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Conjunctivitis in dupilumab clinical trials

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Running head: Conjunctivitis in dupilumab clinical trials

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Summary

Background Dupilumab, which blocks the shared receptor component for interleukin (IL)-4 and IL-13, is approved for inadequately-controlled moderate-to-severe atopic dermatitis (AD) and moderate-to-severe eosinophilic or oral corticosteroid-dependent asthma. AD trials reported increased conjunctivitis incidence for dupilumab vs. placebo.

Objectives To further characterise conjunctivitis occurrence and risk factors in dupilumab clinical trials.

Methods We evaluated randomised placebo-controlled trials of dupilumab in AD (n=2629), asthma (n=2876), chronic rhinosinusitis with nasal polyps (CRSwNP) (n=60), and eosinophilic esophagitis (EoE) (n=47).

Results In most AD trials, dupilumab-treated patients had higher conjunctivitis incidence than placebo controls. Higher baseline AD severity and previous conjunctivitis history were associated with increased conjunctivitis incidence. Conjunctivitis was mostly mild to moderate. Most cases recovered/resolved during the treatment period; 2 patients permanently discontinued dupilumab due to conjunctivitis/keratitis. Common treatments included ophthalmic corticosteroids, antibiotics, and anti-histamines/mast cell stabilisers. Most cases were diagnosed by investigators. In asthma and CRSwNP trials, conjunctivitis incidence was lower for both dupilumab and placebo than in AD trials; dupilumab did not increase incidence vs. placebo. In the EoE trial, no patients had conjunctivitis.

Conclusions Conjunctivitis was more frequent with dupilumab treatment in most AD trials. In dupilumab trials in other type 2 diseases, incidence of conjunctivitis was overall very low, and was similar for dupilumab and placebo. In AD, conjunctivitis incidence was associated with AD severity and prior history of conjunctivitis. The aetiology and treatment of conjunctivitis in dupilumab-treated patients require further study.

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Keywords: Dupilumab, conjunctivitis, atopic dermatitis, asthma, nasal polyps

What's already known about this topic?

- Ocular disorders, including allergic conjunctivitis, are common in patients with atopic dermatitis (AD)
- In most dupilumab AD trials, dupilumab-treated patients had higher conjunctivitis incidence vs. placebo; most cases were mild-to-moderate, and recovered or were recovering during study treatment; study treatment discontinuation due to conjunctivitis was rare
- Conjunctivitis incidence was very low and similar for dupilumab and placebo in clinical trials in asthma, chronic rhinosinusitis with nasal polyps, and eosinophilic esophagitis

What does this study add?

- This analysis confirms and extends the results of the individual clinical trials
- Baseline disease-related factors, including AD severity, prior conjunctivitis history, and certain biomarkers (thymus and activation-regulated chemokine, IgE, eosinophils), were associated with increased incidence of conjunctivitis
- Patients who responded well to dupilumab had reduced incidence of conjunctivitis
- Further study is needed to elucidate the aetiology and treatment of conjunctivitis in dupilumab-treated patients with AD

Ocular surface diseases, such as allergic conjunctivitis, blepharitis, and keratitis, are well-known ophthalmic complications in patients with severe atopic dermatitis (AD), with incidence rates of 32.4%–55.8%.^{1–8} Incidence of ophthalmic complications increases with AD severity.^{4,8} Allergic conjunctivitis and other ocular surface disorders are also common comorbidities of other atopic disorders such as asthma and allergic rhinitis.^{9–17}

Dupilumab is a fully human VelocImmune[®]-derived^{18,19} monoclonal antibody blocking the shared receptor component for interleukin-4 (IL-4) and IL-13, thus inhibiting signalling of both IL-4 and IL-13.

Dupilumab is approved for subcutaneous administration at 300 mg every 2 weeks (q2w) for adults with moderate-to-severe AD inadequately controlled with topical prescription therapies or when

those therapies are not advisable²⁰ and adults with inadequately controlled, moderate-to-severe AD who are candidates for systemic therapy;²¹ and as an add-on maintenance treatment in patients aged ≥ 12 years with moderate-to-severe asthma and an eosinophilic phenotype or oral corticosteroid dependence.²⁰ In clinical trials, dupilumab demonstrated efficacy and safety in AD,^{22–26} asthma,^{27–31} chronic rhinosinusitis with nasal polyps (CRSwNP),³² and eosinophilic esophagitis (EoE),³³ demonstrating that IL-4 and IL-13 are key drivers of multiple type 2 inflammatory diseases. Ocular surface disorders, including conjunctivitis, blepharitis, keratitis, eye pruritus, and dry eye, are commonly-reported adverse events (AEs) in dupilumab-treated patients with AD.^{20,21} Conjunctivitis of all aetiologies and phenotypes with or without eyelid or corneal involvement was dominant among all ocular AEs reported in dupilumab clinical trials in AD.^{20,21,24–26,34,35} To characterise conjunctivitis in patients treated with dupilumab, we reviewed the results of published clinical trials, and synthesised available data on incidence rates, disease course, and associated baseline characteristics of patients who developed conjunctivitis in randomised, double-blinded, placebo-controlled trials of dupilumab in AD, asthma, CRSwNP, and EoE.

PATIENTS AND METHODS

Studies

Eleven randomised, double-blinded, placebo-controlled phase II and phase III clinical trials were included in this analysis: 2629 patients in six AD trials (R668-AD-1021 [NCT01859988], LIBERTY AD SOLO 1 [NCT02277743], LIBERTY AD SOLO 2 [NCT02277769]; LIBERTY AD CHRONOS [NCT02260986]; LIBERTY AD CAFÉ [NCT02755649]; and LIBERTY AD SOLO-CONTINUE [NCT02395133])^{23–26,36}; 2876 patients in three asthma trials (DRI12544 [NCT01854047], LIBERTY ASTHMA QUEST [NCT02414854], and LIBERTY ASTHMA VENTURE [NCT02528214])^{28–31}; 60 patients in one CRSwNP trial (ACT12340 [NCT01920893])³²; and 47 patients in one EoE trial (R668-EE-1324 [NCT02379052]) (Table S1; see Supporting Information).³³ Details of study methodologies were previously published.^{23–33,36} Data

were pooled for the three AD 16-week monotherapy studies (monotherapy pool: R668-AD-1021, SOLO 1, and SOLO 2).

All trials were conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and are consistent with the International Council for Harmonisation guidelines for Good Clinical Practice and applicable regulatory requirements.^{23–33,36}

Endpoints and assessments

Clinical trial investigators (mostly dermatologists or allergists) diagnosed and reported conjunctivitis AEs, which were subsequently coded using Medical Dictionary for Regulatory Activities (MedDRA) preferred terms (PTs). Unless otherwise specified, the term “conjunctivitis” refers to the group of PTs that included the term “conjunctivitis”, i.e., conjunctivitis, allergic conjunctivitis, bacterial conjunctivitis, viral conjunctivitis, adenoviral conjunctivitis, and atopic keratoconjunctivitis. All conjunctivitis cases were included regardless of aetiology (including blepharoconjunctivitis, which was coded as the MedDRA PT conjunctivitis; and excluding blepharitis in the absence of conjunctivitis). The study protocols did not require any specific query about ocular symptoms. AEs were generally reported by patients spontaneously, in response to the query “did you have any problems?”, or by investigators on physical examination during clinical visits. Investigators who reported conjunctivitis of unspecified aetiology were asked for more details, and whether they could use a more specific PT. In most cases, the aetiology remained unspecified or was designated “allergic” by the investigator. Investigators differed in how they categorised conjunctivitis to type, as there were no prespecified classification guidelines. Most cases reported as infectious (e.g., viral or bacterial) did not have laboratory confirmation of infectious aetiology. Most cases were not referred to ophthalmologists or other eye specialists.

Impact of baseline demographic and disease characteristics; baseline serum levels of thymus and activation-regulated chemokine (TARC; CCL17), immunoglobulin E (IgE), and blood eosinophil counts; and efficacy responses on conjunctivitis incidence rates were summarised for the monotherapy pool,

CHRONOS, and CAFÉ. We evaluated the relationship between dupilumab concentration and conjunctivitis in pooled data from SOLO 1, SOLO 2, and CHRONOS.

Statistical analysis methods

These analyses evaluated all patients who received ≥ 1 dose of study drug by treatment and dose regimen received.

Incidence rates described proportions of patients with ≥ 1 conjunctivitis event, without modelling or censoring for patient withdrawal or rescue medication use. Hazard ratios (HR) and 95% confidence intervals (CI) were estimated based on a Cox regression model (with censoring after patients' withdrawal), to describe the relative risk for time to first conjunctivitis event, comparing the dupilumab and placebo groups, with treatment group as fixed effects, stratified by study and baseline disease severity (Investigator's Global Assessment [IGA]=3 vs. 4 for AD-1021, SOLO, CHRONOS, and CAFÉ; or IGA=0 vs. 1 vs. 2 for SOLO-CONTINUE). Medians, percentiles, and 95% CIs were obtained from Kaplan–Meier estimates. Relationships of baseline characteristics and treatment response with conjunctivitis incidence were evaluated using descriptive statistics. Results from post-hoc analyses showing annualised rate ratios by various factors were extracted from a duration-adjusted Poisson model. Relationships between dupilumab concentration and conjunctivitis incidence were evaluated by dupilumab concentration (observed C_{trough} , predicted C_{trough} , and AUC_{tau}) in the placebo and dupilumab groups, based on pooled data from SOLO 1, SOLO 2, and CHRONOS, for Weeks 0–16.

RESULTS

AD clinical trials

Incidence of conjunctivitis

Incidence and HR of treatment-emergent conjunctivitis were higher in dupilumab-treated vs. placebo-treated patients in the monotherapy pool, CHRONOS, and CAFÉ. In the monotherapy pool, incidence rates (HR) for dupilumab vs placebo after 16 weeks of treatment were 8.6% vs. 2.1% (HR 4.13 [95% CI, 2.21–7.72]) (Table 1); a similar pattern was seen when adjusting for patient exposure (29.98 vs. 7.29 patients, respectively, per 100 patient-years [PY]) (Table S2; see Supporting Information). In CHRONOS, incidence rates (HR) for dupilumab+topical corticosteroid (TCS) vs. placebo+TCS over the 52-week treatment period were 17.9% vs. 7.9%, respectively (HR 2.31 [95% CI, 1.47–3.63]) (Table 1); when adjusting for exposure, rates were 21.44 vs. 9.24 patients per 100 PY, respectively (Table S2; see Supporting Information). The highest conjunctivitis rates were reported in CAFÉ, with incidence rates (HR) for dupilumab+TCS vs. placebo+TCS over the 16-week treatment period of 22.1% vs. 11.1%, respectively (HR 2.06 [95% CI, 1.09–3.88]) (Table 1); duration-adjusted rates were 81.13 vs. 38.94 patients per 100 PY, respectively (Table S2; see Supporting Information). In contrast to the other AD trials, in SOLO-CONTINUE, in which patients who responded well to dupilumab in either SOLO 1 or SOLO 2 were re-randomised to 36 weeks of treatment at their original dose regimen or longer-interval regimens (every 4 weeks [q4w] or every 8 weeks [q8w]) or placebo, there was no apparent difference in conjunctivitis incidence and HR between dupilumab and placebo (4.7% vs. 4.9%; HR of 1.00 [0.33–2.98]; 7.25 vs. 7.45 patients per 100 PY) (Table 1; Table S2; see Supporting Information). In the monotherapy pool, CHRONOS, and SOLO-CONTINUE, conjunctivitis incidence rates were similar across dupilumab dose regimens within each study. In CAFÉ, incidence rates were numerically lower for dupilumab 300 mg qw+TCS than 300 mg q2w+TCS (Table 1).

Conjunctivitis severity, treatment, and resolution

Conjunctivitis AEs were mostly mild to moderate. Severe conjunctivitis was reported in $\leq 0.5\%$ of dupilumab-treated and $\leq 0.3\%$ of placebo-treated patients (Fig. 1). One patient in the 300 mg qw group in the monotherapy pool permanently discontinued study drug due to conjunctivitis, and one patient in the 300 mg qw+TCS group in CHRONOS permanently discontinued study drug due to allergic keratitis (MedDRA PT; verbatim term was “worsening of allergic keratoconjunctivitis”). Most cases were resolved/resolving by the end of the treatment period (Table 2). The most common treatments were ophthalmic preparations of corticosteroids, antibiotics, and anti-histamine/mast cell stabilisers. The proportion of patients who required continued or intermittent ongoing therapy for conjunctivitis could not be determined with the available data.

Onset of conjunctivitis

Numeric differences between placebo and dupilumab in new conjunctivitis events were apparent after Week 2 in the monotherapy pool, after about Weeks 6–8 in CHRONOS, and after about Weeks 4–8 in CAFÉ (Fig. 2). For the monotherapy pool and CAFÉ, new conjunctivitis events appeared at a relatively constant rate throughout the 16-week studies. In CHRONOS, new cases appeared to level off around Weeks 20–24 and were relatively uncommon after Week 44 (Fig. 2B). Mean time to first event was similar between dupilumab dose regimens in these studies (Fig. 2).

Baseline characteristics of patients with and without conjunctivitis

Patients who reported conjunctivitis during the treatment period had more severe AD at baseline than patients who did not report conjunctivitis, regardless of assigned treatment group (dupilumab or placebo) (Fig. 3; Table S3; see Supporting Information). In addition, higher baseline levels of the serum biomarkers TARC and IgE and higher baseline circulating eosinophil counts (all suggestive of higher disease severity), and prior history of conjunctivitis were associated with conjunctivitis in both dupilumab- and placebo-treated patients (Fig. 3; Table S3; see Supporting Information).

Conjunctivitis and response to dupilumab

The relationship between treatment response and conjunctivitis incidence varied between treatment groups and studies. Patients who achieved high-level efficacy outcomes (IGA 0/1; 75% improvement from baseline in Eczema Area and Severity Index [EASI-75]) in the monotherapy pool were less likely to develop conjunctivitis than those who did not achieve those outcomes. In CHRONOS and CAFÉ, this pattern was only apparent in the dupilumab q2w and placebo groups (Fig. 4).

Dupilumab exposure and conjunctivitis

Pooled data from baseline to Week 16 in SOLO 1 and 2 and CHRONOS showed a trend suggesting that conjunctivitis incidence may decrease with higher trough concentrations of dupilumab (Table S4; see Supporting Information).

Asthma, CRSwNP, and EoE

In all asthma trials, incidence rates of conjunctivitis were low, with no apparent differences between dupilumab- and placebo-treated patients (Table 3). In DRI12544, 7/611 dupilumab-treated (1.1%) and 2/158 placebo-treated patients (1.3%) developed conjunctivitis; in QUEST, 22/1263 dupilumab-treated (1.7%) and 15/634 placebo-treated patients (2.4%) developed conjunctivitis; while in VENTURE, only 1/103 dupilumab-treated (1.0%) and 1/107 placebo-treated patients (0.9%) developed conjunctivitis (Table 3).

In the CRSwNP trial, no dupilumab-treated patients and 1/30 placebo-treated patients (3.3%) developed conjunctivitis (Table 3).

In the EoE trial, no patients developed conjunctivitis.

In all these trials, all cases were mild or moderate (Fig. S1; see Supporting Information), and nearly all recovered by the end of the treatment period (Table S5; see Supporting Information).

DISCUSSION

This analysis confirmed that patients with AD treated with dupilumab had greater incidence of conjunctivitis (8.6%–22.1%) than placebo-treated patients (2.1%–11.1%) in most of the randomised, placebo-controlled AD clinical trials included in this analysis, except for SOLO-CONTINUE,^{23–26,36} consistent with the higher rates of external eye disorders, including conjunctivitis, blepharitis, keratitis, eye pruritus, and dry eye, described for AD patients in the dupilumab prescribing information.^{20,21} Patients with AD were more likely to develop conjunctivitis if they had higher baseline AD severity, high levels of certain biomarkers, or self-reported history of conjunctivitis. By contrast, randomised, placebo-controlled clinical trials of dupilumab in asthma, CRSwNP, and EoE had low and similar incidence rates of conjunctivitis in dupilumab- (0–1.7%) and placebo-treated (0–3.3%) patients.^{28–33} In all trials, most cases of conjunctivitis were mild or moderate, and most resolved while continuing dupilumab treatment.

Multiple factors (disease-based and treatment-based) are associated with incidence of conjunctivitis in these studies. Baseline AD severity and prior conjunctivitis history are most likely independent risk factors for conjunctivitis irrespective of treatment, since incidence increases with baseline severity and prior history in placebo-treated patients (as well as in dupilumab-treated patients). CAFÉ, which had both the highest baseline level of AD severity and the highest rates of prior conjunctivitis history among all the AD trials, also had the highest rates of conjunctivitis. CAFÉ was a later trial in this series, which may have resulted in higher awareness of conjunctivitis as a potential AE. In contrast, conjunctivitis rates were lowest in SOLO-CONTINUE, in which high-level responders to dupilumab from SOLO 1 and SOLO 2 were re-randomised to continued dupilumab treatment or placebo.

Levels of certain biomarkers (TARC, IgE, and eosinophils) increase with AD severity^{22,37,38}; thus, it is not surprising that both baseline AD severity and increased biomarker levels were associated with increased conjunctivitis incidence in these studies. AD severity has been associated with increased

incidence of conjunctivitis,^{3,8} and IgE levels are increased in patients with both AD and ocular complications.^{3,4}

High-level efficacy responses (IGA 0/1; EASI-75) showed an apparent association with lower conjunctivitis incidence in dupilumab-treated patients in the monotherapy pool; however, this trend was inconsistent or reversed in CHRONOS and CAFÉ. Fewer patients with severe AD at baseline achieved IGA 0/1 and EASI-75. Increased disease severity is associated with higher incidence of comorbidities and higher AD biomarkers, so these predictors may be interrelated.

Pharmacokinetic data suggested, somewhat paradoxically, that lower dupilumab exposure might be associated with increased incidence of conjunctivitis compared with higher dupilumab exposure.

This finding would not be expected if there was a positive dose-response relationship between dupilumab exposure and occurrence of conjunctivitis. Furthermore, 80% of cases resolved whilst continuing on dupilumab treatment. Thus, further study is warranted to better understand the underlying cause of the imbalance in events between treatment groups.

Currently, there is no consensus on optimal approaches to prevent and manage conjunctivitis in dupilumab-treated patients. Ophthalmic preparations of corticosteroids, antibiotics, and anti-histamine/mast cell stabilisers were the most common treatments used for conjunctivitis in these trials. Case series and case reports have described several therapeutic approaches used successfully in clinical practice for treatment of conjunctivitis associated with dupilumab without discontinuation of dupilumab, including hyaluronic acid eye drops, topical tacrolimus, topical corticosteroids (e.g., fluorometholone, dexamethasone, hydrocortisone), artificial tears, compounded oily cyclosporin eye drops, and antibiotic/TCS combination therapies.^{39–45} Since long-term treatment with ophthalmic TCS can lead to more serious eye disorders such as cataracts and glaucoma, products with poor penetration into the anterior chamber of the eye (e.g. fluorometholone) should be considered. In addition, topical preparations of calcineurin inhibitors appear to be a reasonable long-term therapeutic alternative.³⁹ Patients who develop ocular symptoms during dupilumab treatment

should receive full ophthalmic evaluations, and addition of an ophthalmologist to the patient management team may be of benefit.^{4,39,46}

An important aspect of these analyses is that, based on existing data, and in the absence of ophthalmologic or microbiologic evaluation, it was neither possible to identify events that were specific or pathognomonic for dupilumab vs. placebo, nor to confirm whether the events were infectious, allergic, or idiopathic. Data on specific clinical features of ocular AEs were not collected in these trials, and inconsistencies in how MedDRA PTs were assigned limit the utility of comparison of conjunctivitis PTs between dupilumab and placebo. Case reports have described common features of conjunctivitis in dupilumab-treated patients from clinical practice, including conjunctival redness, hyperaemia, blepharitis, dryness, irritation, discharge, itch, stinging, burning, tearing, foreign-body sensation, occasional decrease in bilateral visual acuity, and ectropion.^{39–45} Further study into the clinical characteristics of conjunctivitis associated with dupilumab is warranted, and ongoing.

The exact pathogenesis of conjunctivitis events observed during dupilumab treatment is unknown.

Ocular comorbidities have high prevalence in patients with AD compared with the overall population.^{1–4,47} Thus, it is possible that pre-existing ocular disorders and a dupilumab–AD-disease-specific interaction may be responsible for this increased incidence in dupilumab-treated patients with AD, particularly since conjunctivitis was not associated with dupilumab in trials in other type 2 diseases.^{28–33} Allergic conjunctivitis is a common comorbidity in asthma and allergic rhinitis, as well as in AD.^{1–4,9–17,47–49} Both lesional and nonlesional skin in AD are characterised by epithelial barrier dysfunction, including abnormalities in keratinocyte terminal differentiation, keratinocyte lipid production, and tight junctions, which all contribute to increased transepidermal water loss.^{50–52}

Ocular surface epithelia have impaired barrier function in patients with AD.⁵³ Although barrier dysfunction is also observed in affected mucosal barrier tissues of other type 2 indications, patients with AD more frequently have ocular disease. If barrier abnormalities in AD differentially affect conjunctival tissues compared with other type 2 diseases, this could in part explain the differences in conjunctivitis incidence rates between AD trials and trials of other type 2 diseases.

Several hypotheses have been proposed for mechanisms driving conjunctivitis in dupilumab-treated patients with AD, including alterations in cytokine activity leading to (variously) increased *Demodex* mites, increased OX40 ligand activity, eosinophilia, disruption of an immune-mediated response of conjunctival associated lymphoid tissue, decreased IL-13–related mucus production, and decreased IL-13–related scarcity of conjunctival goblet cells; it is possible that multiple mechanisms may be in effect.^{40,43,54–59} In addition, different mechanisms may affect the development of conjunctivitis in dupilumab-treated patients with AD vs. those with asthma or other type 2 diseases. Further investigation is needed, including collection of ocular samples, to characterise the molecular, cellular, and inflammatory changes in the eye during these events as well as during and after recovery/resolution.

There are several limitations to this analysis. First, there was no prespecified ocular assessment in these trials; patients were not examined by ophthalmologists at enrolment or during the trials. Thus, overall changes from baseline and/or objective differentiation of changes in ocular symptoms over time could not be determined. Second, conjunctivitis AEs were reported by the trial investigators (typically dermatologists or allergists). Patients were usually not referred to ophthalmologists, and few AEs reported as viral or bacterial conjunctivitis had microbiologic confirmation. Nonetheless, within the limits of diagnostic accuracy of the investigators, the data show that dupilumab-treated patients had higher rates of conjunctivitis. Third, there are limitations related to classification of AEs by MedDRA. Lower-level terms (LLTs) with higher specificity are very numerous (>100), so the analysis had to be done at the PT level; e.g., the LLT of “blepharoconjunctivitis” would default to the PT of conjunctivitis. For the purpose of signal detection, it was necessary to cluster multiple PTs to avoid this fragmentation. In addition, during AE coding, the MedDRA PTs of “conjunctivitis” and “conjunctivitis allergic” were sometimes used interchangeably; therefore, these two terms should be considered equivalent. MedDRA coding of conjunctivitis AEs may result in classification of these events as either the MedDRA System Organ Class of “Eye Disorders” or as “Infections and Infestations” depending on the verbatim report of the investigator. Fourth, history of conjunctivitis

was self-reported by patients, with likelihood of recall bias, as different symptoms from patients' history could be misinterpreted by patients and/or investigators as conjunctivitis. Fifth, the increasing incidence of conjunctivitis reported in the placebo groups of the different AD trials over time suggests that both an "awareness bias" of the trial investigators in the later AD trials and a possible initial underdiagnosis of conjunctivitis in earlier trials may have influenced apparent increases in reported incidences of dupilumab-associated conjunctivitis across studies over time. Finally, conclusions on incidence of conjunctivitis in CRSwNP and EoE are limited by the small number of patients in the proof-of-concept trials included in this analysis.^{32,33} These indications are still in development; future analyses will incorporate data from larger ongoing and future studies.

In conclusion, the higher incidence of conjunctivitis in dupilumab-treated patients with AD appears to be associated with several disease-based factors, including baseline AD severity and previous history of conjunctivitis. Dupilumab treatment was not associated with increased incidence of conjunctivitis in asthma, CRSwNP, and EoE trials. In most cases, conjunctivitis AEs were mild to moderate. Most cases resolved or were resolving while patients continued their dupilumab treatment, but the data do not allow for determination of the proportion of patients who required continued or intermittent ongoing therapy for conjunctivitis. For timely appropriate intervention, we recommend referral for a detailed eye examination in patients who develop this complication while on dupilumab treatment. Further studies, including mechanistic investigations of ocular/conjunctival samples, are needed to characterise clinical phenotypes and understand the aetiology of the observed conjunctivitis AEs in the setting of dupilumab treatment, and to develop guidance for prevention and management.

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Table 1 Proportion of patients with ≥ 1 AE of conjunctivitis during the treatment period in AD trials, and hazard ratios (95% CI; dupilumab vs. placebo): (a) monotherapy pool; (b) CHRONOS; (c) CAFÉ; (d) SOLO-CONTINUE^a

(a) Monotherapy pool

	Patients with ≥ 1 event, n (%)	Patients with ≥ 1 event, n (%); (HR vs. placebo [95% CI])		
	Placebo (n = 517)	Dupilumab 300 mg q2w (n = 529)	Dupilumab 300 mg qw (n = 518)	Dupilumab combined (n = 1047)
Patients with ≥ 1 event	11 (2.1%)	49 (9.3%); (4.43 [2.30–8.51])	41 (7.9%); (3.80 [1.95–7.40])	90 (8.6%); [4.13 (2.21–7.72)]
Conjunctivitis ^a	3 (0.6%)	21 (4.0%); [6.84 [2.04–22.92]]	20 (3.9%); [6.69 (1.99–22.52)]	41 (3.9%); [6.77 (2.10–21.87)]
Conjunctivitis allergic ^a	5 (1.0%)	16 (3.0%); [3.05 [1.12–8.34]]	12 (2.3%); [2.38 (0.84–6.75)]	28 (2.7%); [2.75 (1.06–7.12)]
Conjunctivitis bacterial ^a	2 (0.4%)	7 (1.3%); (3.37 [0.70–16.21])	8 (1.5%); (3.94 [0.84–18.55])	15 (1.4%); (3.64 [0.83–15.91])
Conjunctivitis viral ^a	1 (0.2%)	4 (0.8%); (3.90 [0.44–34.92])	1 (0.2%); (1.00 [0.06–15.92])	5 (0.5%); (2.44 [0.28–20.86])
Atopic keratoconjunctivitis ^a	0	1 (0.2%); (2.96 x 10 ⁷ [0.00–NC])	1 (0.2%); (2.77 x 10 ⁷ [0.00–NC])	2 (0.2%); (1.70 x 10 ⁷ [0.00–NC])

(b) CHRONOS

	Patients with ≥ 1 event, n (%)	Patients with ≥ 1 event, n (%); (HR vs. placebo [95% CI])		
	Placebo + TCS (n = 315)	Dupilumab 300 mg q2w + TCS (n = 110)	Dupilumab 300 mg qw + TCS (n = 315)	Dupilumab + TCS combined (n = 425)
Patients with ≥ 1 event	25 (7.9%)	15 (13.6%); (1.76 [0.93–3.33])	61 (19.4%); (2.51 [1.57–3.99])	76 (17.9%); (2.31 [1.47–3.63])
Conjunctivitis allergic ^a	15 (4.8%)	12 (10.9%); (2.33 [1.09–4.98])	47 (14.9%); (3.16 [1.77–5.66])	59 (13.9%); (2.95 [1.67–5.20])
Conjunctivitis bacterial ^a	5 (1.6%)	2 (1.8%); (1.11 [0.22–5.75])	9 (2.9%); (1.76 [0.59–5.27])	11 (2.6%); (1.60 [0.55–4.59])
Conjunctivitis ^a	5 (1.6%)	1 (0.9%); (0.56 [0.07–4.79])	8 (2.5%); (1.56 [0.51–4.76])	9 (2.1%); (1.30 [0.43–3.87])
Atopic keratoconjunctivitis ^a	1 (0.3%)	0; (0 [0–NC])	2 (0.6%); (1.92 [0.17–21.13])	2 (0.5%); (1.42 [0.13–15.66])

(c) CAFÉ

	Patients with ≥ 1 event, n (%)	Patients with ≥1 event, n (%); (HR vs. placebo [95% CI])		
	Placebo + TCS (n = 108)	Dupilumab 300 mg q2w + TCS (n = 107)	Dupilumab 300 mg qw + TCS (n = 110)	Dupilumab + TCS combined (n = 217)
Patients with ≥ 1 event	12 (11.1%)	30 (28.0%); (2.69 [1.38–5.26])	18 (16.4%); (1.47 [0.71–3.06])	48 (22.1%); (2.06 [1.09–3.88])
Conjunctivitis allergic ^a	7 (6.5%)	16 (15.0%); (2.34 [0.96–5.68])	10 (9.1%); (1.40 [0.53–3.68])	26 (12.0%); (1.87 [0.81–4.30])
Conjunctivitis ^a	3 (2.8%)	12 (11.2%); (4.28 [1.21–15.17])	8 (7.3%); (2.70 [0.71–10.17])	20 (9.2%); (3.44 [1.02–11.56])
Bacterial conjunctivitis ^a	2 (1.9%)	1 (0.9%); (0.50 [0.05–5.57])	0; (0.00 [0.00–NC])	1 (0.5%); (0.25 [0.02–2.77])
Viral conjunctivitis ^a	1 (0.9%)	1 (0.9%); (0.99 [0.06–15.75])	0; (0.00 [0.00–NC])	1 (0.5%); (0.49 [0.03–7.88])
Adenoviral conjunctivitis ^a	0	1 (0.9%); (3.0 × 10 ⁷ [0.00–NC])	0; [NC]	1 (0.5%); (1.7 × 10 ⁷ [0.00–NC])

(d) SOLO-CONTINUE

	Patients with ≥ 1 event, n (%)	Patients with ≥ 1 event, n (%); (HR vs. placebo [95% CI])			
	Placebo (n = 82)	Dupilumab 300 mg q8w (n = 84)	Dupilumab 300 mg q4w (n = 87)	Dupilumab 300 mg qw/q2w (n = 167)	Dupilumab combined (n = 338)
Patients with ≥ 1 event	4 (4.9%)	3 (3.6%); (0.75 [0.17–3.36])	4 (4.6%); (1.00 [0.25–3.99])	9 (5.4%); (1.13 [0.35–3.68])	16 (4.7%); (1.00 [0.33–2.98])
Conjunctivitis ^a	2 (2.4%)	2 (2.4%); (1.00 [0.14–7.10])	2 (2.3%); (0.99 [0.14–7.00])	6 (3.6%); (1.51 [0.30–7.46])	10 (3.0%); (1.24 [0.27–5.65])
Allergic conjunctivitis ^a	1 (1.2%)	1 (1.2%); (1.05 [0.0–16.85])	2 (2.3%); (2.05 [0.19–22.65])	2 (1.2%); (1.02 [0.09–11.24])	5 (1.5%); (1.26 [0.15–10.78])
Bacterial conjunctivitis ^a	1 (1.2%)	0; (0.00 [0.00–NC])	0; (0.00 [0.00–NC])	1 (0.6%); (0.48 [0.03–7.64])	1 (0.3%); (0.24 [0.02–3.90])

HR and its 95% CI are from a Cox regression model, which includes treatment group as fixed effects, stratified by study identifier and baseline disease severity (IGA = 3 vs. IGA = 4).

CI, confidence interval; HR, hazard ratio; IGA, Investigators' Global Assessment; NC, not calculable; q2w, every 2 weeks; q4w, every four weeks; q8w, every 8 weeks; qw, weekly; TCS, topical corticosteroids.

^aMedDRA, Medical Dictionary for Regulatory Activities preferred term.

Table 2 Resolution of conjunctivitis events during the treatment period (a) in the monotherapy pool, (b) CHRONOS, (c) CAFÉ, and (d) SOLO-CONTINUE

(a) Monotherapy pool

	Placebo qw (n = 517)	Dupilumab 300 mg q2w (n = 529)	Dupilumab 300 mg qw (n = 518)	Dupilumab combined (n = 1047)
Overall number of conjunctivitis events, n	12	57	46	103
Resolution of events, n (% [95% CI])				
Recovered/resolved	11 (90% [62–100])	35 (61% [48–74])	32 (70% [54–82])	67 (65% [55–74])
Not recovered/resolved	1 (10% [0–38])	14 (25% [14–38])	6 (13% [5–26])	20% (19 [12–28])
Recovered/resolved with sequelae	0	0	1 (2% [0–12])	1 (1% [0–5])
Recovering/resolving	0	7 (12% [5–24])	6 (13% [5–26])	13 (13% [7–21])
Unknown	0	1 (2% [0–9])	1 (2% [0–12])	2 (2% [0–7])

(b) CHRONOS

	Placebo + TCS (n = 315)	Dupilumab 300 mg q2w + TCS (n = 110)	Dupilumab 300 mg qw + TCS (n = 315)	Dupilumab + TCS combined (n = 425)
Overall number of conjunctivitis events, n	29	23	91	114
Resolution of events, n (% [95% CI])				
Recovered/resolved	27 (93% [77–99])	18 (78% [56–93])	81 (89% [81–95])	99 (87% [79–92])
Not recovered/resolved	1 (3% [0–18])	3 [13% [3–34])	7 (8% [3–15])	10 (9% [4–16])
Recovered/resolved with sequelae	0	0	1 (1% [0–6])	1 (1% [0–5])
Recovering/resolving	1 (3% [0–18])	2 (9% [1–28%])	2 (2% [0–8])	4 (4% [1–9])

(c) CAFÉ

	Placebo + TCS (n = 108)	Dupilumab 300 mg q2w + TCS (n = 107)	Dupilumab 300 mg qw + TCS (n = 110)	Dupilumab + TCS combined (n = 217)
Overall number of conjunctivitis events, n	15	37	19	56
Resolution of events, n (% [95% CI])				
Recovered/resolved	11 (73% [45–92])	14 (38% [22–55])	15 (79% [54–94])	29 (52% [38–65])
Not recovered/resolved	2 (13% [2–40])	13 (35% [20–53])	2 (11% [1–33])	15 (27% [16–40])
Recovered/resolved with sequelae	1 (7% [0–32])	1 (3% [0–14])	0	1 (2% [0–10])
Recovering/resolving	1 (7% [0–32])	8 (22% [10–38])	2 (11% [1–33])	10 (18% [9–30])
Unknown	0	1 (3% [0–14])	0	1 (2% [0–16])

(d) SOLO-CONTINUE

	Placebo (n = 82)	Dupilumab 300 mg q8w (n = 84)	Dupilumab 300 mg q4w (n = 87)	Dupilumab 300 mg qw/q2w (n = 167)	Dupilumab combined (n = 338)
Overall number of conjunctivitis events, n	4	5	4	11	20
Resolution of events, n (% [95% CI])					
Recovered/resolved	4 (100%)	4 (80% [28–99])	2 (50% [7–93])	9 (82% [48–98])	15 (75% [51–91])
Not recovered/resolved	0	1 (20% [1–72])	2 (50% [7–93])	1 (9% [0–41])	4 (20% [6–44])
Recovered/resolved with sequelae	0	0	0	0	0
Recovering/resolving	0	0	0	1 (9% [0–41])	1 (5% [0–25])

CI, confidence interval; qw, weekly; q2w, every 2 weeks; q4w, every 4 weeks; q8w, every 8 weeks; TCS, topical corticosteroids.

CI, confidence interval; qw, weekly; q2w, every 2 weeks; q4w, every 4 weeks; q8w, every 8 weeks; TCS, topical corticosteroids.

Table 3 Incidence of conjunctivitis in asthma: (a) phase IIb (DRI12544); (b) LIBERTY ASTHMA QUEST; (c) LIBERTY ASTHMA VENTURE; and CRSwNP: (d)

ACT12340

(a) Phase IIb DRI12544

		Dupilumab				
	Placebo (n = 158)	200 mg q4w (n = 150)	300 mg q4w (n = 157)	200 mg q2w (n = 148)	300 mg q2w (n = 156)	Combined (n = 611)
Patients with ≥ 1 event, n (%)	2 (1.3)	3 (2.0)	2 (1.3)	2 (1.4)	0	7 (1.1)
Conjunctivitis ^a	1 (0.6)	3 (2.0)	1 (0.6)	1 (0.7)	0	5 (0.8)
Conjunctivitis allergic ^a	1 (0.6)	0	1 (0.6)	1 (0.7)	0	2 (0.3)

(b) LIBERTY ASTHMA QUEST

	1.14 mL/200 mg q2w		2 mL/300 mg q2w		Combined	
	Placebo (n = 313)	Dupilumab (n = 631)	Placebo (n = 321)	Dupilumab (n = 632)	Placebo (n = 634)	Dupilumab (n = 1263)
Patients with ≥ 1 event, n (%)	6 (1.9)	8 (1.3)	9 (2.8)	14 (2.2)	15 (2.4)	22 (1.7)
Conjunctivitis ^a	1 (0.3)	2 (0.3)	4 (1.2)	4 (0.6)	5 (0.8)	6 (0.5)
Conjunctivitis allergic ^a	4 (1.3)	5 (0.8)	4 (1.2)	8 (1.3)	8 (1.3)	13 (1.0)
Conjunctivitis viral ^a	1 (0.3)	1 (0.2)	0	2 (0.3)	1 (0.2)	3 (0.2)
Conjunctivitis bacterial ^a	0	0	1 (0.3)	0	1 (0.2)	0

(c) LIBERTY ASTHMA VENTURE

Patients, n (%)	Placebo (n = 107)	Dupilumab 300 mg q2w (n = 103)
Patients with ≥ 1 event, n (%)	1 (0.9)	1 (1.0)
Conjunctivitis ^a	0	1 (1.0)
Conjunctivitis allergic ^a	1 (0.9)	0

(d) CRSwNP: ACT12340

Patients, n (%)	Placebo (n = 30)	Dupilumab 300 mg qw (n = 30)
Patients with ≥ 1 event, n (%)	1 (3.3)	0
Conjunctivitis ^a	1 (3.3)	0

^aMedDRA PT.

CRSwNP, chronic rhinosinusitis with nasal polyposis; MedDRA, Medical Dictionary for Regulatory Activities; PT, preferred term; qw, weekly; q2w, every 2 weeks; q4w, every 4 weeks.

Figure legends

Fig 1. Conjunctivitis incidence by severity in the (a) monotherapy pool, (b) CHRONOS, (c) CAFÉ, and (d) SOLO-CONTINUE

Percentages above the bars represent incidence rate overall; percentages inside the bars may not add up to the percentages above the bars, due to rounding. qw, weekly; q2w, every 2 weeks; q4w, every 4 weeks; q8w, every 8 weeks; TCS, topical corticosteroids.

Fig 2. Time to first conjunctivitis event: (a) monotherapy pool; (b) CHRONOS; and (c) CAFÉ.

qw, weekly; q2w, every 2 weeks; TCS, topical corticosteroids. Symbols represent patients who discontinued study treatment.

Fig 3. Baseline characteristics and annualised event rate for patients' first event of conjunctivitis

(event rate per 100 PY) in the monotherapy pool, CHRONOS, and CAFÉ: (a) baseline IGA = 3 or 4; (b) baseline prior history of conjunctivitis; (c) baseline TARC; (d) baseline total IgE.

Rates were estimated from Poisson regression with treatment as fixed factors. Log values of duration of treatment were used as offset variables. CI, confidence interval; EASI, Eczema Area and Severity Index; IGA, Investigator's Global Assessment; IgE, immunoglobulin E; PY, patient-years; qw, weekly; q2w, every 2 weeks; RR, risk ratio; TARC, thymus and activation-regulated chemokine; TCS, topical corticosteroids.

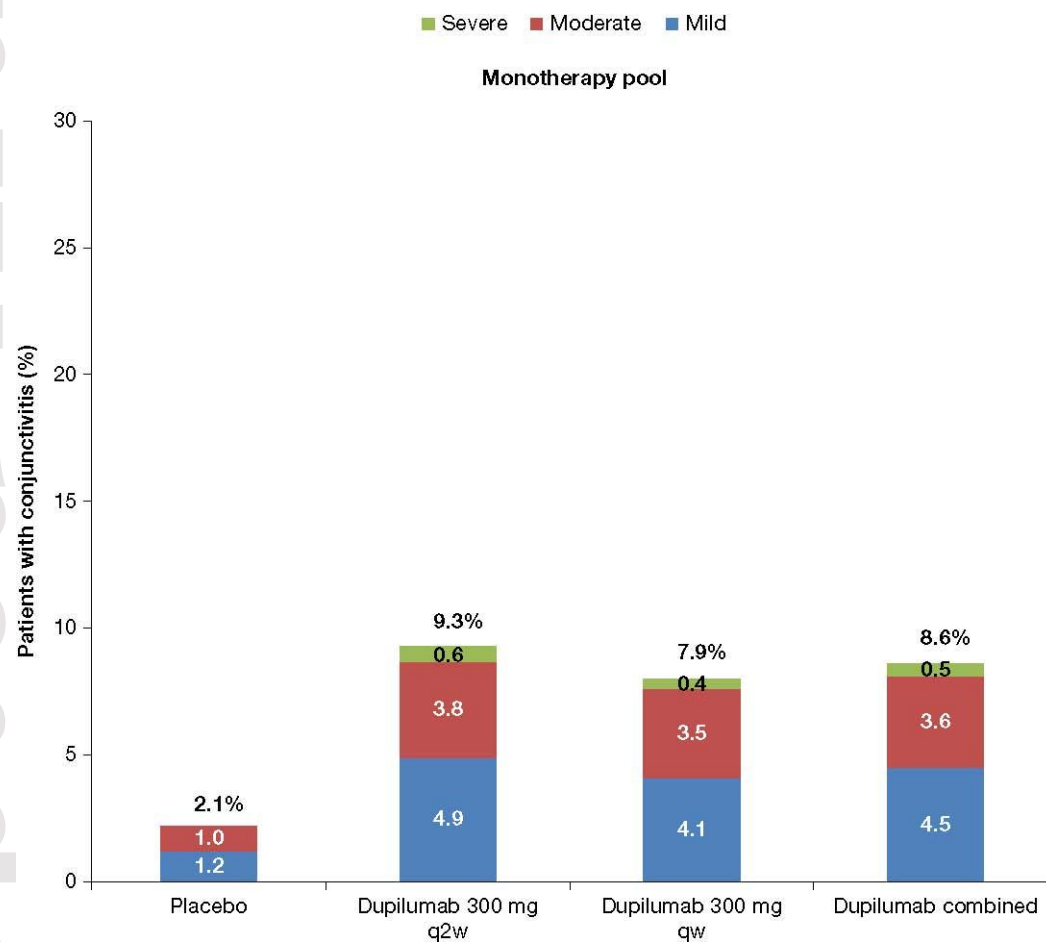
Fig 4. AD efficacy response and annualised event rate for patients' first event of conjunctivitis (event rate per 100 PY) in the monotherapy pool, CHRONOS, and CAFÉ: (a) IGA 0/1; (b) EASI-75

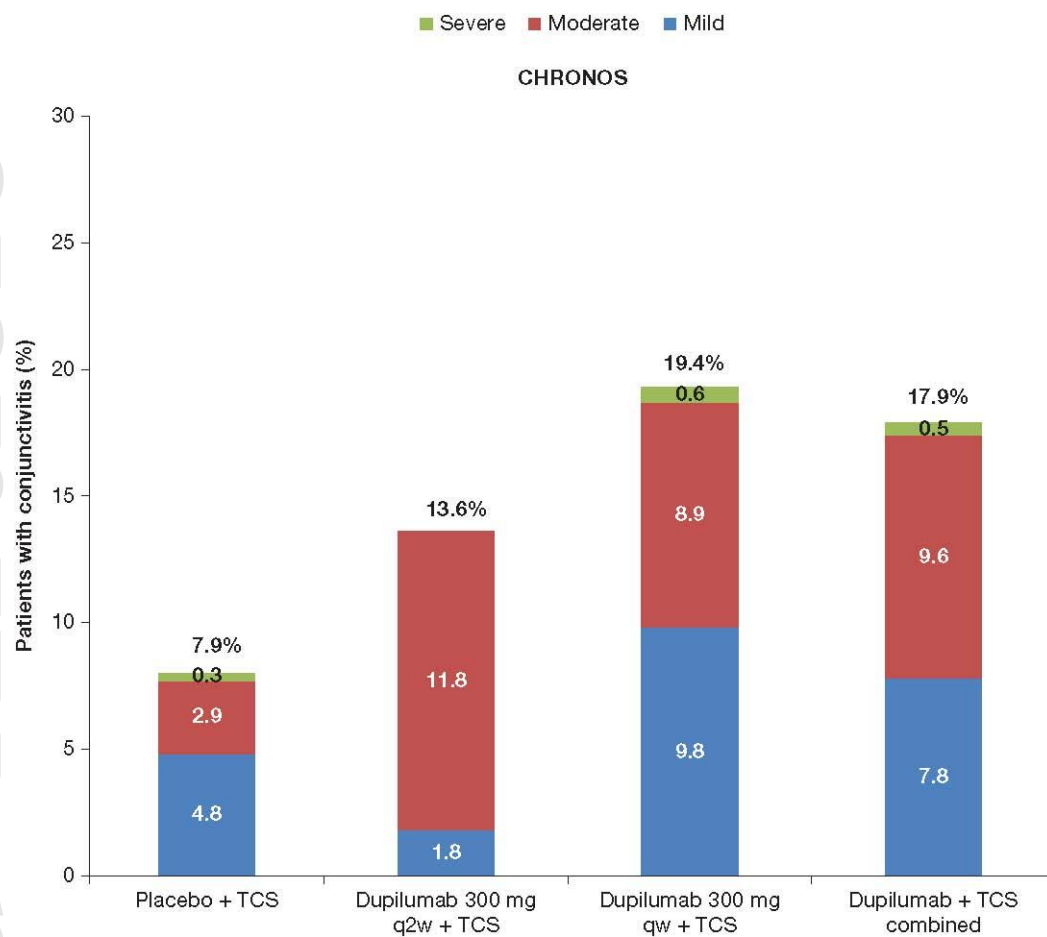
For analysis of IGA 0/1 and EASI-75, patients were considered non-responders after rescue treatment. For analysis of change and % change of EASI and pruritus NRS, LOCF method with censoring after rescue treatment was used. Rates were estimated from Poisson regression with

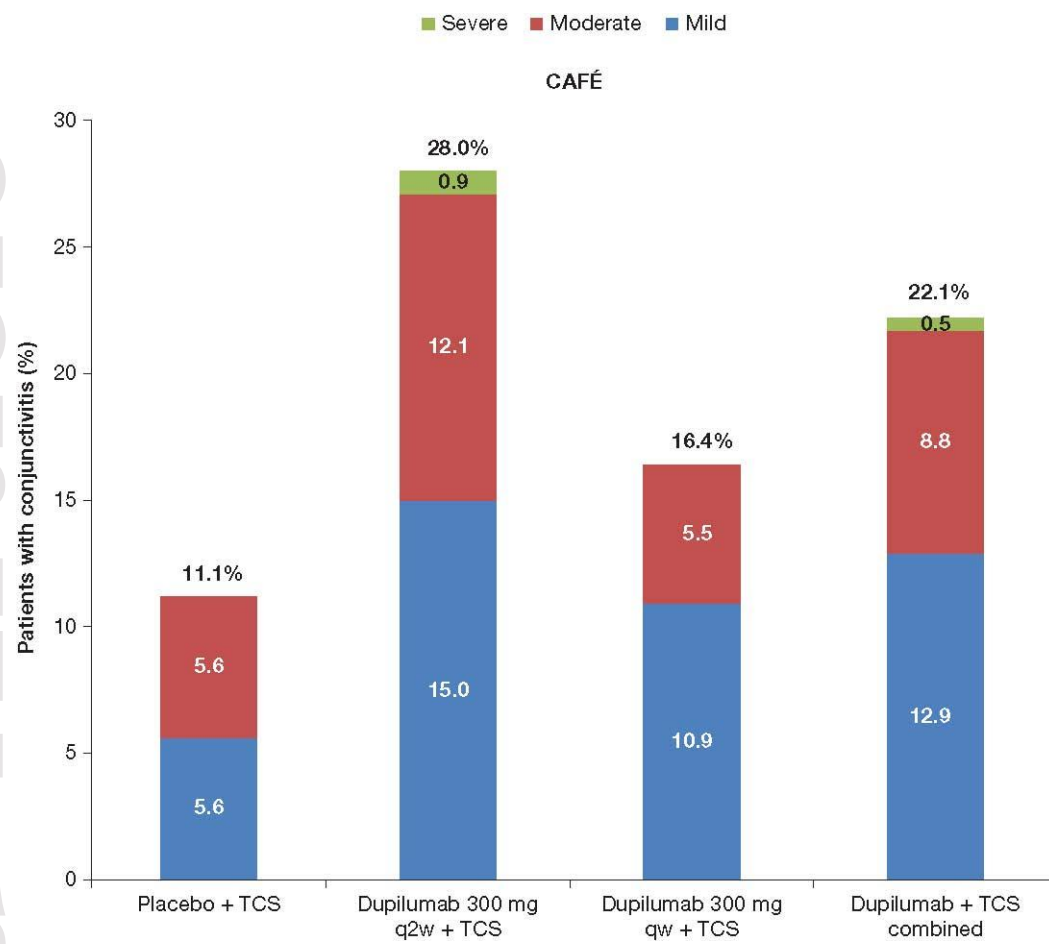
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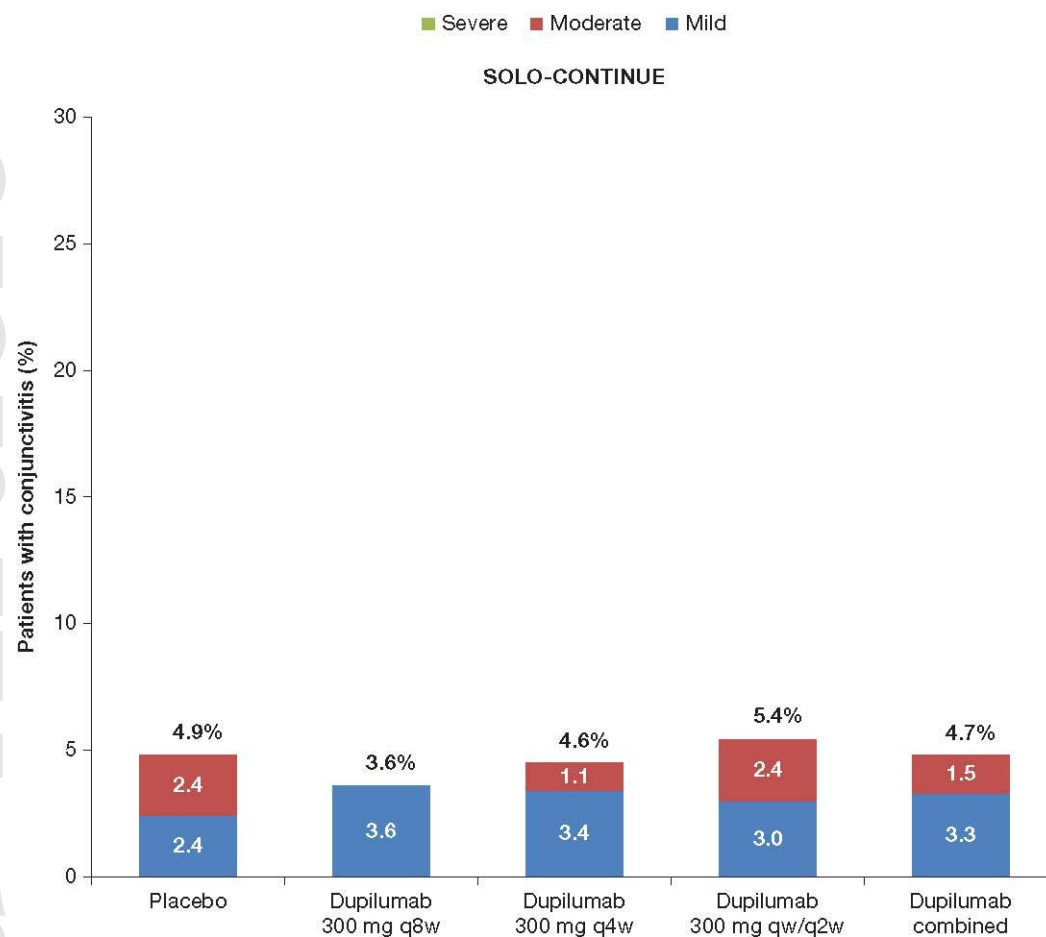
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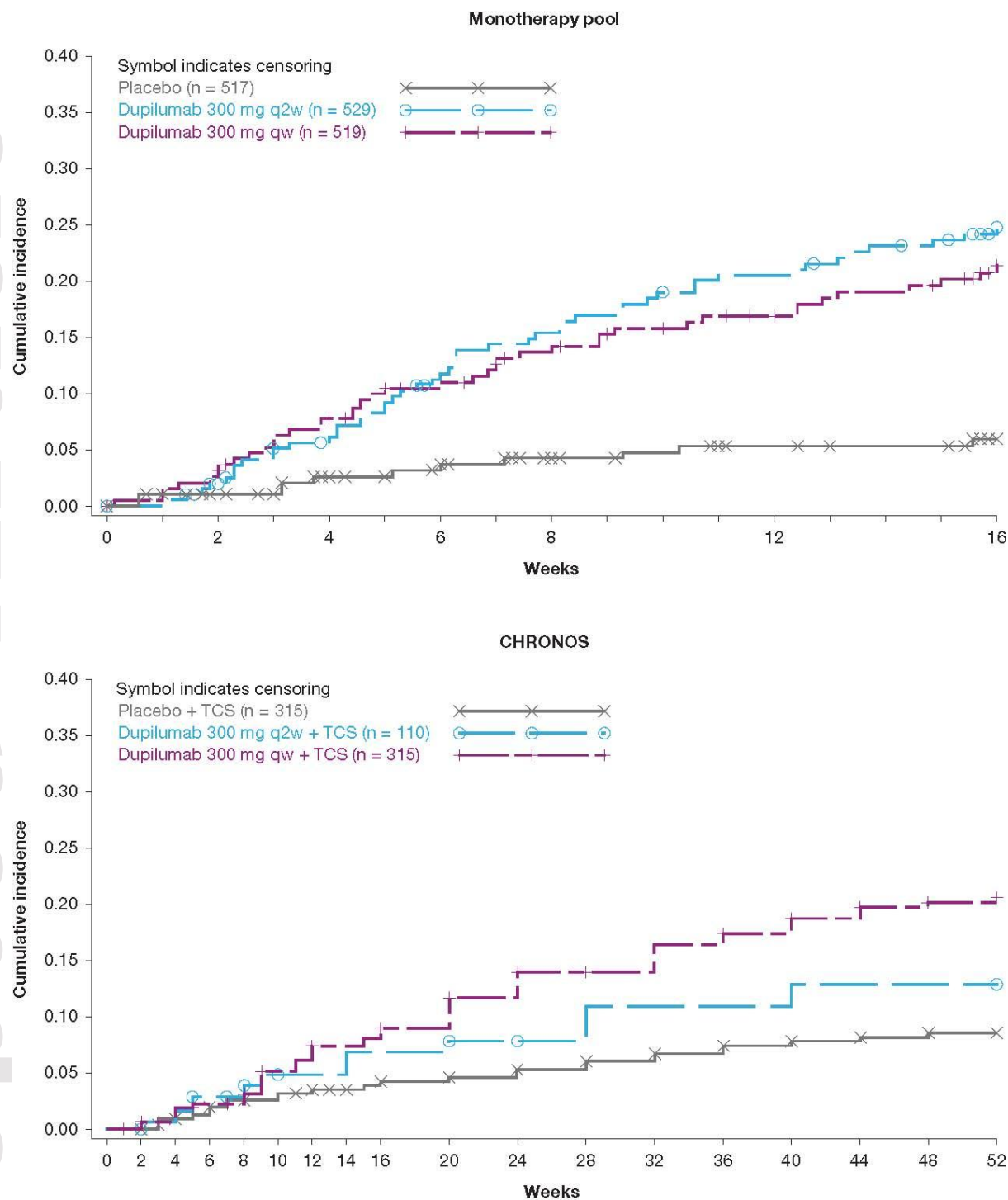
treatment as fixed factors. Log values of duration of treatment were used as offset variables. CI, confidence interval; EASI, Eczema Area and Severity Index (scale of 0–72; higher scores are more severe); EASI-75, $\geq 75\%$ improvement in EASI from baseline; IGA, Investigator's Global Assessment (0 = clear; 1 = almost clear; 2 = mild; 3 = moderate; 4 = severe); LOCF, last observation carried forward; PY, patient-years; qw, weekly; q2w, every 2 weeks; RR, risk ratio; TCS, topical corticosteroids.

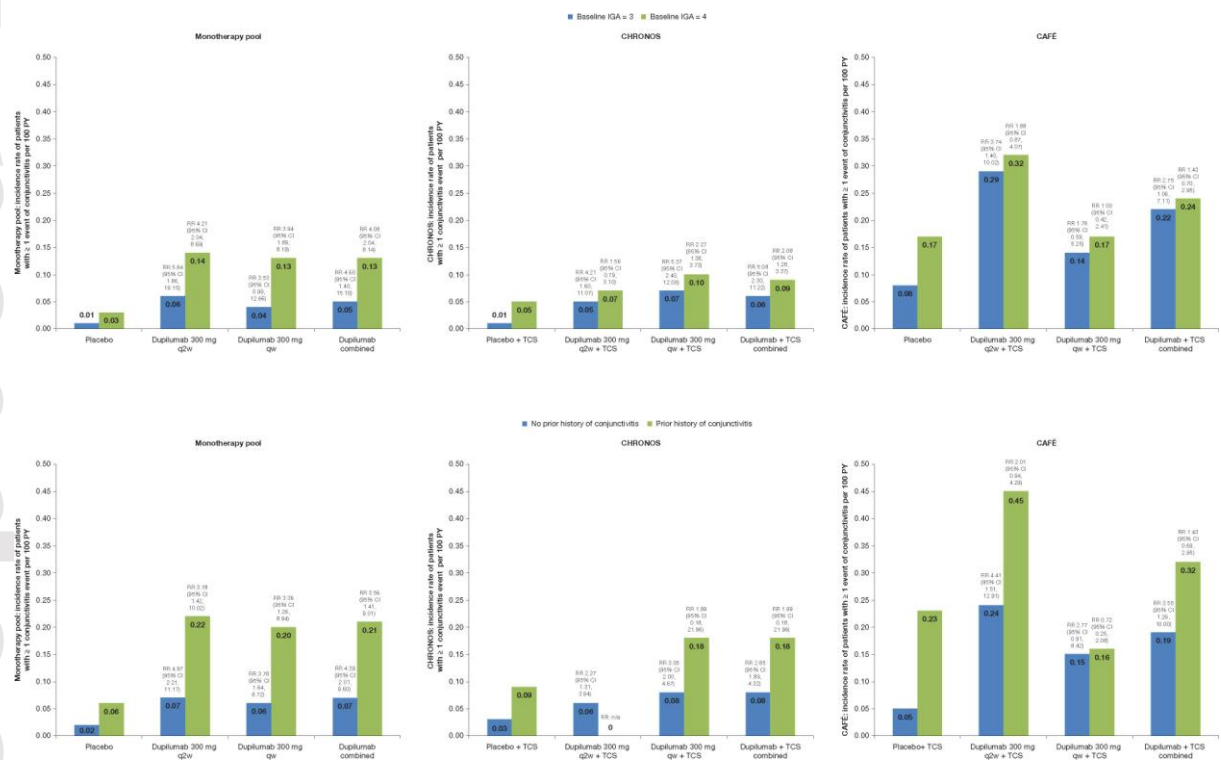
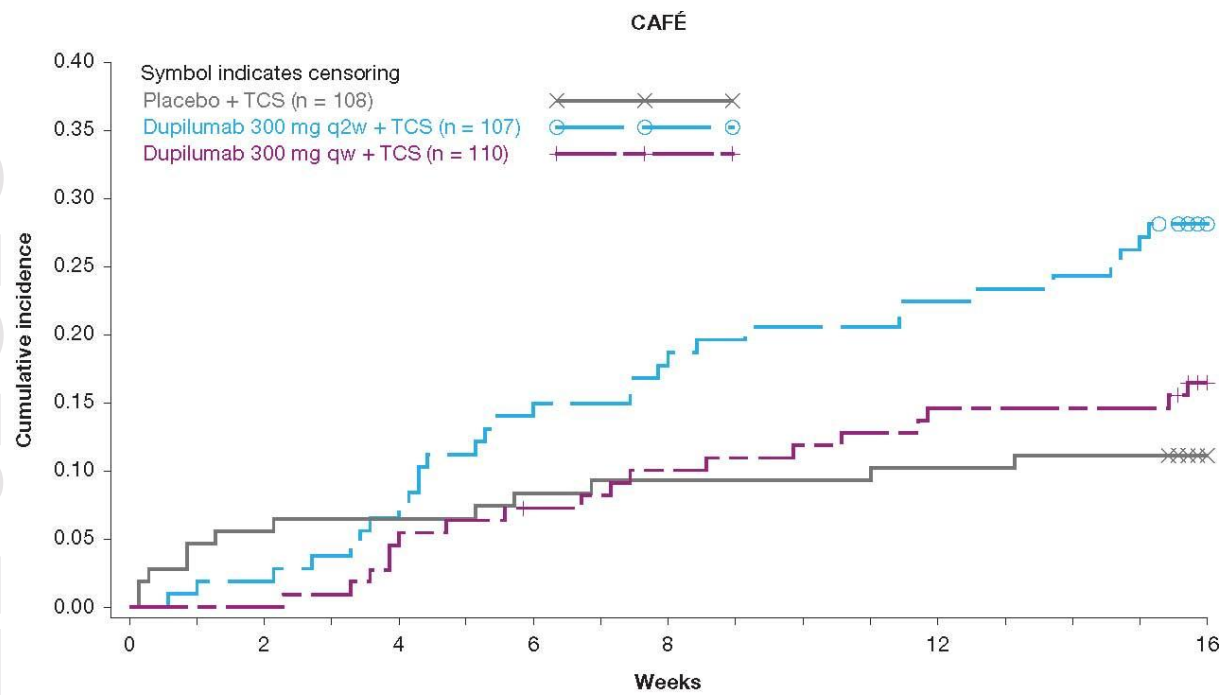


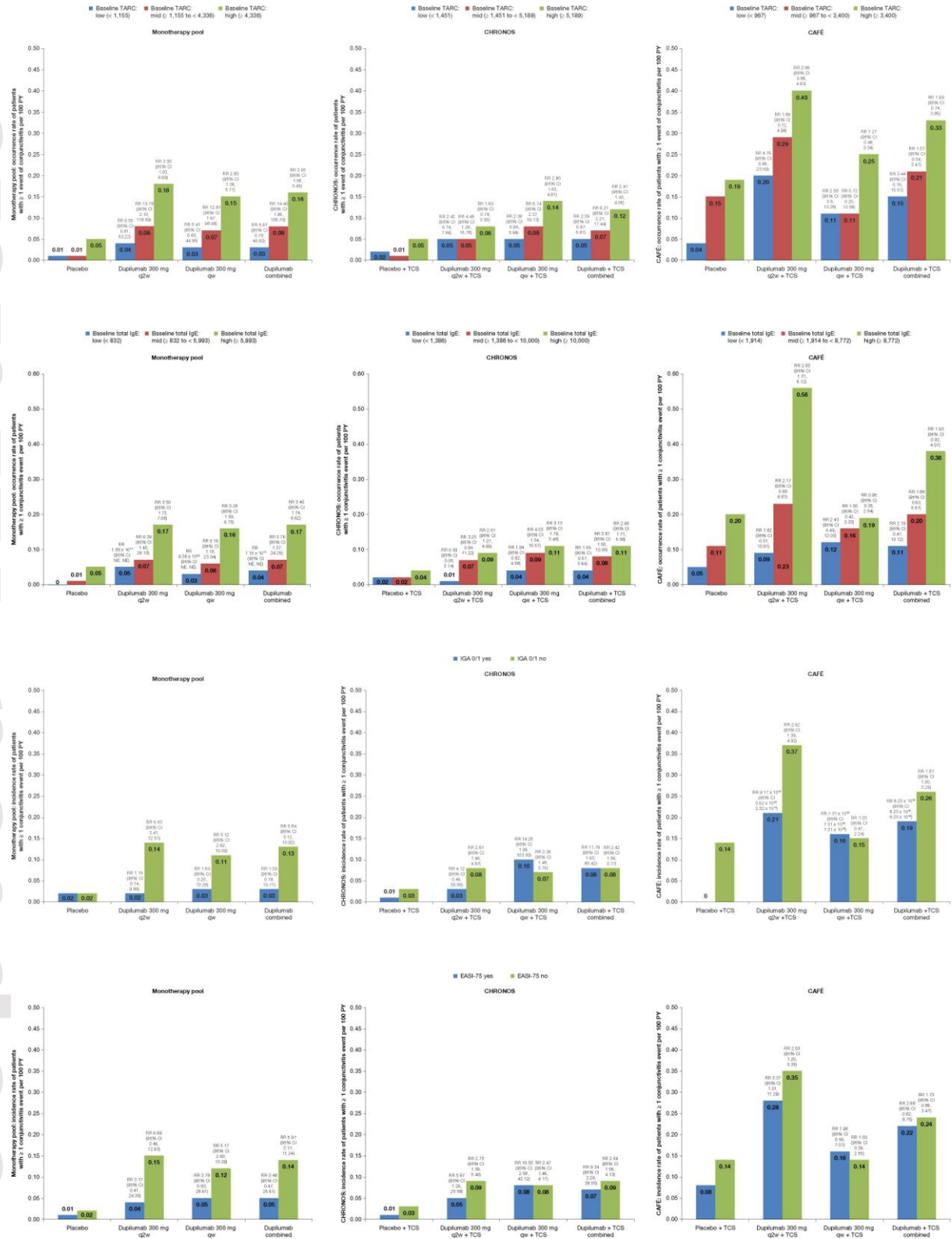












Supplementary appendix to:

Conjunctivitis in dupilumab clinical trials

Contents

Supplemental Table S1. Randomized clinical trials of dupilumab in atopic dermatitis (AD), asthma, chronic rhinosinusitis with nasal polyposis (CRSwNP), and eosinophilic esophagitis (EoE) included in this analysis.....	3
Supplemental Table S2. Incidence of conjunctivitis: number of patients with at least 1 event per 100 patient-years: (A) monotherapy pool, (B) CHRONOS, (C) CAFÉ, (D) SOLO-CONTINUE.....	8
Supplemental Table S3. Baseline characteristics and conjunctivitis in patients with AD: annualized event rate for patients' first event of conjunctivitis during the treatment period in the (A) monotherapy pool, (B) CHRONOS, and (C) CAFÉ trial.....	11
Supplemental Table S4. Incidence of conjunctivitis per 100 PY by dupilumab concentration from baseline to Week 16 in pooled data from SOLO 1, SOLO 2, and CHRONOS	24
Supplemental Table S5. Conjunctivitis resolution in (A, B, C) asthma and (D) CRSwNP: (A) DRI12544, (B) QUEST, (C) VENTURE, and (D) ACT12340.....	26
Supplemental Fig. S1. Conjunctivitis severity in asthma phase IIb (DRI12544), QUEST, VENTURE, and CRSwNP (ACT12340)	28
No cases of severe conjunctivitis were reported in these studies.	28
References	30

Supplemental Table S1. Randomized clinical trials of dupilumab in atopic dermatitis (AD), asthma, chronic rhinosinusitis with nasal polyposis (CRSwNP), and eosinophilic esophagitis (EoE) included in this analysis

Trial	Patients	N ^a	Treatment ^b	Duration of treatment, weeks	Concomitant medication ^c
AD					
Monotherapy pool					
R668-AD-1021 (NCT01859988) ¹	Adults with moderate-to-severe AD inadequately controlled with topical treatment	63	Dupilumab 300 mg qw	16	None required ^d
		64	Dupilumab 300 mg q2w		
		61	Placebo		
LIBERTY AD SOLO 1 (R668-AD-1334; NCT02277743) ²	Adults with moderate-to-severe AD inadequately controlled with topical treatment	218	Dupilumab 300 mg qw	16	None required ^e
		229	Dupilumab 300 mg q2w		
		222	Placebo		
LIBERTY AD SOLO 2 (R668-AD-1416; NCT02277769) ²	Adults with moderate-to-severe AD inadequately controlled with topical treatment	237	Dupilumab 300 mg qw	16	None required ^e
		236	Dupilumab 300 mg q2w		
		234	Placebo		
LIBERTY AD CHRONOS (R668-	Adults with moderate-to-severe AD and inadequate	315	Dupilumab 300 mg qw + TCS	52	Medium-potency TCS, or low-potency TCS for sensitive skin areas ± TCI in
		110	Dupilumab 300 mg q2w + TCS		

Trial	Patients	N ^a	Treatment ^b	Duration of treatment, weeks	Concomitant medication ^c
AD-1224; NCT02260986) ³	response to TCS	315	Placebo + TCS		place of TCS in locations such as face, intertriginous areas, and genital areas. TCS ± TCI could be tapered and stopped, or restarted as needed ^f
LIBERTY AD CAFÉ (R668-AD-1424; NCT02755649) ⁴	Adults with moderate-to- severe AD and inadequate response to or intolerance of CsA or for whom CsA was medically inadvisable	110	Dupilumab 300 mg qw + TCS	16	Medium-potency TCS, or low-potency TCS for sensitive skin areas ± TCI in place of TCS in locations such as face, intertriginous areas, and genital areas. TCS ± TCI could be tapered but not stopped ^e
		107	Dupilumab 300 mg q2w + TCS		
		108	Placebo + TCS		
LIBERTY AD SOLO- CONTINUE (R668- AD-1415; NCT02395133) ⁵	Patients from SOLO 1 and SOLO 2 who responded to dupilumab	167	Dupilumab 300 mg q2w/qw	36	None required ^e
		87	Dupilumab 300 mg q4w		
		84	Dupilumab 300 mg q8w		
		82	Placebo		
Asthma					
DRI12544 (NCT01854047) ⁶	Adults with uncontrolled persistent asthma despite use of medium-to-high-dose	156	Dupilumab 300 mg q2w	24	Continued inhaled corticosteroids plus a long-acting β ₂ -agonist ^g
		148	Dupilumab 200 mg q2w		
		157	Dupilumab 300 mg q4w		

Trial	Patients	N^a	Treatment^b	Duration of treatment, weeks	Concomitant medication^c
	ICS + LABA	150	Dupilumab 200 mg q4w		
		158	Placebo		
LIBERTY ASTHMA QUEST (EFC13579; NCT02414854) ⁷	Adults and adolescents with uncontrolled moderate-to- severe asthma despite use of medium-to-high-dose ICS + LABA	631	Dupilumab 200 mg q2w	52	Continued asthma controller medicines at a stable dose; long- acting β_2 -agonists, long-acting muscarinic antagonists, anti- leukotrienes, and methylxanthines were permitted ^g
		632	Dupilumab 300 mg q2w		
		313	Placebo 1.14 mL		
		321	Placebo 2 mL		
LIBERTY ASTHMA VENTURE (EFC13691; NCT02528214) ^{8,9}	Adults and adolescents (age ≥ 12 years) with glucocorticoid-dependent severe asthma	103	Dupilumab 300 mg q2w	24	3–10 weeks oral glucocorticoid (prednisone or prednisolone) dose- adjustment period prior to randomization; after randomization, patients continued on the adjusted dose for 4 weeks, followed by a 16- week period of glucocorticoid dose reduction (Weeks 4–20); patients then maintained the glucocorticoid dose from Week 20 for another 4
		107	Placebo		

Trial	Patients	N ^a	Treatment ^b	Duration of treatment, weeks	Concomitant medication ^c
					weeks (Weeks 21–24) Background asthma controllers were continued at a stable dose, and short-acting β ₂ -agonists were permitted as needed for asthma symptoms
CRSwNP					
ACT12340 (NCT01920893) ¹⁰	Adults with chronic sinusitis and nasal polyposis refractory to intranasal corticosteroids	30	Placebo plus mometasone furoate nasal spray	16	Mometasone furoate nasal spray ^h
		30	Dupilumab 300 mg qw plus mometasone furoate nasal spray		
EoE					
R668-EE-1324 (NCT02379052) ¹¹	Adult patients with active eosinophilic esophagitis	23	Dupilumab 300 mg qw	12	None required ⁱ
		24	Placebo		

^aSafety analysis set, comprising patients who had received ≥ 1 dose of study drug, as treated.

^bFor all studies, patients on a dupilumab 300 mg dose regimen received a loading dose of 600 mg at the first study visit; those on a 200 mg or 100 mg dose regimen received a loading dose of 400 mg at the first study visit; placebo-treated patients received matching placebo. For R668-AD-1021, other treatment arms (dupilumab 200 mg q2w, dupilumab 300 mg q4w, and dupilumab 100 mg q4w) were not included in this analysis.

^cFor all studies, this refers to concomitant medication that was required by the study design; please see study publications for other permitted and prohibited concomitant medications.

^dRescue treatment was permitted if medically necessary. Patients receiving rescue treatment discontinued study treatment.

^eRescue treatment was permitted if medically necessary. Patients receiving topical medication as rescue treatment could continue with study treatment, but those receiving systemic rescue medications discontinued study treatment.

^fRescue treatment was permitted if medically necessary after Week 2. Patients receiving topical medication as rescue treatment could continue with study treatment, but those receiving systemic rescue medications discontinued study treatment.

^gPatients could administer short-acting β_2 -adrenergic receptor agonists (either salbutamol or levosalbutamol) as relief medication for asthma symptoms.

^hContinuing inhaled asthma control therapies were permitted.

ⁱRescue treatment was permitted as needed; patients who received rescue treatment discontinued study treatment.

CRSwNP, chronic rhinosinusitis with nasal polyposis; CsA, cyclosporine A; ICS, inhaled corticosteroid; LABA, long-acting β -agonist; qw, weekly; q2w, every 2 weeks; q4w, every 4 weeks; q8w, every 8 weeks; TCI, topical calcineurin inhibitors; TCS, topical corticosteroids.

Supplemental Table S2. Incidence of conjunctivitis: number of patients with at least 1 event per 100 patient-years: (A) monotherapy pool, (B) CHRONOS, (C) CAFÉ, (D) SOLO-CONTINUE

A. Monotherapy pool

Patients with ≥ 1 event per 100 PY, nP/PY (nP/100 PY)	Placebo (n = 517)	Dupilumab 300 mg q2w (n = 529)	Dupilumab 300 mg qw (n = 518)	Dupilumab combined (n = 1047)
Patients with ≥ 1 event	11/151.0 (7.285)	49/152.2 (32.197)	41/148.1 (27.690)	90/300.3 (29.975)
Conjunctivitis ^a	3/152.6 (1.966)	21/157.0 (13.374)	20/151.3 (13.216)	41/308.3 (13.297)
Conjunctivitis allergic ^a	5/152.4 (3.282)	16/157.7 (10.146)	12/153.3 (7.826)	28/311.0 (9.002)
Conjunctivitis bacterial ^a	2/152.6 (1.311)	7/159.1 (4.399)	8/154.0 (5.196)	15/313.1 (4.791)
Conjunctivitis viral ^a	1/152.9 (0.654)	4/159.4 (2.510)	1/154.9 (0.646)	5/314.3 (1.591)
Atopic keratoconjunctivitis ^a	0/153.1 (0)	1/160.1 (0.625)	1/155.0 (0.645)	2/315.1 (0.635)

B. CHRONOS

Patients with ≥ 1 event per 100 PY, nP/PY (nP/100 PY)	Placebo + TCS (n = 315)	Dupilumab 300 mg q2w + TCS (n = 110)	Dupilumab 300 mg qw + TCS (n = 315)	Dupilumab combined (n = 425)
Patients with ≥ 1 event	25/270.5 (9.244)	15/93.4 (16.055)	61/261.0 (23.370)	76/354.4 (21.442)
Conjunctivitis allergic ^a	15/276.0 (5.436)	12/95.0 (12.629)	47/270.8 (17.358)	59/365.8 (16.130)
Conjunctivitis bacterial ^a	5/283.3 (1.765)	2/101.3 (1.975)	9/291.3 (3.089)	11/392.6 (2.802)
Conjunctivitis ^a	5/282.8 (1.768)	1/101.6 (0.984)	8/292.6 (2.734)	9/394.2 (2.283)
Atopic keratoconjunctivitis ^a	1/285.1 (0.351)	0/102.3 (0.000)	2/296.3 (0.675)	2/398.6 (0.502)

C. CAFÉ

Patients with ≥ 1 event per 100 PY, nP/PY (nP/100 PY)	Placebo + TCS (n = 108)	Dupilumab 300 mg q2w + TCS (n = 107)	Dupilumab 300 mg qw + TCS (n = 110)	Dupilumab + TCS combined (n = 217)
Patients with ≥ 1 event	12/30.8 (38.936)	30/28.1 (106.590)	18/31.0 (58.022)	48/59.2 (81.125)
Adenoviral conjunctivitis ^a	0/33.6	1/33.0 (3.030)	0/34.0	1/67.0 (1.493)
Conjunctivitis ^a	3/33.2 (9.047)	12/31.0 (38.770)	8/33.0 (24.271)	20/63.9 (31.293)
Conjunctivitis allergic ^a	7/31.9 (21.931)	16/30.8 (51.887)	10/32.0 (31.229)	26/62.9 (41.363)
Conjunctivitis bacterial ^a	2/33.2 (6.022)	1/33.1 (3.022)	0/34.0	1/67.1 (1.491)
Conjunctivitis viral ^a	1/33.3 (3.001)	1/33.0 (3.029)	0/34.0	1/67.0 (1.493)

D. SOLO-CONTINUE

Patients with ≥ 1 event per 100 PY, nP/PY (nP/100 PY)	Placebo (n = 82)	Dupilumab			
		300 mg q8w (n = 84)	300 mg q4w (n = 87)	300 mg q2w/qw (n = 167)	Combined (n = 338)
Patients with ≥ 1 event	4/53.7 (7.447)	3/55.7 (5.386)	4/57.1 (7.008)	9/107.9 (8.344)	16/220.6 (7.251)
Conjunctivitis ^a	2/53.9 (3.708)	2/55.8 (3.585)	2/58.0 (3.449)	6/109.7 (5.468)	10/223.5 (4.474)
Conjunctivitis allergic ^a	1/54.7 (1.828)	1/56.8 (1.760)	2/57.3 (3.489)	2/110.8 (1.805)	5/224.9 (2.223)
Bacterial conjunctivitis ^a	1/54.5 (1.835)	0/56.9 (0)	0/58.2 (0)	1/111.5 (0.897)	1/226.6 (0.441)

^aMedical Dictionary for Regulatory Activities preferred term.

nP, number of patients with ≥ 1 event; PY, patient-year; qw, weekly; q2w, every 2 weeks; q4w, every 4 weeks; q8w, every 8 weeks; TCS, topical corticosteroids.

Supplemental Table S3. Baseline characteristics and conjunctivitis in patients with AD: annualized event rate for patients' first event of conjunctivitis during the treatment period in the (A) monotherapy pool, (B) CHRONOS, and (C) CAFÉ trial

A. Monotherapy pool

Monotherapy pool		Conjunctivitis event rate per 100 PY (95% CI), n1				Risk ratio vs. placebo (95% CI)		
Category	Population	Placebo qw (n = 517)	Dupilumab 300 mg q2w (n = 529)	Dupilumab 300 mg qw (n = 518)	Dupilumab combined (n = 1047)	Dupilumab 300 mg q2w (n = 529)	Dupilumab 300 mg qw (n = 518)	Dupilumab combined (n = 1047)
Baseline IGA score	IGA = 3	0.01 (0, 0.03), 263	0.06 (0.04, 0.09), 275	0.04 (0.02, 0.07), 271	0.05 (0.03, 0.07), 546	5.64 (1.66, 19.15)	3.53 (0.99, 12.66)	4.60 (1.40, 15.10)
	IGA = 4	0.03 (0.02, 0.06), 254	0.14 (0.10, 0.19), 254	0.13 (0.09, 0.18), 247	0.13 (0.11, 0.17), 501	4.21 (2.04, 8.69)	3.94 (1.89, 8.19)	4.08 (2.04, 8.14)
Baseline EASI	Low (< 24.0)	0.01 (0, 0.05), 155	0.06 (0.03, 0.10), 187	0.05 (0.03, 0.09), 170	0.05 (0.04, 0.08), 357	4.86 (1.09, 21.73)	4.11 (0.89, 19.02)	4.51 (1.06, 19.23)
	Mid (≥ 24.0 to < 36.7)	0.03 (0.01, 0.06), 181	0.10 (0.06, 0.16), 163	0.07 (0.04, 0.12), 186	0.08 (0.06, 0.12), 349	3.91 (1.45, 10.53)	2.68 (0.97, 7.45)	3.26 (1.27, 8.36)
	High (≥ 36.7)	0.03 (0.01, 0.06), 181	0.135 (0.09, 0.20), 179	0.13 (0.09, 0.19), 162	0.13 (0.10, 0.17), 341	5.34 (2.06, 13.87)	5.03 (1.91, 13.24)	5.20 (2.07, 13.03)
Baseline worst pruritus NRS score	Low (< 6.80)	0.01 (0, 0.05), 165	0.10 (0.06, 0.15), 177	0.07 (0.04, 0.12), 174	0.08 (0.06, 0.12), 351	8.63 (2.01, 37.04)	6.04 (1.36, 26.76)	7.35 (1.76, 30.66)

Monotherapy pool		Conjunctivitis event rate per 100 PY (95% CI), n1				Risk ratio vs. placebo (95% CI)		
Category	Population	Placebo qw (n = 517)	Dupilumab 300 mg q2w (n = 529)	Dupilumab 300 mg qw (n = 518)	Dupilumab combined (n = 1047)	Dupilumab 300 mg q2w (n = 529)	Dupilumab 300 mg qw (n = 518)	Dupilumab combined (n = 1047)
	Mid (≥ 6.80 to < 8.29)	0.03 (0.01, 0.07), 184	0.11 (0.07, 0.16), 171	0.10 (0.06, 0.16), 164	0.10 (0.07, 0.14), 335	3.49 (1.40, 8.69)	3.31 (1.31, 8.34)	3.40 (1.44, 8.05)
	High (≥ 8.29)	0.02 (0.01, 0.06), 164	0.09 (0.05, 0.14), 179	0.07 (0.04, 0.12), 176	0.08 (0.06, 0.11), 355	3.85 (1.30, 11.44)	3.25 (1.07, 9.87)	3.55 (1.25, 10.07)
Baseline age, years	Low (< 29)	0.01 (0, 0.05), 165	0.06 (0.03, 0.11), 153	0.07 (0.04, 0.12), 162	0.06 (0.04, 0.10), 315	5.25 (1.15, 23.98)	6.17 (1.38, 27.58)	5.72 (1.35, 24.32)
	Mid (≥ 29 to < 44)	0.03 (0.02, 0.07), 166	0.11 (0.07, 0.16), 199	0.05 (0.03, 0.10), 176	0.08 (0.06, 0.12), 375	3.29 (1.35, 8.05)	1.54 (0.56, 4.24)	2.47 (1.04, 5.88)
	High (≥ 44)	0.02 (0.01, 0.05), 186	0.12 (0.08, 0.18), 177	0.12 (0.08, 0.18), 180	0.12 (0.09, 0.16), 357	5.87 (2.03, 16.98)	6.07 (2.11, 17.49)	5.97 (2.15, 16.57)
Baseline duration of AD, years	Low (< 20.0)	0.02 (0.01, 0.06), 147	0.06 (0.03, 0.11), 168	0.05 (0.02, 0.09), 168	0.05 (0.03, 0.08), 336	3.16 (0.88, 11.32)	2.40 (0.64, 9.03)	2.79 (0.82, 9.41)
	Mid (≥ 20.0 to < 34.0)	0.02 (0.01, 0.06), 180	0.09 (0.06, 0.15), 179	0.09 (0.06, 0.14), 173	0.09 (0.07, 0.13), 352	4.49 (1.52, 13.26)	4.29 (1.44, 12.76)	4.39 (1.56, 12.35)
	High (≥ 34.0)	0.03 (0.01, 0.06), 187	0.14 (0.10, 0.20), 179	0.11 (0.07, 0.17), 173	0.13 (0.10, 0.17), 352	5.58 (2.16, 14.46)	4.42 (1.67, 11.73)	5.02 (2.00, 12.60)
Baseline	Low (< 67.6)	0.03 (0.01, 0.07), 184	0.09 (0.06, 0.16), 171	0.07 (0.04, 0.16), 164	0.08 (0.06, 0.14), 335	3.63 (1.35, 8.69)	2.68 (0.94, 8.34)	3.18 (1.23, 8.05)

Monotherapy pool		Conjunctivitis event rate per 100 PY (95% CI), n1				Risk ratio vs. placebo (95% CI)		
Category	Population	Placebo qw (n = 517)	Dupilumab 300 mg q2w (n = 529)	Dupilumab 300 mg qw (n = 518)	Dupilumab combined (n = 1047)	Dupilumab 300 mg q2w (n = 529)	Dupilumab 300 mg qw (n = 518)	Dupilumab combined (n = 1047)
weight, kg		0.06), 180	0.15), 174	0.12), 164	0.12), 338	9.77)	7.60)	8.19)
	Mid (≥ 67.6 to < 83.5)	0.01 (0, 0.04), 176	0.13 (0.08, 0.19), 168	0.09 (0.05, 0.14), 180	0.10 (0.08, 0.14), 348	23.66 (3.20, 175.19)	16.08 (2.14, 120.85)	19.71 (2.71, 143.39)
	High (≥ 83.5)	0.04 (0.02, 0.08), 161	0.08 (0.05, 0.13), 187	0.09 (0.06, 0.14), 174	0.08 (0.06, 0.12), 361	2.24 (0.88, 5.73)	2.58 (1.02, 6.54)	2.40 (1.01, 5.73)
Conjunctivitis medical history	Yes	0.06 (0.03, 0.14), 77	0.22 (0.15, 0.34), 83	0.20 (0.13, 0.31), 90	0.21 (0.16, 0.29), 173	3.78 (1.42, 10.02)	3.36 (1.26, 8.94)	3.56 (1.41, 9.01)
	No	0.02 (0.01, 0.03), 440	0.07 (0.05, 0.10), 446	0.06 (0.04, 0.08), 428	0.07 (0.05, 0.08), 874	4.97 (2.21, 11.17)	3.78 (1.64, 8.72)	4.39 (2.01, 9.60)
Baseline TARC, pg/mL	Low (< 1155)	0.01 (0.00, 0.04), 162	0.04 (0.02, 0.08), 174	0.03 (0.01, 0.07), 181	0.03 (0.02, 0.06), 355	6.55 (0.81, 53.22)	5.41 (0.65, 44.95)	5.97 (0.78, 45.63)
	Mid (≥ 1155 to < 4336)	0.01 (0, 0.04), 177	0.08 (0.05, 0.13), 184	0.07 (0.04, 0.12), 161	0.08 (0.05, 0.11), 345	15.78 (2.10, 118.59)	12.81 (1.67, 98.49)	14.40 (1.96, 105.70)
	High (≥ 4336)	0.05 (0.03, 0.10), 176	0.18 (0.13, 0.25), 170	0.15 (0.10, 0.22), 173	0.16 (0.13, 0.21), 343	3.30 (1.63, 6.69)	2.802 (1.36, 5.77)	3.05 (1.56, 5.95)
Baseline	Low (< 0.30)	0.02 (0, 0.06),	0.02 (0.01,	0.03 (0.01,	0.03 (0.01,	1.66 (0.30,	2.04 (0.40,	1.85 (0.40,

Monotherapy pool		Conjunctivitis event rate per 100 PY (95% CI), n1				Risk ratio vs. placebo (95% CI)		
Category	Population	Placebo qw (n = 517)	Dupilumab 300 mg q2w (n = 529)	Dupilumab 300 mg qw (n = 518)	Dupilumab combined (n = 1047)	Dupilumab 300 mg q2w (n = 529)	Dupilumab 300 mg qw (n = 518)	Dupilumab combined (n = 1047)
eosinophils, 10 ⁹ /L		128	0.06), 150	0.07), 152	0.05), 302	9.06)	10.52)	8.57)
	Mid (≥ 0.30 to < 0.60)	0.01 (0.01, 0.04), 197	0.10 (0.06, 0.15), 179	0.05 (0.03, 0.10), 159	0.08 (0.05, 0.11), 338	6.84 (2.02, 23.10)	3.74 (1.01, 13.82)	5.40 (1.64, 17.76)
	High (≥ 0.60)	0.03 (0.02, 0.07), 190	0.15 (0.11, 0.22), 200	0.14 (0.10, 0.20), 205	0.15 (0.11, 0.19), 405	4.51 (2.00, 10.17)	4.06 (1.79, 9.21)	4.28 (1.96, 9.34)
Baseline total IgE, kU/L	Low (< 832)	0 (0, NE), 168	0.05 (0.02, 0.09), 175	0.03 (0.01, 0.07), 177	0.04 (0.02, 0.07), 352	1.36 x 10 ¹¹ (NE, NE)	9.38 x 10 ¹⁰ (NE, NE)	1.15 x 10 ¹¹ (NE, NE)
	Mid (≥ 832 to < 5,993)	0.01 (0.00, 0.05), 162	0.07 (0.04, 0.12), 176	0.06 (0.03, 0.10), 185	0.07 (0.05, 0.10), 361	6.39 (1.45, 28.13)	5.16 (1.15, 23.04)	5.76 (1.37, 24.25)
	High (≥ 5,993)	0.05 (0.03, 0.09), 187	0.17 (0.12, 0.24), 178	0.16 (0.11, 0.23), 156	0.17 (0.13, 0.21), 334	3.50 (1.73, 7.08)	3.28 (1.59, 6.75)	3.40 (1.74, 6.62)
Baseline antigen- specific IgE	Negative	0 (0, NE), 29	0 (0, NE), 26	0 (0, NE), 27	0 (0, NE), 53	0.93 (NE, NE)	1.29 (NE, NE)	1.10 (NE, NE)
	≥ 1 positive	0.02 (0.01, 0.04), 488	0.10 (0.08, 0.13), 503	0.09 (0.06, 0.11), 491	0.09 (0.08, 0.11), 994	4.51 (2.42, 8.41)	3.75 (1.99, 7.07)	4.14 (2.27, 7.52)

B. CHRONOS

CHRONOS		Conjunctivitis event rate per 100 PY (95% CI)				Risk ratio vs. placebo (95% CI)		
Category	Population	Placebo + TCS (n = 315)	Dupilumab 300 mg q2w + TCS (n = 110)	Dupilumab 300 mg qw + TCS (n = 315)	Dupilumab + TCS combined (n = 425)	Dupilumab 300 mg q2w + TCS (n = 110)	Dupilumab 300 mg qw + TCS (n = 315)	Dupilumab + TCS combined (n = 425)
Baseline IGA score	IGA = 3	0.01 (0.01, 0.03), 168	0.05 (0.03, 0.10), 56	0.07 (0.05, 0.09), 168	0.06 (0.05, 0.09), 224	4.21 (1.60, 11.07)	5.37 (2.40, 12.00)	5.08 (2.30, 11.22)
	IGA = 4	0.05 (0.03, 0.07), 147	0.07 (0.04, 0.12), 54	0.10 (0.08, 0.13), 146	0.09 (0.07, 0.120), 200	1.560 (0.79, 3.10)	2.27 (1.38, 3.73)	2.08 (1.28, 3.37)
Baseline EASI	Low (< 24.3)	0.02 (0.01, 0.04), 104	0.08 (0.04, 0.16), 33	0.07 (0.05, 0.11), 109	0.08 (0.06, 0.10), 142	4.62 (1.65, 12.99)	4.25 (1.76, 10.26)	4.34 (1.83, 10.27)
	Mid (≥ 24.3 to < 36.4)	0.01 (0, 0.03), 107	0.03 (0.01, 0.08), 40	0.07 (0.05, 0.11), 100	0.06 (0.04, 0.09), 140	3.41 (0.76, 15.24)	8.40 (2.53, 27.88)	6.95 (2.11, 22.85)
	High (≥ 36.4)	0.06 (0.04, 0.09), 104	0.08 (0.04, 0.15), 37	0.11 (0.08, 0.14), 106	0.10 (0.08, 0.13), 143	1.40 (0.66, 2.99)	1.82 (1.06, 3.12)	1.71 (1.02, 2.88)
Baseline worst pruritus NRS score	Low (< 6.83)	0.04 (0.02, 0.07), 96	0.04 (0.02, 0.10), 30	0.10 (0.07, 0.14), 114	0.09 (0.07, 0.12), 144	1.05 (0.34, 3.26)	2.72 (1.43, 5.18)	2.38 (1.26, 4.50)
	Mid (≥ 6.83 to < 8.20)	0.02 (0.01, 0.05), 104	0.07 (0.04, 0.13), 44	0.09 (0.06, 0.13), 99	0.08 (0.06, 0.11), 143	3.00 (1.21, 7.45)	3.84 (1.76, 8.37)	3.570 (1.67, 7.61)
	High (≥ 8.20)	0.02 (0.01, 0.05), 104	0.07 (0.04, 0.13), 44	0.06 (0.04, 0.10), 106	0.06 (0.04, 0.10), 143	2.95 (1.14, 7.45)	2.49 (1.14, 5.18)	2.60 (1.23, 5.18)

CHRONOS		Conjunctivitis event rate per 100 PY (95% CI)				Risk ratio vs. placebo (95% CI)		
Category	Population	Placebo + TCS (n = 315)	Dupilumab 300 mg q2w + TCS (n = 110)	Dupilumab 300 mg qw + TCS (n = 315)	Dupilumab + TCS combined (n = 425)	Dupilumab 300 mg q2w + TCS (n = 110)	Dupilumab 300 mg qw + TCS (n = 315)	Dupilumab + TCS combined (n = 425)
		0.05), 115	0.14), 36	0.09), 102	0.09), 138	7.64)	5.44)	5.50)
Baseline age, years	Low (< 28)	0.02 (0.01, 0.05), 98	0.08 (0.04, 0.16), 27	0.07 (0.05, 0.11), 99	0.07 (0.05, 0.10), 126	3.44 (1.21, 9.80)	3.24 (1.40, 7.50)	3.28 (1.45, 7.44)
	Mid (≥ 28 to < 43)	0.03 (0.01, 0.05), 113	0.04 (0.02, 0.10), 36	0.10 (0.07, 0.14), 108	0.09 (0.06, 0.11), 144	1.54 (0.53, 4.51)	3.68 (1.83, 7.40)	3.16 (1.59, 6.30)
	High (≥ 43)	0.03 (0.02, 0.06), 104	0.07 (0.04, 0.12), 47	0.08 (0.06, 0.11), 108	0.08 (0.06, 0.10), 155	2.04 (0.90, 4.62)	2.36 (1.20, 4.62)	2.26 (1.19, 4.31)
Baseline duration of AD, years	Low (< 20.0)	0.03 (0.02, 0.06), 100	0.02 (0.01, 0.10), 26	0.08 (0.05, 0.12), 102	0.07 (0.05, 0.10), 128	0.72 (0.16, 3.23)	2.35 (1.17, 4.75)	2.03 (1.02, 4.07)
	Mid (≥ 20.0 to < 33.0)	0.01 (0.01, 0.03), 108	0.08 (0.04, 0.14), 38	0.08 (0.06, 0.12), 102	0.08 (0.06, 0.11), 140	5.42 (1.85, 15.87)	5.59 (2.16, 14.46)	5.54 (2.18, 14.08)
	High (≥ 33.0)	0.04 (0.02, 0.06), 107	0.07 (0.04, 0.12), 46	0.09 (0.07, 0.13), 110	0.09 (0.06, 0.11), 156	1.92 (0.86, 4.29)	2.60 (1.38, 4.90)	2.40 (1.30, 4.44)
Baseline weight, kg	Low (< 64.5)	0.03 (0.02, 0.06), 98	0.05 (0.02, 0.11), 40	0.09 (0.06, 0.12), 107	0.08 (0.06, 0.10), 147	1.63 (0.62, 4.29)	2.72 (1.34, 5.53)	2.43 (1.21, 4.86)
	Mid (≥ 64.5)	0.03 (0.02, 0.06), 98	0.09 (0.05, 0.12), 40	0.08 (0.05, 0.12), 107	0.08 (0.06, 0.10), 147	2.63 (1.14, 4.29)	2.34 (1.19, 5.53)	2.41 (1.26, 4.86)

CHRONOS		Conjunctivitis event rate per 100 PY (95% CI)				Risk ratio vs. placebo (95% CI)		
Category	Population	Placebo + TCS (n = 315)	Dupilumab 300 mg q2w + TCS (n = 110)	Dupilumab 300 mg qw + TCS (n = 315)	Dupilumab + TCS combined (n = 425)	Dupilumab 300 mg q2w + TCS (n = 110)	Dupilumab 300 mg qw + TCS (n = 315)	Dupilumab + TCS combined (n = 425)
	to < 79.5)	0.06), 108	0.16), 35	0.11), 104	0.11), 139	6.09)	4.61)	4.62)
	High (≥ 79.5)	0.02 (0.01, 0.04), 109	0.05 (0.02, 0.11), 35	0.09 (0.06, 0.13), 104	0.08 (0.06, 0.11), 139	2.55 (0.86, 7.58)	4.59 (2.02, 10.43)	4.06 (1.81, 9.11)
Conjunctivitis medical history	Yes	0.09 (0.01, 0.65), 3	n/a (n/a, n/a), 0	0.18 (0.05, 0.73), 3	0.18 (0.05, 0.73), 3	n/a	1.99 (0.18, 21.96)	1.99 (0.18, 21.96)
	No	0.03 (0.02, 0.04), 312	0.06 (0.04, 0.09), 110	0.08 (0.07, 0.10), 312	0.08 (0.06, 0.09), 422	2.27 (1.31, 3.94)	3.05 (2.00, 4.67)	2.85 (1.89, 4.32)
Baseline TARC, pg/mL	Low (< 1451)	0.02 (0.01, 0.04), 97	0.05 (0.02, 0.11), 32	0.05 (0.03, 0.07), 116	0.05 (0.03, 0.07), 148	2.42 (0.74, 7.94)	2.38 (0.94, 5.99)	2.39 (0.97, 5.87)
	Mid (≥ 1451 to < 5189)	0.01 (0, 0.03), 101	0.05 (0.02, 0.12), 34	0.08 (0.06, 0.11), 111	0.07 (0.05, 0.10), 145	4.45 (1.26, 15.78)	6.74 (2.37, 19.13)	6.21 (2.21, 17.44)
	High (≥ 5189)	0.05 (0.03, 0.08), 115	0.08 (0.05, 0.14), 44	0.14 (0.10, 0.19), 87	0.12 (0.09, 0.16), 131	1.60 (0.78, 3.30)	2.80 (1.63, 4.81)	2.41 (1.43, 4.06)
Baseline eosinophils, 10 ⁹ /L	Low (< 0.30)	0.03 (0.01, 0.05), 99	0.02 (0, 0.07), 37	0.05 (0.03, 0.08), 106	0.04 (0.03, 0.06), 143	0.66 (0.14, 3.13)	1.95 (0.85, 4.49)	1.64 (0.72, 3.71)

CHRONOS		Conjunctivitis event rate per 100 PY (95% CI)				Risk ratio vs. placebo (95% CI)		
Category	Population	Placebo + TCS (n = 315)	Dupilumab 300 mg q2w + TCS (n = 110)	Dupilumab 300 mg qw + TCS (n = 315)	Dupilumab + TCS combined (n = 425)	Dupilumab 300 mg q2w + TCS (n = 110)	Dupilumab 300 mg qw + TCS (n = 315)	Dupilumab + TCS combined (n = 425)
	Mid (≥ 0.30 to < 0.56)	0.02 (0.01, 0.04), 93	0.08 (0.04, 0.15), 31	0.08 (0.06, 0.12), 120	0.08 (0.06, 0.11), 151	4.87 (1.59, 14.89)	5.36 (2.10, 13.69)	5.26 (2.08, 13.29)
	High (≥ 0.56)	0.04 (0.02, 0.07), 122	0.09 (0.05, 0.15), 42	0.13 (0.09, 0.17), 89	0.11 (0.09, 0.15), 131	2.20 (1.06, 4.57)	3.13 (1.75, 5.61)	2.83 (1.62, 4.96)
Baseline total IgE, kU/L	Low (< 1386)	0.02 (0.01, 0.05), 110	0.01 (0, 0.06), 33	0.04 (0.03, 0.07), 102	0.04 (0.02, 0.06), 135	0.39 (0.05, 3.14)	1.94 (0.82, 4.58)	1.56 (0.67, 3.64)
	Mid (≥ 1386 to < 10,000)	0.02 (0.01, 0.05), 68	0.07 (0.03, 0.17), 23	0.09 (0.06, 0.13), 81	0.08 (0.06, 0.12), 104	3.25 (0.94, 11.22)	4.03 (1.54, 10.57)	3.87 (1.50, 10.00)
	High (≥ 10,000)	0.04 (0.02, 0.06), 134	0.091 (0.06, 0.15), 54	0.11 (0.09, 0.15), 131	0.11 (0.08, 0.14), 185	2.51 (1.27, 4.96)	3.13 (1.79, 5.48)	2.95 (1.71, 5.08)
Baseline antigen- specific IgE	Negative	0 (0, NE), 13	0 (0, NE), 8	0.02 (0, 0.17), 12	0.02 (0, 0.11), 20	1.51 (NE, NE)	5.46 x 10 ¹¹ (NE, NE)	1.29 x 10 ¹¹ (NE, NE)
	≥ 1 positive	0.03 (0.02, 0.04), 300	0.07 (0.04, 0.10), 102	0.09 (0.07, 0.11), 302	0.08 (0.07, 0.10), 404	2.25 (1.30, 3.89)	2.97 (1.95, 4.51)	2.79 (1.85, 4.19)

C. CAFÉ

CAFÉ		Conjunctivitis event rate per 100 PY (95% CI), n1				Risk ratio vs. placebo (95% CI)		
Category	Population	Placebo + TCS (n = 108)	Dupilumab 300 mg q2w + TCS (n = 107)	Dupilumab 300 mg qw + TCS (n = 110)	Dupilumab + TCS combined (n = 217)	Dupilumab 300 mg q2w + TCS n = 107	Dupilumab 300 mg qw + TCS n = 110	Dupilumab + TCS combined (n = 217)
Baseline IGA score	IGA = 3	0.08 (0.03, 0.19), 56	0.29 (0.19, 0.46), 57	0.14 (0.07, 0.27), 58	0.22 (0.15, 0.31), 115	3.74 (1.40, 10.02)	1.76 (0.59, 5.25)	2.75 (1.06, 7.11)
	IGA = 4	0.17 (0.09, 0.31), 52	0.32 (0.20, 0.50), 50	0.17 (0.09, 0.32), 52	0.24 (0.17, 0.35), 102	1.88 (0.87, 4.07)	1.00 (0.42, 2.41)	1.43 (0.70, 2.95)
Baseline EASI	Low (< 26.4)	0.05 (0.01, 0.18), 39	0.32 (0.17, 0.59), 28	0.09 (0.04, 0.25), 38	0.19 (0.11, 0.32), 66	6.97 (1.53, 31.82)	2.09 (0.38, 11.41)	4.18 (0.95, 18.39)
	Mid (≥ 26.4 to < 36.6)	0.09 (0.03, 0.26), 31	0.26 (0.15, 0.44), 45	0.28 (0.15, 0.50), 35	0.27 (0.18, 0.40), 80	3.01 (0.86, 10.57)	3.28 (0.92, 11.75)	3.13 (0.94, 10.39)
	High (≥ 36.6)	0.23 (0.13, 0.43), 38	0.36 (0.22, 0.61), 34	0.10 (0.04, 0.25), 37	0.22 (0.14, 0.35), 71	1.56 (0.69, 3.52)	0.41 (0.13, 1.31)	0.96 (0.44, 2.08)
Baseline worst pruritus NRS score	Low (< 5.64)	0.10 (0.04, 0.25), 37	0.32 (0.18, 0.58), 30	0.16 (0.08, 0.33), 40	0.23 (0.14, 0.36), 70	3.41 (1.09, 10.71)	1.65 (0.48, 5.65)	2.41 (0.82, 7.13)
	Mid (≥ 5.64 to < 7.67)	0.22 (0.11, 0.44), 32	0.33 (0.19, 0.56), 35	0.22 (0.12, 0.41), 40	0.27 (0.18, 0.41), 75	1.49 (0.62, 3.59)	1.00 (0.40, 2.54)	1.23 (0.55, 2.75)
	High	0.07 (0.02, 0.14), 25	0.27 (0.16, 0.40), 25	0.06 (0.02, 0.13), 25	0.18 (0.11, 0.29), 25	3.92 (1.12, 13.42)	0.85 (0.14, 5.00)	2.64 (0.76, 9.50)

CAFÉ		Conjunctivitis event rate per 100 PY (95% CI), n1				Risk ratio vs. placebo (95% CI)		
Category	Population	Placebo + TCS (n = 108)	Dupilumab 300 mg q2w + TCS (n = 107)	Dupilumab 300 mg qw + TCS (n = 110)	Dupilumab + TCS combined (n = 217)	Dupilumab 300 mg q2w + TCS n = 107	Dupilumab 300 mg qw + TCS n = 110	Dupilumab + TCS combined (n = 217)
	(≥ 7.67)	0.22), 38	0.47), 42	0.24), 30	0.31), 72	13.76)	5.06)	9.12)
Baseline age, years	Low (< 31)	0.13 (0.05, 0.30), 35	0.16 (0.08, 0.34), 38	0.13 (0.05, 0.31), 34	0.15 (0.08, 0.26), 72	1.29 (0.41, 4.06)	1.03 (0.30, 3.55)	1.17 (0.41, 3.31)
	Mid (≥ 31 to < 44)	0.16 (0.08, 0.34), 38	0.38 (0.22, 0.66), 30	0.11 (0.05, 0.27), 39	0.23 (0.15, 0.36), 69	2.36 (0.94, 5.92)	0.70 (0.22, 2.21)	1.43 (0.60, 3.41)
	High (≥ 44)	0.08 (0.02, 0.24), 35	0.39 (0.24, 0.62), 39	0.22 (0.11, 0.42), 37	0.31 (0.21, 0.45), 76	5.10 (1.50, 17.41)	2.88 (0.78, 10.65)	4.03 (1.22, 13.31)
Baseline duration of AD, years	Low (< 22.0)	0.08 (0.02, 0.24), 35	0.14 (0.06, 0.32), 37	0.13 (0.05, 0.34), 28	0.14 (0.07, 0.25), 65	1.89 (0.47, 7.57)	1.67 (0.37, 7.44)	1.80 (0.49, 6.52)
	Mid (≥ 22.0 to < 38.0)	0.19 (0.10, 0.36), 42	0.36 (0.21, 0.61), 34	0.14 (0.06, 0.30), 39	0.24 (0.16, 0.37), 73	1.93 (0.84, 4.46)	0.72 (0.26, 2.03)	1.29 (0.59, 2.83)
	High (≥ 38.0)	0.09 (0.03, 0.27), 31	0.42 (0.26, 0.67), 36	0.19 (0.10, 0.36), 43	0.29 (0.20, 0.43), 79	4.87 (1.43, 16.63)	2.19 (0.59, 8.10)	3.42 (1.04, 11.31)
Baseline weight, kg	Low (< 68.0)	0.06 (0.01, 0.23), 31	0.19 (0.09, 0.37), 38	0.09 (0.03, 0.24), 39	0.14 (0.08, 0.24), 77	3.28 (0.70, 15.45)	1.59 (0.29, 8.69)	2.42 (0.54, 10.83)
	Mid (≥ 68.0)	0.15 (0.07, 0.36), 42	0.36 (0.21, 0.61), 34	0.16 (0.08, 0.30), 39	0.25 (0.17, 0.37), 73	2.41 (0.92, 6.13)	1.05 (0.35, 3.00)	1.68 (0.68, 4.23)

CAFÉ		Conjunctivitis event rate per 100 PY (95% CI), n1				Risk ratio vs. placebo (95% CI)		
Category	Population	Placebo + TCS (n = 108)	Dupilumab 300 mg q2w + TCS (n = 107)	Dupilumab 300 mg qw + TCS (n = 110)	Dupilumab + TCS combined (n = 217)	Dupilumab 300 mg q2w + TCS n = 107	Dupilumab 300 mg qw + TCS n = 110	Dupilumab + TCS combined (n = 217)
	to < 81.6)	0.34), 35	0.61), 34	0.33), 39	0.39), 73	6.26)	3.13)	4.17)
	High (≥ 81.6)	0.15 (0.07, 0.31), 42	0.38 (0.23, 0.63), 35	0.23 (0.11, 0.45), 32	0.31 (0.20, 0.46), 67	2.58 (1.05, 6.32)	1.53 (0.56, 4.23)	2.08 (0.89, 4.85)
Conjunctivitis medical history	Yes	0.23 (0.13, 0.41), 43	0.45 (0.28, 0.73), 33	0.16 (0.07, 0.39), 27	0.32 (0.21, 0.49), 60	2.01 (0.94, 4.29)	0.72 (0.25, 2.08)	1.43 (0.69, 2.95)
	No	0.05 (0.02, 0.14), 65	0.24 (0.15, 0.37), 74	0.15 (0.09, 0.25), 83	0.19 (0.14, 0.27), 157	4.41 (1.51, 12.91)	2.77 (0.91, 8.42)	3.55 (1.26, 10.00)
Baseline TARC, pg/mL	Low (< 967)	0.04 (0.01, 0.17), 41	0.20 (0.09, 0.45), 26	0.11 (0.05, 0.26), 40	0.15 (0.08, 0.27), 66	4.76 (0.96, 23.59)	2.58 (0.50, 13.28)	3.44 (0.76, 15.51)
	Mid (≥ 967 to < 3400)	0.15 (0.07, 0.34), 35	0.29 (0.17, 0.49), 40	0.11 (0.04, 0.29), 33	0.21 (0.13, 0.33), 73	1.89 (0.72, 4.98)	0.72 (0.20, 2.56)	1.37 (0.54, 3.47)
	High (≥ 3400)	0.19 (0.09, 0.41), 32	0.40 (0.25, 0.63), 40	0.25 (0.13, 0.46), 36	0.33 (0.23, 0.47), 76	2.06 (0.86, 4.93)	1.27 (0.48, 3.34)	1.69 (0.74, 3.86)
Baseline eosinophils, 10 ⁹ /L	Low (< 0.30)	0.13 (0.060, 0.32), 33	0.24 (0.11, 0.50), 26	0.03 (0, 0.22), 29	0.13 (0.06, 0.26), 55	1.79 (0.57, 5.63)	0.23 (0.03, 1.96)	0.97 (0.32, 2.95)

CAFÉ		Conjunctivitis event rate per 100 PY (95% CI), n1				Risk ratio vs. placebo (95% CI)		
Category	Population	Placebo + TCS (n = 108)	Dupilumab 300 mg q2w + TCS (n = 107)	Dupilumab 300 mg qw + TCS (n = 110)	Dupilumab + TCS combined (n = 217)	Dupilumab 300 mg q2w + TCS n = 107	Dupilumab 300 mg qw + TCS n = 110	Dupilumab + TCS combined (n = 217)
	Mid (≥ 0.30 to < 0.60)	0.09 (0.04, 0.25), 38	0.27 (0.15, 0.49), 36	0.19 (0.10, 0.38), 37	0.23 (0.15, 0.36), 73	2.90 (0.92, 9.11)	2.05 (0.62, 6.81)	2.47 (0.84, 7.26)
	High (≥ 0.60)	0.14 (0.06, 0.32), 37	0.37 (0.24, 0.58), 45	0.20 (0.11, 0.38), 44	0.29 (0.20, 0.42), 89	2.61 (1.04, 6.54)	1.43 (0.52, 3.93)	2.03 (0.84, 4.89)
Baseline total IgE, kU/L	Low (< 1914)	0.05 (0.01, 0.20), 35	0.09 (0.03, 0.28), 29	0.12 (0.06, 0.27), 44	0.11 (0.06, 0.21), 73	1.82 (0.31, 10.91)	2.43 (0.49, 12.03)	2.19 (0.47, 10.12)
	Mid (≥ 1914 to < 8772)	0.11 (0.04, 0.28), 33	0.23 (0.13, 0.42), 42	0.16 (0.07, 0.36), 33	0.20 (0.12, 0.32), 75	2.17 (0.69, 6.81)	1.50 (0.42, 5.33)	1.88 (0.63, 5.57)
	High (≥ 8772)	0.20 (0.10, 0.38), 40	0.56 (0.37, 0.85), 36	0.19 (0.09, 0.39), 33	0.38 (0.27, 0.55), 69	2.83 (1.31, 6.12)	0.95 (0.35, 2.54)	1.93 (0.92, 4.07)
Baseline antigen- specific IgE	Negative	n/a	n/a	n/a	n/a	n/a	n/a	n/a
	≥ 1 positive	n/a	n/a	n/a	n/a	n/a	n/a	n/a

Rates were estimated from Poisson regression with treatment as fixed factors; log values of duration of treatment were used as offset variables. AD, atopic dermatitis; CI, confidence interval; EASI, Eczema Area and Severity Index (scale of 0–72; higher scores are more severe); IGA, Investigator's Global Assessment (0 = clear; 1 = almost clear; 2 = mild; 3 = moderate; 4 = severe); IgE, immunoglobulin E; n, number of patients in the treatment group in the safety analysis set; n1, number of patients in the category's population in that treatment group in the safety analysis

set; n/a, not applicable; NE, not evaluable; pruritus NRS, pruritus Numerical Rating Scale (scale of 0–10; higher scores are more severe); PY, patient years; qw, weekly; q2w, every 2 weeks; TARC, thymus and activation-regulated chemokine; TCS, topical corticosteroids.

Supplemental Table **S4**. Incidence of conjunctivitis per 100 PY by dupilumab concentration from baseline to Week 16 in pooled data from SOLO 1, SOLO 2, and CHRONOS

PK parameters	Quartile	Range (mg/L)	Number of patients	Number of events	Incidence rate: number of events per 100 PY
Quartile of observed C _{trough}	Placebo	n/a	771	23	0.013
	Q1	0–72.4	323	45	0.155
	Q2	72.4–120	323	33	0.109
	Q3	120–190	325	20	0.063
	Q4	190–447	327	13	0.040
Quartile of predicted C _{trough}	Placebo	n/a	771	23	0.013
	Q1	5.45–72.8	324	56	0.197
	Q2	72.8–123	325	27	0.087
	Q3	123–187	324	17	0.054
	Q4	187–469	325	11	0.034
Quartile of predicted AUC _{tau}	Placebo	n/a	771	23	0.013
	Q1	146–958	324	59	0.211
	Q2	958–1270	325	24	0.076
	Q3	1,270–1,620	324	18	0.057
	Q4	1,620–3,470	325	10	0.031

AUC, area under the curve; C_{trough} , steady-state trough concentration; n/a, not applicable; PK, pharmacokinetic; PY, patient-years; Q1, first quartile; Q2, second quartile; Q3, third quartile; Q4, fourth quartile.

Supplemental Table S5. Conjunctivitis resolution in (A, B, C) asthma and (D) CRSwNP: (A) DRI12544, (B) QUEST, (C) VENTURE, and (D) ACT12340

A. DRI12544

		Dupilumab				
	Placebo (n = 158)	200 mg q4w (n = 150)	300 mg q4w (n = 157)	200 mg q2w (n = 148)	300 mg q2w (n = 156)	Combined (n = 611)
Patients with ≥ 1 event, n (%)	2 (1.3)	3 (2.0)	2 (1.3)	2 (1.4)	0	7 (1.1)
Recovered	2 (1.3)	3 (2.0)	2 (1.3)	2 (1.4)	0	7 (1.1)

B. QUEST

	1.14 mL/200 mg q2w		2 mL/300 mg q2w		Combined	
	Placebo (n = 313)	Dupilumab (n = 631)	Placebo (n = 321)	Dupilumab (n = 632)	Placebo (n = 634)	Dupilumab (n = 1263)
Patients with ≥ 1 event, n (%)	6 (1.9)	8 (1.3)	9 (2.8)	14 (2.2)	15 (2.4)	22 (1.7)
Recovered	6 (1.9)	8 (1.3)	9 (2.8)	14 (2.2)	15 (2.4)	22 (1.7)

C. VENTURE

	Placebo (n = 107)	Dupilumab 300 mg q2w (n = 103)
Patients with ≥ 1 event, n (%)	1 (0.9)	1 (1.0)
Recovered	0	1 (1.0)
Not recovered/not resolved	1 (0.9)	0

D. ACT12340

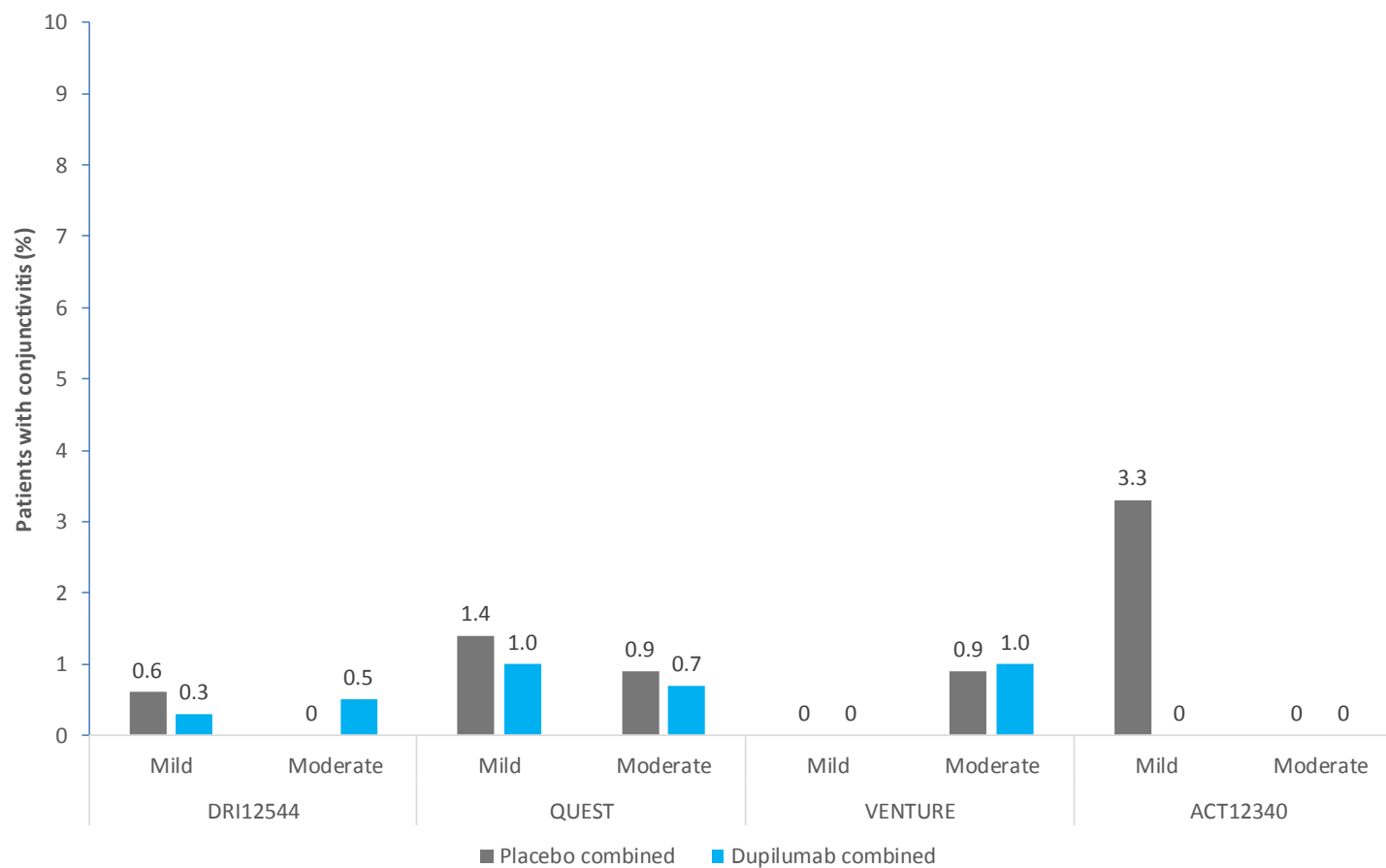
	Placebo (n = 30)	Dupilumab 300 mg qw (n = 30)
Patients with ≥ 1 event, n (%)	1 (3.3)	0
Recovered	1 (3.3)	0

qw, weekly; q2w, every 2 weeks; q4w, every 4 weeks.

Supplemental Fig. S1. Conjunctivitis severity in asthma phase IIb (DRI12544), QUEST, VENTURE, and CRSwNP (ACT12340)

No cases of severe conjunctivitis were reported in these studies.

Conjunctivitis incidence by severity: asthma and CRSwNP trials



Dupilumab combined, all dupilumab dose regimens in a study; placebo combined, all placebo dose regimens in a study; qw, weekly; q2w, every 2 weeks; q4w, every 4 weeks.

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