Total |
|----------------------------|------|----------|--------|-------|
| Placebo + TCS              | 4.1  | 0.3      | 0.6    | 8.0   |
| Dupilumab 300 mg q2w + TCS | 1.8  | 11.8     | 0      | 13.6  |
| Dupilumab 300 mg qw + TCS  | 10.5 | 8.9      | 0.6    | 20.0  |

**Patients with keratitis (%)**

| Treatment                  | Mild | Moderate | Severe | Total |
|----------------------------|------|----------|--------|-------|
| Placebo + TCS              | 1.3  | 0        | 0      | 1.3   |
| Dupilumab 300 mg q2w + TCS | 2.7  | 0.9      | 0      | 3.6   |
| Dupilumab 300 mg qw + TCS  | 0.2  | 1.0      | 0.6    | 1.9   |

**at 16 weeks**

**Patients with conjunctivitis (%)**

| Treatment                                                     | Mild | Moderate | Severe | Total |
|---------------------------------------------------------------|------|----------|--------|-------|
| Placebo + TCS                                                 | 2.0  | 0.5      | 0      | 2.5   |
| Dupilumab 200/300 mg q4w + TCS and dupilumab 200 mg q2w + TCS | 3.8  | 2.7      | 0      | 6.5   |

**Patients with keratitis (%)**

| Treatment                                                     | Mild | Moderate | Severe | Total |
|---------------------------------------------------------------|------|----------|--------|-------|
| Placebo + TCS                                                 | 0    | 0        | 0      | 0     |
| Dupilumab 200/300 mg q4w + TCS and dupilumab 200 mg q2w + TCS | 0.4  | 0        | 0      | 0.4   |

Regulatory Activities, *q2w* every 2 weeks, *q4w* every 4 weeks, *qw* once weekly, *RCT* randomized clinical trial, *TCS* topical corticosteroids

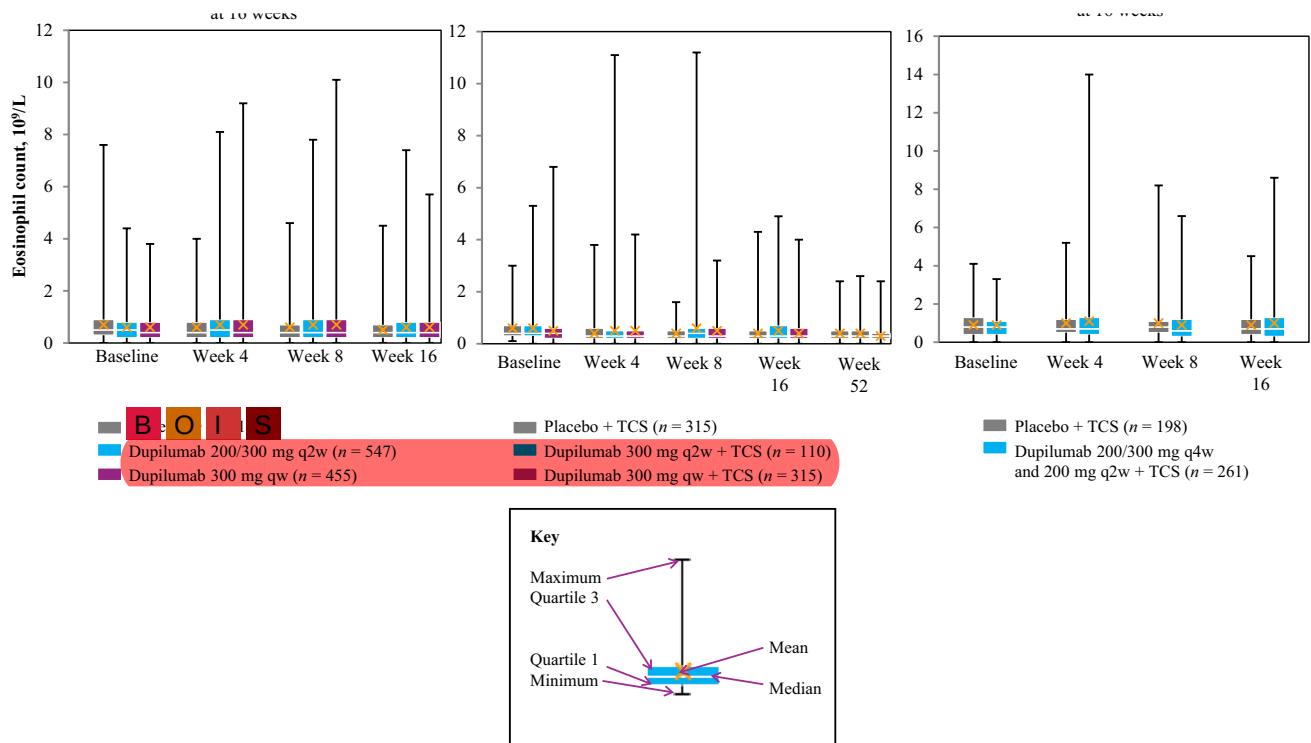
incidence in adults and adolescents in the 16- and 52-week RCTs was low and similar for patients receiving placebo and dupilumab (Table 3). In the adult OLE, EAIRs of arthralgia were lower than those in the 52-week RCT (Table 4). Most patients did not have prior history of arthralgia/arthritis.

Other ocular TEAEs, such as blepharitis, eye pruritus, Re, and ectropion, were uncommon in the infant/Adultren, adult/adolescent RCTs, and PED-OLE; incidence rates across treatment groups were fairly similar in the RCTs (Table 3; Tables 3 and 4 of the ESM). In the 52-week adult RCT, these TEAEs occurred more frequently with dupilumab + TCS treatment compared with placebo (Table 3). Incidence of these ocular TEAEs was lower in the adult OLE than in the adult 52-week RCT (Table 4).

No clinically meaningful differences were observed between the placebo and dupilumab groups in hematology, serum chemistry, or urinary analysis parameters, with the exception of lactate dehydrogenase (LDH), a marker of tissue damage, and alkaline phosphatase (ALP), a marker of bone mineralization. A greater decrease from baseline in mean values of LDH was observed in the dupilumab groups than in the placebo groups during the treatment period in all analysis populations, with a shift from above-normal baseline mean values to normal post-baseline mean values (Fig. 2 of the ESM). In infants/children in the RCTs, ALP increased slightly from baseline to week 16 in dupilumab-treated patients compared with placebo (Fig. 3 of the ESM).

In the adolescent/adult monotherapy RCTs, dupilumab **R**s associated with mild, transient increases in eosinophil counts from baseline, which declined to near baseline levels by week 16 (Fig. 2). A similar pattern was seen in the 52-week RCT, with a slight transient increase at week 8 that declined to baseline levels by week 12 [30, 31]. In the children/infants RCTs, eosinophil counts increased from

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**Fig. 2** Eosinophil counts from baseline to week 16 or 52 in dupilumab RCTs. *q2w* every 2 weeks, *q4w* every 4 weeks, *qw* once weekly, *RCT* randomized placebo-controlled clinical trial, *TCS* topical corticosteroids

baseline and remained elevated at week 16 in the dupilumab group (Fig. 2) [32]. The magnitude of the increase was **A** **B** **t**, and the median values remained within the normal range. No abnormalities in eosinophil counts were associated with clinically symptomatic events or treatment discontinuation.

In the RCTs, median platelet and neutrophil counts decreased slightly with dupilumab treatment but remained within normal ranges in all age groups (Figs. 4 and 5 of the ESM). These changes were not associated with clinically symptomatic events or treatment discontinuation.

#### 4 Discussion

This comprehensive safety analysis reports data from > 7000 patient-years of dupilumab use from infants, children, adolescents, and adults with uncontrolled moderate-to-severe AD who participated in phase 3 RCTs and OLEs in the dupilumab AD clinical trial program. Across multiple clinical trials, dupilumab with or without TCS demonstrated a short- and long-term safety profile across all age groups consistent with the known safety profile of dupilumab [16–20, 23, 24, 27, 33, 34].

Overall, 16-week dupilumab monotherapy and 16- and 52-week concomitant therapy with TCS had similar safety profiles. Safety outcomes with long-term treatment up to 5 years were generally consistent with the safety profiles in the 16-week and 52-week trials. EAIRs of TEAEs were generally similar or lower in the adult OLE at 5-year duration and the 52-week adult RCT, suggesting that longer exposure to dupilumab does not increase incidence of adverse events (AEs).

Most TEAEs were nonserious and mild to moderate in severity. Few events necessitated dupilumab discontinuation, and most patients recovered or were recovering by the end of treatment. Fewer patients receiving dupilumab versus placebo reported TEAEs, which may reflect the fact that many TEAEs in placebo groups were related to the lack of disease control [3, 35–38].

Similar rates of TEAEs overall were observed across age groups. In the RCTs, conjunctivitis, injection site reaction, herpes viral, and keratitis were less frequent in infants/children than in adolescents/adults receiving dupilumab. Rates of serious or severe infections were similarly low across age groups and had no discernable pattern.

In the present analysis, the incidence of worsening of AD, serious/severe infections, and non-herpetic skin infections was consistently greater in the placebo groups versus



that were more frequent with dupilumab than placebo included injection-site reactions and the conjunctivitis cluster. Injection-site reactions, which are commonly observed with injected protein therapeutics [39, 40], were nearly all of mild or moderate severity in this analysis.

Conjunctivitis of all etiologies and phenotypes with or without eyelid or corneal involvement was dominant among all ocular TEAEs reported in dupilumab clinical trials in AD [16–20, 23, 24, 27, 33, 34, 41, 42]. In the present analysis, conjunctivitis events were generally mild to moderate in severity, were more common with dupilumab treatment than placebo, and most cases recovered or resolved during R A O S period, consistent with previous analyses [41, 42]. The majority of conjunctivitis cases did not result in permanent discontinuation of study drug. In the adult OLE, R incidence of conjunctivitis decreased throughout the up to 5-year course of treatment [25, 28], and the EAIR of conjunctivitis was lower than in the 52-week CHRONOS trial, suggesting that conjunctivitis incidence is not increased with continued long-term dupilumab treatment. It is important to note that conjunctivitis events reported here are the sum of incidences of events for the cluster of conjunctivitis PTs (i.e., all PTs with the word “conjunctivitis” in the term [Table 1 of the ESM]), as opposed to the single PT “conjunctivitis.” Across trials, these diagnoses were made by study investigators, mainly dermatologists and allergists, and most cases were not referred for ophthalmologic or laboratory evaluation. Therefore, it can be difficult to make definitive conclusions related to the incidence of conjunctivitis compared with other therapies [41].

Ocular surface conditions are common in patients with severe AD, with incidence rates ranging from 32 to 56% [41, 43–45]. The increased incidence of conjunctivitis seen in patients with AD treated with dupilumab may reflect the increased prevalence of ocular disorders in AD, as well as interactions between dupilumab and AD [41]. Of note, keratitis cluster events were uncommon, and few events were severe or ongoing at the end of treatment. In previous analyses, higher baseline AD severity and previous history of conjunctivitis were associated with increased conjunctivitis incidence in dupilumab clinical trials in patients with AD [41, 42]. Notably, a slight increased incidence of conjunctivitis was also reported in dupilumab recipients in clinical trials in prurigo nodularis and CRSwNP [12, 46, 47] but was not observed in dupilumab trials of other type 2 inflammatory conditions such as asthma and eosinophilic esophagitis [12, 41, 42]. The pathogenesis of conjunctivitis during dupilumab treatment is still unknown. Evaluations of dupilumab-associated conjunctivitis events have been A B gated in a dedicated trial (NCT04287608), where most cases resolved with ocular local treatments and did not require dupilumab treatment discontinuation [48].

ions in dupilumab-treated patients across all age groups in this analysis. Clinically important herpetic infections (eczema herpeticum and herpes zoster) were uncommon in all dupilumab trials. Oral herpes accounted for most of the herpetic infections reported in dupilumab-treated I patients, with incidence rates slightly higher versus placebo in 16-week studies but with rates similar to placebo in the 52-week RCT. EAIRs of herpetic infections in the adult OLE and PED-OLE were generally similar to the corresponding RCTs, confirming that the incidence of herpes viral infections does not increase with long-term dupilumab treatment. Opportunistic infections, eczema herpeticum, herpes zoster, hematologic AEs, and cardiovascular AEs were only infrequently reported with dupilumab, both in the clinical studies described here and in real-world studies [49]. Rigorous long-term additional surveillance will be needed to confirm the incidence of SAEs with Janus kinase inhibitors (JAKi) in patients with AD; these studies have been required by health authorities [50–57].

The incidence of non-herpetic skin infections was lower in dupilumab-treated patients than patients receiving placebo, and incidence rates were lower over the OLE trials than the RCTs. Skin infections are common in AD, particularly in patients with severe AD [58–61]. Several aspects of AD pathobiology may increase susceptibility to skin infections, including skin barrier dysfunction, skin damage associated with scratching, skin microbiome alterations, and reduced expression of antimicrobial peptides [60, 62–64]. Patients with AD are at increased risk of serious bacterial and viral skin infections [44, 48–61, 65–67] and are also at increased risk of serious extracutaneous and systemic infections, compared with the general population [61, 68–70].

In previous placebo-controlled clinical trials, dupilumab treatment has been shown to reduce rates of hospitalizations in patients with AD, largely driven by decreases in skin infections [71]. The reduced incidence of skin infections may be attributed to dupilumab-mediated indirect (e.g., type 2 cytokine inhibition) or direct (e.g., reduced mechanical damage via scratching) improvements in skin barrier function and favorable changes to the skin microbial barrier [64, 72–75]. Dupilumab has been previously shown to significantly and rapidly reduce the abundance of *Staphylococcus aureus* and increase microbial diversity on lesional and nonlesional skin in patients with AD [64, 73–75]. One of the potential mechanisms for the reduction of *S. aureus* colonization of the skin is that IL-4 induces increases in endothelial permeability and leakage of plasma proteins to the epidermis. The plasma proteins, fibronectin and fibrinogen, are adhesion factors that promote *S. aureus* colonization and growth. Dupilumab treatment inhibited the expression of plasma proteins at lesional and nonlesional skin sites of patients with AD, suggesting the potential to



ity [12, 10, 11].

Dupilumab targets the activity of IL-4 and IL-13, two of the cytokines important in type 2 immune pathways, which are not crucial to host defense mechanisms against most infectious agents, except endoparasites, specifically intestinal helminths [78, 79]. No reports of parasitic infections were reported in the adult RCTs; one case of ascariasis was reported in the adult OLE. Among children, nonsevere helminthic infections were reported in one dupilumab recipient in the 16-week child/infant RCTs and eight patients in PED-OLE; no patients withdrew treatment because of these events, and all cases recovered/resolved by the end of the treatment period. Most cases of helminthic infections in children were enterobiasis, which is relatively common in the general pediatric population, with prevalence approaching 50% [80]. These studies were not conducted in regions where parasitic infections are endemic.

The dupilumab label includes a warning for hypersensitivity reactions, including anaphylaxis, serum sickness-like reactions, angioedema, generalized urticaria, rash, erythema nodosum, and erythema multiforme [12]. No events of anaphylactic reaction considered related to dupilumab treatment for AD were reported in this dataset. One TE-SAE of serum sickness was reported in a patient in the adult OLE after two doses of dupilumab 300 mg qw; this patient had high levels of anti-dupilumab antibodies. In addition, two cases of serum-sickness/serum sickness-like reaction were reported in RCTs not included in this analysis: a serum sickness-like reaction was reported in a patient in LIBERTY AD EVALUATE (NCT02210780)—this patient had high titers of anti-dupilumab antibodies and developed the reaction after three doses of dupilumab; one case of serum sickness was reported in a patient in LIBERTY AD CAFÉ (NCT02755649)—this patient had low titers of anti-dupilumab antibodies and developed serum sickness after use of dupilumab [12, 81]. Both events were judged by the respective investigators as related to study treatment and both led to permanent study treatment discontinuation; both patients recovered without sequelae.

Since the initial US Food and Drug Administration (FDA) approval of dupilumab in March 2017, spontaneous reports of adverse reactions have been collected via postmarketing surveillance. Because these reactions are reported voluntarily from a population of uncertain size, it is not possible to reliably estimate their frequency or establish a causal relationship to drug exposure. These reactions include arthralgia and facial skin reactions, including erythema, rash, scaling, papules, pruritus, burning, and pain [12].

In this analysis, one case of CTCL was reported in an -treated patient, which was deemed unrelated to study drug. More severe AD is known to be correlated with an increased risk of CTCL [82, 83]. Previous studies have

with AD treatments, such as topical calcineurin inhibitors, but with disease severity [82, 84, 85]. There is currently no evidence associating CTCL and dupilumab treatment; however, case reports and analyses have been published documenting the diagnosis of CTCL in patients with AD who have been treated with dupilumab. Many of these reports are retrospective in nature, lack clinical data, and do not take into account misdiagnosis of AD prior to dupilumab treatment, misdiagnosis of CTCL after treatment initiation, co-existence of AD and CTCL, and the development of CTCL later in life [86, 87]. In the present analysis, arthralgia incidence was infrequent, mild to moderate in severity, and most cases resolved or were resolving by the end of the treatment period. Arthralgia has been reported at slightly higher rates in dupilumab-treated patients compared with placebo in clinical trials in CRSwNP and eosinophilic esophagitis as well as in postmarketing data [12, 47, 88]. In some case reports, arthralgia was associated with gait disturbances or decreased mobility, with some patients requiring hospitalization. Some patients' symptoms resolved while continuing treatment with dupilumab, and other patients recovered or were recovering after treatment discontinuation.

Postmarketing data have identified facial skin reactions as adverse reactions that may be associated with dupilumab treatment in patients with AD, including scaling, redness, edema, plaques, burning, itching, and flushing on regions of the head and neck [12, 89–104]. While the precise etiology of these facial reactions and their relationship to dupilumab treatment is unknown, proposed mechanisms include refractory face and neck dermatitis, which is a common phenotype of AD [105, 106], as well as TCS withdrawal, hypersensitivity reactions, seborrheic dermatitis, allergic contact dermatitis, *Malassezia* hypersensitivity infection, and rosacea [89–104]. Notably, in RCTs, dupilumab monotherapy or TCS withdrawal provided rapid, significant, and sustained improvement in the severity of AD clinical signs on the head and neck (measured by regional Eczema Area and Severity Index [EASI] component scores for erythema, infiltrations/papulation, excoriation, and lichenification) in adults and children [17, 107].

Long-term treatment of moderate-to-severe AD with systemic broad immunosuppressive agents is limited by safety concerns and a need for repeated tests to monitor clinical laboratory abnormalities and/or organ (e.g., liver and kidney) toxicities, which increase treatment burden and may negatively impact patient adherence to treatment [4, 108–110]. No changes in hematology, serum chemistry (including liver function tests), or urinalysis laboratory values were clinically meaningful in the present analyses. Consistent with previous analyses, laboratory abnormalities of grade 3 or above were extremely rare in the dupilumab and placebo groups; no laboratory

labeling requirement for routine laboratory monitoring [30, 32, 111].

In the present analysis, transient eosinophilia was reported in a limited number of patients across the studies, with no clinical sequelae [28, 30, 32, 75, 111]. Type 2 inflammation mediated by IL-4, IL-13, and IL-5 has been reported to promote eosinophil growth, differentiation, and trafficking to sites of inflammation [79]. The increase in blood eosinophil counts in the dupilumab clinical trials is consistent with the hypothesis that dupilumab blocks IL-4 and IL-13 function in eosinophil survival, activation, and recruitment to tissues but does not affect egress from bone marrow, which is regulated by IL-5 [30, 112, 113]. Of note, eosinophilia was less marked in the adult 52-week RCT, which may be due to the use of concomitant TCS, which may blunt the effect of dupilumab on eosinophils [30]. Platelet and neutrophil counts decreased slightly from baseline in patients in all age groups treated with dupilumab (with or without TCS) compared with placebo [30, 32, 111, 114]. Variations from baseline were largely within the normal range, and dupilumab treatment was not associated with thrombocytopenia or neutropenia. These observations may reflect a reduction in systemic inflammation.

Serum levels of LDH were elevated at baseline in all studies in these analyses and decreased slightly with dupilumab treatment to normal post-baseline mean values, as previously reported [30, 32, 111]. LDH is considered a marker of tissue damage and is strongly correlated with disease severity in AD [115–118]. Thus, decreases in LDH with dupilumab treatment may reflect tissue normalization. In addition, there was a slight increase in ALP levels in dupilumab-treated patients versus in patients receiving placebo in the pooled infant/children RCTs but not in the older age groups. This is consistent with a previous analysis that showed increased bone ALP in pediatric patients treated with dupilumab [119] and may be beneficial, as children with AD have lower bone mineral density and ALP levels than healthy children [120, 121].

Strengths of this analysis include the large number of patients (especially pediatric patients), as well as the inclusion of long-term data up to 5 years. Another strength is that these analyses evaluated both the 300-mg q2w and 300-mg qw (not yet approved) dose regimens in the adolescent and adult RCTs, which could increase the likelihood of identifying safety issues. Limitations of this analysis are that data from phase 3 clinical trials are not always reflective of real-world usage and that post-marketing data were not included. Registries and other real-world studies will provide further data on dupilumab safety.

This comprehensive analysis of 3882 dupilumab-treated patients and > 7000 patient-years, including infants, children, adolescents, and adults with uncontrolled moderate-to-severe AD, confirms that dupilumab is well tolerated with an acceptable and consistent long-term safety profile. The TEAEs identified occurred with relatively low frequency, were generally mild or moderate, and the majority did not lead to treatment discontinuation. TE-SAEs were infrequent, and no increased overall infection risk was observed. Treatment for up to 5 years in OLEs revealed safety consistent with shorter-term studies. This safety profile allows for dupilumab to be used without the labeling requirement of laboratory testing before treatment initiation or monitoring during the treatment. As the first approved targeted agent that selectively inhibits the type 2 inflammation pathway, dupilumab has consistently demonstrated significant and clinically meaningful benefits combined with the known safety profile in infants through adults, without the toxicity and side effects commonly observed with existing systemic immunosuppressants.

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## Declarations

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**Conflict of interest** R.G. Langley received honoraria as a principal investigator, scientific advisor, or speaker for AbbVie, Amgen, Boehringer Ingelheim, Bristol-Myers-Squibb, Dermavant, Dermira, Eli Lilly, GlaxoSmithKline, Janssen, Leo Pharma, Novartis, Ortho Dermatologics, Pfizer, Sanofi-Genzyme, Sun Pharma, UCB Pharma, and Union. G. Gherardi, A. Rodríguez-Marco, and A.B. Rossi are employees of Sanofi and may hold stock and/or stock options in the company. A. Coleman, M. Ardeleanu, S. Levy, A. Bansal, Z. Chen, B. Shumel, and F.A. Khokhar are employees and shareholders of Regeneron Pharmaceuticals Inc.

**Availability of data and material** Qualified researchers may request access to study documents (including the clinical study report, study protocol with any amendments, blank case report form, statistical

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manuscript that could identify individual participant data will be considered for sharing (1) once the product and indication has been approved by major health authorities (e.g., FDA, EMA, PMDA, etc.) or development of the product has been discontinued globally for all indications on or after April 2020 and there are no plans for future development (2) if there is legal authority to share the data and (3) there is not a reasonable likelihood of participant re-identification. Submit requests to <https://vivli.org/>.

**Ethics statement** Ethical approval was obtained for individual studies included in this analysis. All trials were conducted in accordance with the Declaration of Helsinki, the International Conference on Harmonisation Good Clinical Practice guideline, and applicable regulatory requirements. Independent data and safety monitoring committees conducted blinded monitoring of patient safety data. The local institutional review boards or ethics committees at each study center oversaw trial conduct and documentation.

**Consent to participate** For each trial, all patients or their parents/guardians provided written informed consent before participating in the trial. Written informed consent was obtained from all patients and the patients' parents/guardians prior to commencement of any study treatment.

**Consent for publication** Not applicable.

**Code availability** Not applicable.

**Author contributions** A.C., A.B.R., B.S., and F.A.K. contributed to concept and design of the analyses described in this manuscript. Z.C. conducted the statistical analyses of the data. All authors interpreted the data, provided critical feedback on the manuscript, approved the final manuscript for submission, and were accountable for the accuracy and integrity of the manuscript.

**Data availability statement** Qualified researchers may request access to study documents (including the clinical study report, study protocol with any amendments, blank case report form, statistical analysis plan) that support the methods and findings reported in this manuscript. Individual anonymized participant data will be considered for sharing (1) once the product and indication has been approved by major health authorities (e.g., FDA, EMA, PMDA, etc.) or development of the product has been discontinued globally for all indications on or after April 2020 and there are no plans for future development (2) if there is legal authority to share the data and (3) there is not a reasonable likelihood of participant re-identification. Submit requests to <https://vivli.org/>.

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