Conjunctivitis in adult patients with moderate-to-severe atopic dermatitis: results from five tralokinumab clinical trials

A. Wollenberg, L.A. Beck, M. de Bruin Weller, E.L. Simpson, S. Imafuku, M. Boguniewicz, R. Zachariae, C.K. Olsen and J.P. Thyssen

1 Klinikum der Universität München, Klinik und Poliklinik für Dermatologie und Allergologie, Munich, Germany
2 Department of Dermatology, Medicine and Pathology, University of Rochester Medical Center, Rochester, NY, USA
3 Department of Dermatology and Allergology, University Medical Center Utrecht, Utrecht, the Netherlands
4 Department of Dermatology, Oregon Health & Science University, Portland, OR, USA
5 Department of Dermatology, Fukuoka University Faculty of Medicine, Fukuoka, Japan
6 Division of Allergy-Immunology, Department of Pediatrics, National Jewish Health, Denver, CO, USA
7 LEO Pharma A/S, Ballerup, Denmark
8 Department of Dermatology and Venereology, Bispebjerg Hospital, University of Copenhagen, Copenhagen, Denmark

Linked Comment: R. Nguyen. Br J Dermatol 2022; 186:391–392.

Summary

Background Tralokinumab, a fully human IgG4 monoclonal antibody that specifically binds with high affinity to interleukin-13, effectively reduces moderate-to-severe atopic dermatitis (AD) when given every 2 weeks. The incidence of conjunctivitis is elevated vs. placebo, but severity and aetiology have not been examined.

Objective To analyse conjunctivitis data recorded in five randomized, placebo-controlled trials of tralokinumab in adult patients with moderate-to-severe AD.

Methods Overall, 2285 adults with AD were studied up to 16 weeks. Cochran–Mantel–Haenszel weights were applied to calculate the adjusted incidence of adverse events.

Results The incidence of conjunctivitis was higher (7–5%) with tralokinumab than with placebo (3–2%). Most events were mild or moderate in severity, and 78–6% and 73–9% of events resolved during the trial in the tralokinumab and placebo groups, respectively. Two (1–4%) events led to the permanent discontinuation of tralokinumab. An increased incidence of conjunctivitis, regardless of treatment group, was associated with more severe baseline AD, and history of allergic conjunctivitis/atopic keratoconjunctivitis, as well as the number of atopic comorbidities.

Limitations This analysis reports events up to week 16 only, with limited confirmation of conjunctivitis and its aetiology by an ophthalmologist, and insufficient reporting of ophthalmic treatments.

Conclusions Treatment with tralokinumab was associated with an increased incidence of conjunctivitis vs. placebo, but these cases were mostly mild and transient.

What is already known about this topic?

- Ocular disorders, including conjunctivitis, occur more frequently in patients with atopic dermatitis (AD).
- When using the interleukin (IL)-4 and IL-13 receptor blocking biologic dupilumab, patients with AD in clinical trials and real-world practice experience higher rates of conjunctivitis, which increases with baseline AD severity.
- Tralokinumab, a fully human monoclonal antibody, binds specifically to IL-13 with high affinity.
- Various rates of conjunctivitis have been observed in different clinical trials of tralokinumab.
Atopic dermatitis (AD) is a chronic, inflammatory skin disease characterized by intense pruritus and eczematous lesions. Ocular surface diseases, including various forms of conjunctivitis, blepharitis and keratitis, are commonly present in patients with AD, with a 2021 review reporting that 31% of patients with AD also report conjunctivitis. Further evidence suggests that patients with AD who have concurrent atopic conditions have higher rates of conjunctivitis. However, the association between type of atopic comorbidity and conjunctivitis risk has not been studied. Drug-induced conjunctivitis has been observed in clinical trials of dupilumab, a therapy that blocks interleukin (IL)-4 and IL-13 signalling via IL-4 receptor (IL-4R)α, and has been suggested to be a drug–disease interaction. In real-world clinical practice, the estimated prevalence of conjunctivitis in dupilumab-treated patients based on a systematic review of the literature is 26%, and can be persistent, despite adequate ophthalmological treatment. Additionally, the incidence of ocular complications, such as conjunctivitis, with dupilumab has been shown to increase with AD severity. Ophthalmological side-effects during dupilumab treatment have only been observed in patients with AD and not in studies of chronic sinusitis with nasal polyps, asthma or eosinophilic oesophagitis, suggesting AD-specific predisposing factors.

IL-13, a key driver of the underlying type 2 inflammation in AD, is overexpressed in lesional and nonlesional AD skin. Conjunctivitis signals have also been observed in phase II and phase III studies of tralokinumab and lebrikizumab, which specifically inhibit IL-13 signalling. Tralokinumab, a fully human IgG4 monoclonal antibody, specifically binds to IL-13 with high affinity, preventing interaction with IL-13Rα1 and subsequent downstream IL-13 signalling, thus inhibiting its proinflammatory activity. Tralokinumab has demonstrated efficacy and safety in a number of phase II and phase III trials in AD.

Since the introduction of dupilumab as a treatment for AD, conjunctivitis has been identified as an important adverse event (AE), resulting in an increased collaboration with ophthalmologists. Conjunctivitis was therefore recorded as an AE of special interest (AESI) in the tralokinumab phase III trials, and it is important to examine these data for insight into the incidence and profile of conjunctivitis in patients treated with tralokinumab.

The objective of this analysis was to characterize the occurrence of and risk factors for conjunctivitis in a large pool of patients with moderate-to-severe AD from five phase II/III trials of tralokinumab.

Materials and methods

Studies

Five completed double-blind, randomized, placebo-controlled, phase II/III trials of tralokinumab in AD comprised the AD pool: three phase III trials [ECZTRA 1 (NCT03131648); ECZTRA 2 (NCT03160885); ECZTRA 3 (NCT03363854)]; one phase II trial [ECZTRA 5 (NCT03562377)]; and one phase Ib dose-finding trial (NCT02347176) (Figure S1 and Table S1; see Supporting Information). The full trial designs have been reported previously.

The phase Ib dose-finding trial was sponsored by MedImmune; the ECZTRA trials were sponsored by LEO Pharma. All trials were conducted in accordance with ethical principles of the Declaration of Helsinki and Good Clinical Practice guidelines, and approved by the local institutional review boards or independent ethics committees of each institution.

Endpoints and assessments

This analysis pools AEs from the initial treatment period of the AD pool (16 weeks in the ECZTRA trials; 12 weeks in the dose-finding trial). Eye disorders were predefined as an AESI in the ECZTRA trials based on potential and established areas of safety interest for monoclonal antibodies in treating AD. Eye disorder AESI categories were prespecified: conjunctivitis AESI; keratoconjunctivitis AESI; and keratitis AESI. Events by preferred terms (PTs) were captured by AESI status (yes/no) from the AE form for the ECZTRA trials and classified retrospectively for the phase Ib dose-finding trial using a prespecified MedDRA search. Assessment of severity (mild, moderate or severe) was made according to the investigator’s judgement following guidance for any AEs. Additional information was
collected for eye disorder AESI, including aetiology (type of infection, noninfectious, other or unknown), bacterial culture outcome (for events with a bacterial aetiology), diagnosis of herpes simplex keratitis (for events with a viral aetiology; keratitis only) and if diagnosis was confirmed by an ophthalmologist (yes/no). History of allergic conjunctivitis/atopic keratoconjunctivitis was requested at screening. This analysis focuses on conjunctivitis AESI, summarizing baseline demographics and disease characteristics, treatments for conjunctivitis and subgroup analysis of medical history, AD severity, biomarker level and number of atopic comorbidities for the AD pool.

**Statistical analysis**

The analyses included all randomized patients exposed to tralokinumab or placebo during the initial treatment period. Cochran–Mantel–Haenszel weights were applied to calculate adjusted AE incidences accounting for different randomization rates between tralokinumab and placebo across trials (Figure S1; see Supporting Information). Incidence is reported as the percentage of patients with at least one event. Exposure-adjusted AE rates were calculated based on the first event as the number of patients per 100 patient-years of exposure (PYE), with PYE calculated until the first event within a particular AE term. Exposure-adjusted AE rates based on all events were calculated as the number of events per 100 PYE, with PYE calculated until the end of exposure. Hazard ratios (HRs) and 95% confidence intervals (CIs) were calculated from a Cox regression model with treatment groups as fixed effects, and stratified by trial and baseline disease severity (Investigator’s Global Assessment [IGA]) to compare the relative risk for the first conjunctivitis event between the two treatment groups. The Proportional Intensity Model (Andersen–Gill) with treatment groups as a fixed effect and stratified by trial and baseline IGA, which handles recurrent event data, was used when analysing all conjunctivitis events. The relationship of baseline characteristics was evaluated using descriptive statistics. Rates and rate ratios by various factors were estimated from a Poisson regression with treatment as fixed effect, and log values of exposure were used as offset variables. The cumulative incidence of time to first conjunctivitis event was estimated based on the Kaplan–Meier estimator (1-KM), which considers right censoring. A log-rank test (stratified by trial) was performed to test the difference in the distribution of time to first conjunctivitis event between the two treatments.

**Results**

**Incidence of conjunctivitis adverse event of special interest**

Overall, 2285 patients comprised the AD pool; 1605 were treated with tralokinumab 300 mg every 2 weeks (Q2W; PYE 473.2) and 680 were treated with placebo Q2W (PYE 193.1). Of these, 147 patients reported at least one conjunctivitis AESI: 126 patients in the tralokinumab group and 21 patients in the placebo group (Table 1). Overall, 179 eye disorder AESI occurred during the initial treatment period; 168 events were classified as conjunctivitis AESI.

The adjusted incidence of conjunctivitis AESI was higher for tralokinumab (7.5%) than placebo (3.2%; HR 2.4, 95% CI 1.5–3.8) (Table 1). A similar pattern was observed for the rate of conjunctivitis AESI, calculated as the number of patients with at least one event per 100 PYE (26.6 patients vs. 11.4 patients, respectively, per 100 PYE) (Table 1), and as the number of events (Table S2; see Supporting Information). Most conjunctivitis AESI were reported as the PTs ‘conjunctivitis’ or ‘conjunctivitis allergic’, the incidences of which were 5.4% and 2.0% in the tralokinumab group and 1.9% and 1.1% in the placebo group, respectively; the incidences of ‘conjunctivitis bacterial’ were 0.2% and 0.2% and ‘conjunctivitis viral’ were 0.1% and 0.1%, respectively. There was a low incidence of keratitis AESI (0.2% and 0.2%) and keratoconjunctivitis AESI (0.3% and 0%) in the tralokinumab and placebo groups, respectively, and all

| AESI category       | Placebo (n = 680) | Tralokinumab (n = 1605) | HR vs. placebo (95% CI) |
|---------------------|------------------|-------------------------|------------------------|
|                     | N (adjusted %)¹  | Adjusted rate,² per 100 PYE | N (adjusted %)²  | Adjusted rate,³ per 100 PYE |                      |
| Conjunctivitis       | 21 (3.2)         | 11.4 190.3               | 126 (7.5)           | 26.6 453.7              | 2.4 (1.5–3.8)        |
| Conjunctivitis       | 13 (1.9)         | 7.0 191.4               | 90 (5.4)            | 19.0 459.6              | 2.8 (1.6–5.0)        |
| Conjunctivitis allergic | 7 (1.1)         | 3.8 191.9               | 34 (2.0)            | 6.7 467.9              | 1.8 (0.8–4.0)        |
| Conjunctivitis bacterial | 1 (0.2)        | 0.6 192.8               | 4 (0.2)             | 0.7 472.6              | 1.3 (0.2–2.0)        |
| Conjunctivitis viral | 1 (0.1)         | 0.5 193.1               | 1 (0.1)             | 0.2 473.0              | 0.4 (0.0–6.5)        |

Adverse events collected during the exposure time in the initial treatment period (12 weeks in the dose-finding trial and 16 weeks in the ECZTRA trials) are shown. Conjunctivitis AESI are shown as preferred terms. At each level of patient summarization, a patient is counted once if they reported one or more events. Data are based on adjusted pooling; N, number of patients with one or more events; n, number of patients; PYE, patient-years of exposure. ⁰Calculated using Cochran–Mantel–Haenszel weights. Rate calculated as number of patients divided by PYE multiplied by 100. HRs and 95% CIs were obtained from a Cox regression model with treatment groups as fixed effects and stratified by trial and baseline disease severity (Investigator’s Global Assessment).

---

© 2021 The Authors. British Journal of Dermatology
published by John Wiley & Sons Ltd on behalf of British Association of Dermatologists

British Journal of Dermatology (2022) 186, pp 453–465

Conjunctivitis in tralokinumab clinical trials, A. Wollenberg et al. 455
were reported as mild or moderate in severity. Blepharitis was not included as an eye disorder AEsI; however, the adjusted incidence of blepharitis reported as a PT was 0.8% for tralokinumab and 0.3% for placebo.

In the ECZTRA trials, investigators were asked to record if cases of conjunctivitis were confirmed by an ophthalmologist. In the tralokinumab group, 39 (27.1%) had an ophthalmologist-confirmed diagnosis, while six (28.6%) were confirmed in the placebo group (Table S3; see Supporting Information).

### Conjunctivitis severity and outcome

No conjunctivitis AEsI were serious AEs. Most first conjunctivitis AEsI were mild, reported in 5% of tralokinumab-treated patients and 2.1% of placebo-treated patients vs. moderate (2.4% and 1.1%, respectively) and severe (0.1% and 0%, respectively) conjunctivitis (Figure 1). The severity of all conjunctivitis AEsI is reported in the Supporting Information; two events of moderate conjunctivitis led to permanent discontinuation of tralokinumab (Table S4; see Supporting Information). The outcome of all conjunctivitis AEsI was similar between treatment groups; most events resolved during the trial (78.6% and 73.9%, respectively) with or without ophthalmological treatment (Table 2).

### Disease course

Conjunctivitis AEsI had onset throughout the initial treatment period in both treatment groups. A difference in the mean number of conjunctivitis AEsI between the treatment groups was observed from week 4 onwards (Figure 2). The median time to first conjunctivitis AEsI was similar for tralokinumab and placebo (50.0 days vs. 54.0 days) (Table S5; see Supporting Information). Figure 2 shows the time to onset of the first AEsI; however, the duration of conjunctivitis AEsI varied between treatment groups. Of 112 events in the tralokinumab group that had an end date, 36 (32.1%) lasted < 15 days and 25 (22.3%) lasted ≥ 91 days. In the placebo group, of 18 events that had an end date, nine (50.0%) lasted < 15 days and three (16.7%) lasted ≥ 91 days (Table S6; see Supporting Information).

### Treatments

Most patients treated with tralokinumab received treatment for their first conjunctivitis AEsI; 80.2% of these events were treated with an ophthalmological treatment (Table 3). The most frequently used treatments in the tralokinumab group were ophthalmic anti-infectives/antibiotics (29.4%), ophthalmic antihistamines (21.4%) and ophthalmic corticosteroids (plain; 20.6%), with calcineurin inhibitors (4.8%) being the least used treatment (Table 3). Information on bacterial culture outcome was recorded for 48 of 145 conjunctivitis AEsI in the tralokinumab group; three events were positive (Staphylococcus aureus), two were negative and a bacterial culture was not performed in 43 events. No patients were treated with antivirals.

| Outcomes                                      | Placebo | Tralokinumab |
|-----------------------------------------------|---------|--------------|
| Fatal                                         | 0       | 0            |
| Not recovered/not resolved                    | 5 (21.7)| 26 (17.9)    |
| Recovering/resolving                          | 1 (4.3) | 4 (2.8)      |
| Recovered/resolved                            | 17 (73.9)| 114 (78.6)   |
| Recovered/resolved with sequelae              | 0       | 1 (0.7)      |
| Unknown                                       | 0       | 0            |

Data are n (%). Adverse events collected during the exposure time in the initial treatment period (12 weeks in the dose-finding trial and 16 weeks in the ECZTRA trials) are shown. Data from the atopnic dermatitis pool using simple pooling. Percentages are calculated based on the number of events divided by the number of events (E) within the category (E/E [for all events] × 100).

### Baseline demographics and disease characteristics of patients with and without conjunctivitis adverse event of special interest

Patients who reported conjunctivitis, regardless of treatment group, were older (median age 39.0 years vs. 35.0 years in patients who did not report conjunctivitis) and more likely to be men (62.6% vs. 56.3%) (Table 4). Patients with
conjunctivitis AESI in the tralokinumab and placebo groups combined had more severe AD (IGA 4: 61.2% vs. 46.3%) (Figure 3, Table 4) and higher median Eczema Area and Severity Index (EASI) score (32.0 vs. 26.7) at baseline (Table 4) vs. patients without conjunctivitis AESI, respectively. Patients with conjunctivitis AESI had a numerically longer median duration of AD at baseline (30.0 years vs. 25.0 years) and higher median body surface area involvement with AD (60.0% vs. 46.0%) (Table 4). Patients with conjunctivitis AESI were more likely to have atopic comorbidities, including asthma, food allergy, hay fever or atopic keratoconjunctivitis, and more than half of patients with conjunctivitis AESI had a history of allergic conjunctivitis (Table 5). Patients with conjunctivitis were more heavily pretreated for their AD (Table S7; see Supporting Information).

Conjunctivitis adverse event of special interest by baseline characteristics: identification of risk factors

Subgroup analysis was performed to identify risk factors for the development of conjunctivitis in patients with AD treated with tralokinumab. Patients with more severe AD were more likely to develop conjunctivitis [EASI < 20.0 rate of 0.18 patients per 100 PYE (95% CI 0.11–0.27); EASI ≥ 39.2 rate of 0.34 patients per 100 PYE (95% CI 0.24–0.46)], as well as patients with a history of allergic conjunctivitis/atopic keratoconjunctivitis [with a history rate of 0.49 patients per 100 PYE (95% CI 0.39–0.62); without history rate of 0.19 patients per 100 PYE (95% CI 0.14–0.24)] (Figure 4). A high incidence of conjunctivitis AESI was observed in patients with higher baseline disease biomarker levels, including eosinophils, IgE and lactate dehydrogenase (Figure 4). A similar pattern was observed for placebo.

There was a broad distribution of atopic comorbidities in the medical history of AD pool patients at baseline (Figure 5a). Approximately 80% of patients in the tralokinumab and placebo groups combined reported a history of one or more atopic comorbidities in addition to AD, and 10-9% of patients had a history of all of the most common atopic comorbidities: asthma, food allergy, hay fever and allergic conjunctivitis/atopic keratoconjunctivitis (Figure 5a). Patients who had several atopic comorbidities were more likely to develop conjunctivitis, regardless of treatment group. In the tralokinumab and placebo groups, the adjusted rate of conjunctivitis AESI in patients with one atopic comorbidity was 20.4 and 7.9 vs. 54.2 and 25.7 in patients with three comorbidities, respectively (Table 6). A higher proportion of patients with history of asthma or allergic conjunctivitis/atopic keratoconjunctivitis developed conjunctivitis vs. patients with a history of hay fever or food allergy, and the combination of both asthma and allergic conjunctivitis/atopic keratoconjunctivitis was associated with the highest number of cases of conjunctivitis (Figure 5b, c).

Discussion

Analysis of the five clinical trials found that the overall incidence of conjunctivitis AESI was higher for tralokinumab (7.5%) than for placebo (3.2%). Most cases of conjunctivitis were mild and resolved with or without ophthalmological...
| Treatment | Total | Recovered/resolving, % total events | Recovered/resolving, % total events | Not recovered/not resolved, % total events | Not recovered/not resolved, % total events | Recovered/resolved with sequelae, % total events | Recovered/resolved with sequelae, % total events | Mild, % total events | Moderate, % total events | Severe, % total events | Severe, % total events |
|-----------|-------|------------------------------------|------------------------------------|------------------------------------------|------------------------------------------|-----------------------------------------------|-----------------------------------------------|-----------------|------------------|-----------------|------------------|
| Totala    | 126   | 98 (77.8) 77 (61.0) 78.6 2 (2.4) 24 (19.0) | 3 (2.4) 77 (61.0) 2 (2.0) 66.7 | 21 (208) 87.5 | 4 (13.4) 16.7 | 0 | 19 (73.1) 2.4 | 0 | 10 (62.5) 11.8 | 6 (37.5) 15.4 |
| Treatment |       |                                    |                                    |                                          |                                          |                                              |                                              |                 |                  |                  |                  |
| Corticosteroids, plain | 26 (20.6) | 21 (80.8) 21.4 | 1 (3.8) 33.3 | 4 (15.4) 16.7 | 0 | 19 (73.1) 2.4 | 0 | 10 (62.5) 11.8 | 6 (37.5) 15.4 |
| Corticosteroids and anti-infectives/antibiotics in combination | 16 (12.7) | 11 (68.8) 11.2 | 0 | 5 (31.3) 2.0 | 0 | 10 (62.5) | 11.8 | 6 (37.5) 15.4 |
| Anti-infectives/antibiotics | 27 (21.4) | 15 (55.6) 15.3 | 1 (3.7) 33.3 | 10 (37.0) 41.7 | 1 (3.7) 110 | 22 (81.5) | 2.5 | 0 | 15 (70.5) | 12.8 |
| Calcineurin inhibitors | 6 (4.8) | 5 (83.3) 5.1 | 0 | 1 (16.7) 33.3 | 0 | 4 (66.7) | 4.7 | 0 | 3 (50) | 16.7 |
| Artificial tears | 12 (9.5) | 9 (75.0) 9.2 | 0 | 3 (25.0) 12.5 | 0 | 25 (66.7) | 10.6 | 0 | 12 (33.3) | 30.8 |
| Artificial tears, plain | 37 (29.4) | 20 (54.1) 32.7 | 5 (13.5) 13.3 | 3 (8.1) 13.3 | 0 | 15 (70.5) | 17.6 | 5 | 25 (23.0) | 12.8 |
| Artificial tears, plain, with concomitant medication given as treatment for the first conjunctivitis event during the initial treatment period | 39 (31.0) | 23 (59.0) 23.5 | 1 (2.6) 33.3 | 14 (35.9) 35.8 | 3 (7.7) 1 | 22 (56.4) | 2.3 | 0 | 27 (69.2) | 31.8 |
| Totalb | 101 (80.2) | 77 (76.2) 78.6 | 2 (2.0) 66.7 | 21 (208) 87.5 | 4 (13.4) 16.7 | 0 | 19 (73.1) 2.4 | 0 | 10 (62.5) 11.8 | 6 (37.5) 15.4 |
| Events treated with ophthalmologicals | 15 (60.0) | 10 (66.7) 66.7 | 1 (3.3) 33.3 | 10 (66.7) | 1 (3.3) 33.3 | 0 | 9 (60.0) | 60.0 | 3 (20.0) | 0 |
| Events not treated | 20 (15.9) | 16 (80.0) 16.3 | 1 (5.0) 33.3 | 3 (15.0) | 1.25 | 0 | 15 (75.0) | 17.6 | 5 | 25 (25.0) | 12.8 |
| Events not treated, with concomitant medication given as treatment for the first conjunctivitis event during the initial treatment period | 39 (31.0) | 23 (59.0) 23.5 | 1 (2.6) 33.3 | 14 (35.9) 35.8 | 3 (7.7) 1 | 22 (56.4) | 2.3 | 0 | 27 (69.2) | 31.8 |

Number of patients with events who did and did not receive treatment for their conjunctivitis. Of the total conjunctivitis events within the given treatment, data are number of events (%). Percentages are calculated based on the number of events divided by the number of events (E) within the category (E/E [for all events] = 100). ECZTRA trials are coded in World Health Organization Drug version Jun17B3. Data are from the atopic dermatitis pool.
### Table 4  Baseline demographics and disease characteristics of patients with and without conjunctivitis adverse events of special interest (AESI)

|                          | With conjunctivitis AESI | Without conjunctivitis AESI |
|--------------------------|--------------------------|-----------------------------|
|                          | Total (n = 147)          | Placebo (n = 21)            | Tralokinumab (n = 126) |
| Median (IQR) age (years) | 39.0 (29.0–52.0)         | 44.0 (26.0–54.0)            | 38.0 (29.0–52.0)      |
| Male                     | 92 (62.6)                | 14 (66.7)                   | 78 (61.9)             |
| Ethnicity                |                          |                             |                           |
| White                    | 119 (81.0)               | 17 (81.0)                   | 102 (81.0)             |
| Black or African American| 4 (2.7)                  | 1 (4.8)                     | 3 (2.4)                |
| Asian                    | 17 (11.6)                | 1 (4.8)                     | 16 (12.7)              |
| Other                    | 6 (4.1)                  | 2 (9.5)                     | 4 (3.2)                |
| Mean (SD) weight (kg)    | 75.3 (16.6)              | 78.3 (18.7)                 | 74.8 (16.2)            |
| Mean (SD) BMI (kg m\(^{-2}\)) | 26.0 (4.7)              | 26.9 (4.5)                  | 25.9 (4.8)             |
| Median (IQR) duration of AD at baseline (years) | 30.0 (20.0–42.0)         | 38.5 (23.0–47.0)            | 29.0 (20.0–39.0)      |
| Median (IQR) BSA at baseline (%) | 60.0 (42.0–85.0)         | 65.0 (45.0–90.0)            | 58.5 (42.0–85.0)      |
| Median (IQR) baseline EASI score | 32.0 (21.8–42.6)         | 33.5 (25.6–43.0)            | 30.8 (21.8–41.5)      |
| Baseline IGA severity    |                          |                             |                           |
| 3 (moderate)             | 57 (38.8)                | 6 (28.6)                    | 51 (40.5)              |
| 4 (severe)               | 90 (61.2)                | 15 (71.4)                   | 75 (59.5)              |
| 5 (very severe)          | 0                        | 0                           | 3 (0.1)                |
| Median (IQR) worst daily pruritus NRS\(^{a}\) | 8.1 (7.0–8.9)            | 8.6 (7.8–9.0)               | 8.0 (7.0–8.9)          |

Data are n (%) unless otherwise stated. AD, atopic dermatitis; BMI, body mass index; BSA, body surface area; AESI, Eczema Area and Severity Index; IGA, Investigator’s Global Assessment; IQR, interquartile range; NRS, numerical rating scale. \(^{a}\)Data are from ECZTRA 1, ECZTRA 2 and ECZTRA 3 only.
treatment during placebo and tralokinumab treatment, although more cases resolved when ophthalmological treatment was used. Independent risk factors for the development of conjunctivitis in patients with AD, irrespective of treatment group, were high AD severity at baseline, history of allergic conjunctivitis/ocular keratoconjunctivitis and the number of atopic comorbidities (past or current). The results of this study provided new insights on atopic comorbidities, showing that some atopic comorbidities pose a higher risk of developing conjunctivitis; in particular, history of asthma and allergic conjunctivitis/ocular keratoconjunctivitis alone or together appeared to drive a higher risk of conjunctivitis, compared to the presence of food allergy or hay fever. Higher baseline disease biomarker levels were also associated with the development of conjunctivitis in patients with AD. Overall, the risk factors for developing conjunctivitis with tralokinumab were generally the same as for the placebo group.

These findings corroborate dupilumab clinical trials and real-world data, which show that patients with AD receiving biological treatment targeted against the Th2 pathway have a greater risk of developing conjunctivitis than patients receiving placebo. \(^5,9,27\) Likewise, conjunctivitis cases with dupilumab were mostly mild to moderate and resolved with ophthalmological treatment. The risk factors observed in this analysis are similar to those identified in dupilumab clinical trials and real-world data\(^5,5,27,28\); however, the overall incidence rates of conjunctivitis vs. clinical trials of dupilumab appear to be lower.

The mechanism underlying the observation that ocular complications increase with AD severity is unknown. Three main hypotheses about the increased incidence of conjunctivitis during biological treatment of AD have been proposed. The first suggests that blocking IL-4 and IL-13 signalling with

| Table 5 | Atopy history of patients with and without conjunctivitis adverse events of special interest (AESI) |
|---------|---------------------------------------------------------------------------------------------------|
|          | With conjunctivitis AESI                                                                                                           | Without conjunctivitis AESI                                                                                     |
|          | Total (n = 145) Placebo (n = 19) Tralokinumab (n = 126)                                                                              | Total (n = 2037) Placebo (n = 610) Tralokinumab (n = 1427)                                                     |
| Asthma   |                                                                                                                                  |                                                                                                               |
| Never    | 46 (31.7) 3 (15.8) 43 (34.1)                                                                                                      | 1016 (49.9) 312 (51.1) 704 (49.3)                                                                            |
| Current  | 81 (55.9) 14 (73.7) 67 (53.2)                                                                                                      | 783 (38.4) 235 (38.5) 548 (38.4)                                                                            |
| Past     | 17 (11.7) 2 (10.5) 15 (11.9)                                                                                                       | 232 (11.4) 63 (10.3) 169 (11.8)                                                                            |
| Unknown  | 1 (0.7) 0 1 (0.8)                                                                                                                  | 6 (0.3) 0 6 (0.4)                                                                                           |
| Food allergy |                                                                                                                             |                                                                                                               |
| Never    | 71 (49.0) 9 (47.4) 62 (49.2)                                                                                                      | 1222 (60.0) 350 (57.4) 872 (61.1)                                                                           |
| Current  | 67 (46.2) 9 (47.4) 58 (46.0)                                                                                                      | 713 (35.0) 235 (38.5) 478 (33.5)                                                                           |
| Past     | 4 (2.8) 0 4 (3.2)                                                                                                                 | 49 (2.4) 8 (1.3) 41 (2.9)                                                                                   |
| Unknown  | 3 (2.1) 1 (5.3) 2 (1.6)                                                                                                          | 53 (2.6) 17 (2.8) 36 (2.5)                                                                                 |
| Hay fever |                                                                                                                                  |                                                                                                               |
| Never    | 45 (31.0) 2 (10.5) 43 (34.1)                                                                                                      | 926 (45.5) 274 (44.9) 652 (45.7)                                                                           |
| Current  | 91 (62.8) 14 (73.7) 77 (61.1)                                                                                                     | 988 (48.5) 307 (50.5) 681 (47.7)                                                                           |
| Past     | 6 (4.1) 2 (10.5) 4 (3.2)                                                                                                         | 97 (4.8) 21 (3.4) 76 (5.3)                                                                                 |
| Unknown  | 3 (2.1) 1 (5.3) 2 (1.6)                                                                                                          | 26 (1.3) 8 (1.3) 18 (1.3)                                                                                  |
| Allergic conjunctivitis |                                                                                                                              |                                                                                                               |
| Never    | 62 (42.8) 5 (26.3) 57 (45.2)                                                                                                      | 1363 (66.9) 394 (64.6) 969 (67.9)                                                                          |
| Current  | 60 (41.4) 12 (63.2) 48 (38.1)                                                                                                     | 387 (19.0) 126 (20.7) 261 (18.3)                                                                          |
| Past     | 22 (15.2) 2 (10.5) 20 (15.9)                                                                                                      | 227 (11.1) 76 (12.5) 151 (10.6)                                                                           |
| Unknown  | 1 (0.7) 0 1 (0.8)                                                                                                                 | 60 (2.9) 14 (2.3) 46 (3.2)                                                                                 |
| Atopic keratoconjunctivitis |                                                                                                                              |                                                                                                               |
| Never    | 128 (88.3) 16 (84.2) 112 (88.9)                                                                                                  | 1847 (90.7) 563 (92.4) 1284 (90.0)                                                                         |
| Current  | 10 (6.9) 2 (10.5) 8 (6.3)                                                                                                        | 63 (3.1) 15 (2.5) 48 (3.4)                                                                                 |
| Past     | 4 (2.8) 0 4 (3.2)                                                                                                                 | 49 (2.4) 13 (2.1) 36 (2.5)                                                                                 |
| Unknown  | 3 (2.1) 1 (5.3) 2 (1.6)                                                                                                          | 78 (3.8) 19 (3.1) 59 (4.1)                                                                                 |

Data are n (%). Data are from the ECZTRA trials only.
dupilumab could lead to decreased numbers of intraepithelial conjunctival goblet cells and lower mucus production. The second hypothesis suggests that blocking the Th2 immune response causes skewing towards a Th1- and Th17-mediated response, and possible overgrowth of Demodex mites. The expression of the Th1 cytokine interferon (IFN)-γ has been associated with more severe allergic conjunctivitis in mouse models, and Th17 cells co-expressing IL-17 and IFN-γ have also been shown to be correlated with the severity of conjunctivitis. Further support for the Th1/Th17 hypothesis is that ciclosporin, which ameliorates conjunctivitis, significantly reduces IL-17 secretion and CD4 expression, a glycoprotein found on the surface of immune cells, including T cells, in conjunctival biopsy specimens.

Unlike dupilumab, tralokinumab specifically binds to the IL-13 cytokine and does not affect IL-4 signalling. However, the mechanistic consequences resulting in ocular complications remain unclear. A comparison of incidence rates of conjunctivitis in dupilumab-treated patients (300 mg Q2W) after 16 weeks of treatment shows that dupilumab had a higher overall incidence rate (9.13%) and HR for conjunctivitis (HR vs. placebo 4.14, 95% CI 2.83–5.95) vs. tralokinumab (7.50%; HR vs. placebo 2.54, 95% CI 1.52–4.18) and a greater percentage of moderate or severe events. This suggests that specific IL-13 neutralization is associated with lower conjunctivitis risk than dual IL-4/IL-13 blockade, and that blocking IL-4 signalling, which has been shown to skew T cells towards a Th1/Th17 phenotype, may result in more severe conjunctivitis. Head-to-head or real-world comparative effectiveness studies would help confirm these observations.

Studies into conjunctivitis in dupilumab trials have been limited owing to a lack of standardized examination by...
Figure 5 Distribution of atopic comorbidities at baseline and in patients with conjunctivitis adverse events of special interest (AESI) in the initial treatment period of the atopic dermatitis (AD) pool (ECZTRA trials only). Data are n (%). (a) Baseline distribution of atopic comorbidity history in all randomized patients (n = 2182). (b) Distribution of atopic comorbidity history at baseline in patients with conjunctivitis AESI in the placebo group (n = 19). (c) Distribution of atopic comorbidity history at baseline in patients with conjunctivitis AESI in the tralokinumab group (n = 126). For (b) and (c), percentage is the number of placebo- or tralokinumab-treated patients with at least one conjunctivitis AESI as a proportion of patients in the atopic comorbidity segment at baseline.

Table 6 Incidence of conjunctivitis adverse events of special interest based on history of comorbidities

| History of comorbidity (current or past) | Placebo (N = 629) | Tralokinumab (N = 1553) | Adjusted rate b Population (N) | Adjusted rate b Population (N) |
|----------------------------------------|------------------|-------------------------|--------------------------------|--------------------------------|
| AD only                                 | 146              | 362                     | 20 (5/3)                       | 27-6 |
| + 1 comorbidity                        | 182              | 450                     | 28 (5/9)                       | 27-6 |
| + 2 comorbidities                      | 175              | 455                     | 37 (7/8)                       | 27-6 |
| + 3 comorbidities                      | 126              | 286                     | 41 (1/4)                       | 27-6 |

Adverse events collected during the exposure time in the initial treatment period (16 weeks in the ECZTRA trials) are shown. Data are from the ECZTRA trials only. AD, atopic dermatitis; N, number of patients with one or more events. aComorbidities included AD, asthma, food allergy and hay fever. bCalculated using Cochran-Mantel-Haenszel weights.
conjunctivitis, including method of application (i.e., eye drops) and treatment dosage, which could have implications for conjunctivitis event resolution.

In conclusion, these results show that a higher incidence of conjunctivitis is seen in patients treated with tralokinumab vs. placebo and is associated with AD severity at baseline and a history of allergic conjunctivitis/keratoconjunctivitis, as well as number of atopic comorbidities, irrespective of treatment group. A greater understanding of the mechanisms behind ocular complications in patients with AD, and the risk factors associated with conjunctivitis in these patients, will help identify those who are likely to develop conjunctivitis AEs with tralokinumab.

Acknowledgments

We thank Petra Amoudruz (Leo Pharma A/S, Ballerup, Denmark) for her help with initiating the development of this article and her input throughout the writing and reviewing process. Open access funding enabled and organized by ProjektDEAL.

References

1. Wollenberg A, Christen-Zach S, Taieb A et al. ETFAD/EADV Eczema task force 2020 position paper on diagnosis and treatment of atopic dermatitis in adults and children. Eur Acad Dermatol Venereol 2020; 34:2717–44.
2. Ravn NH, Ahmadzay ZF, Christensen TA et al. Bidirectional association between atopic dermatitis, conjunctivitis and other ocular surface diseases: a systematic review and meta-analysis. J Am Acad Dermatol 2021; 85:453–61.
3. Thysen JP, Toft PB, Halling-Overgaard AS et al. Incidence, prevalence, and risk of selected ocular disease in adults with atopic dermatitis. J Am Acad Dermatol 2017; 77:280–6.
4. Treister AD, Kraff-Cooper C, Lio PA. Risk factors for dupilumab-associated conjunctivitis in patients with atopic dermatitis. JAMA Dermatol 2018; 154:1208–11.
5. Akinlade B, Guttman-Yassky E, de Bruin-Weller M et al. Conjunctivitis in dupilumab clinical trials. Br J Dermatol 2019; 181:459–73.
6. Simpson EL, Bieber T, Guttman-Yassky E et al. Two phase 3 trials of dupilumab versus placebo in atopic dermatitis. N Engl J Med 2016; 375:2335–48.
7. Schneeweiss MC, Kim SC, Wyss R et al. Dupilumab and the risk of conjunctivitis and serious infection in patients with atopic dermatitis: a propensity score-matched cohort study. J Am Acad Dermatol 2021; 84:300–11.
8. Beck KM, Seitzman GD, Yang EJ et al. Ocular co-morbidities of atopic dermatitis. Part II: ocular disease secondary to treatments. Am J Clin Dermatol 2019; 20:807–15.
9. Halling AS, Loft N, Silverberg JI et al. Real-world evidence of dupilumab efficacy and risk of adverse events: a systematic review and meta-analysis. J Am Acad Dermatol 2021; 84:139–47.
10. Achten R, Bakker D, Ariens L et al. Long-term follow-up and treatment outcomes of conjunctivitis during dupilumab treatment in patients with moderate-to-severe atopic dermatitis. J Allergy Clin Immunol Pract 2021; 9:1389–92.

© 2021 The Authors. British Journal of Dermatology published by John Wiley & Sons Ltd on behalf of British Association of Dermatologists

British Journal of Dermatology (2022) 186, pp453–465

ophthalmologists, potentially contributing to the increased incidence rates observed in real-world studies vs. clinical trials. In our analysis, a consistent proportion of cases, approximately 30% in each treatment group, were confirmed as conjunctivitis by an ophthalmologist, potentially reflecting the similar severity of cases between treatment groups. A limitation of the study is that ophthalmologist review was not required or centralized, and further information is not available for the reason that cases were or were not reviewed or confirmed. Additionally, blepharitis is commonly observed with dupilumab but was seen in < 1% of patients at the PT level in this pooled analysis of tralokinumab.

The most common treatments for conjunctivitis across the pooled studies were ophthalmic anti-infectives/antibiotics, even though this does not reflect the current expert recommendation for treatment in most cases. The recommended treatment for conjunctivitis occurring during dupilumab treatment in patients with AD is low-potency corticosteroid eye drops or the off-label use of tacrolimus 0.03% eye ointment, while lubricants have been suggested as a preventative treatment option. Other case series and case reports have described various therapeutic management options, depending on conjunctivitis severity, which have been validated by the International Eczema Council (IEC), for patients receiving dupilumab. Mild conjunctivitis is typically treated with artificial tears, sodium hyaluronate, trehalose/hyaluronate tear substitute, or antibiotic eye drops, while moderate-to-severe conjunctivitis is usually managed using corticosteroids, calcineurin inhibitors or antibiotic–corticosteroid combination therapies. These treatment strategies are consistent with the treatment of patients in the AD pool.

The IEC and other experts advise dermatologists to initiate eye treatment in patients who develop conjunctivitis during AD treatment, before referring to an ophthalmologist who would manage and tailor further conjunctivitis therapy, as appropriate. The IEC cautions against unmonitored long-term use of corticosteroid eye drops due to the possible increased risk of superinfection and increased intraocular pressure, and suggests patients be informed about the possibility of developing conjunctivitis while being treated with biologics for AD. No standard guidelines exist for the diagnosis or treatment of conjunctivitis in patients who are receiving biological treatment for AD.

There are a number of limitations to this analysis. Firstly, only around 30% of the conjunctivitis events were confirmed by an ophthalmologist as an ophthalmologist’s confirmation was not required. It is therefore not possible to determine whether conjunctivitis was over-reported owing to increased awareness bias, as has been suggested previously. Secondly, this analysis only considered tralokinumab treatment up to week 16 and therefore did not allow for the determination of patients who would require continued or intermittent treatment for conjunctivitis. As tralokinumab is a long-term treatment option for AD, the incidence of conjunctivitis over a longer period has been assessed for tralokinumab and the event rates did not increase over this period. Thirdly, trial participants were not assessed for current ocular health or ophthalmological comorbidities, other than as part of their overall medical history, before the start of the trials. Finally, there was insufficient reporting on the treatment used for conjunctivitis, including method of application (i.e., eye drops) and treatment dosage, which could have implications for conjunctivitis event resolution.

In conclusion, these results show that a higher incidence of conjunctivitis is seen in patients treated with tralokinumab vs. placebo and is associated with AD severity at baseline and a history of allergic conjunctivitis/keratoconjunctivitis, as well as number of atopic comorbidities, irrespective of treatment group. A greater understanding of the mechanisms behind ocular complications in patients with AD, and the risk factors associated with conjunctivitis in these patients, will help identify those who are likely to develop conjunctivitis AEs with tralokinumab.
11 Simpson EL, Akinlade B, Ardeleanu M. Letter to the Editor: Two phase 3 trials of dupilumab versus placebo in atopic dermatitis. Br J Dermatol 2017; 176:1090–1.

12 Bachert C, Mannent L, Nacerio RM et al. Effect of subcutaneous dupilumab on nasal polyposis in patients with chronic sinusitis and nasal polyposis: a randomized clinical trial. JAMA 2016; 315:469–79.

13 Castro M, Corren J, Pavord ID et al. Dupilumab efficacy and safety in moderate-to-severe uncontrolled asthma. N Engl J Med 2018; 378:2486–96.

14 Hirano I, Dollen ES, Hamilton JD et al. Efficacy of dupilumab in a phase 2 randomized trial of adults with active eosinophilic esophagitis. Guttmannology 2020; 158:111–22.

15 Silverberg JI, Toth D, Bieber T et al. Tralokinumab plus topical corticosteroids for the treatment of moderate-to-severe atopic dermatitis: results from the double-blind, randomized, multicentre, placebo-controlled phase III ECZTRA 3 trial. Br J Dermatol 2021; 184:450–63.

16 Guttman-Yassky E, Blauvelt A, Eichenfeld LF et al. Efficacy and safety of lebrikizumab, a high-affinity interleukin 13 inhibitor, in adults with moderate to severe atopic dermatitis: a phase 2b randomized clinical trial. JAMA Dermatol 2020; 156:411–20.

17 Simpson EL, Flohr C, Eichenfeld LF et al. Efficacy of lebrikizumab (an anti-IL-13 monoclonal antibody) in adults with moderate-to-severe atopic dermatitis inadequately controlled by topical corticosteroids: a randomized, placebo-controlled phase II trial (TREBLE). J Am Acad Dermatol 2018; 78:637–71.

18 Silverberg JI, Blauvelt A, Guttman-Yassky E et al. Tralokinumab for moderate-to-severe atopic dermatitis: results from two 52-week, randomized, double-blind, multicentre, placebo-controlled phase III trials (ECZTRA 1 and ECZTRA 2). Br J Dermatol 2021; 184:437–49.

19 Tsoi LC, Rodriguez E, Degenhardt F et al. Atopic dermatitis is an IL-13 dominant disease with greater molecular heterogeneity compared to psoriasis. J Invest Dermatol 2019; 139:1480–9.

20 Bieber T. Interleukin-13: targeting an underestimated cytokine in atopic dermatitis. Allergy 2020; 75:54–62.

21 Popovic B, Breed J, Rees DG et al. Structural characterisation reveals mechanism of IL-13-neutralising monoclonal antibody tralokinumab as inhibition of binding to IL-13Ra1 and IL-13Ra2. J Mol Biol 2017; 429:208–19.

22 Silverberg A, Howell MD, Guttman-Yassky E et al. Treatment of atopic dermatitis with tralokinumab, an anti-IL-13 mAb. J Allergy Clin Immunol 2019; 143:135–41.

23 Merola JF, Bagel J, Ahngren P et al. Tralokinumab does not impact vaccine-induced immunity: results from a 30-week, randomized, placebo-controlled trial in adults with moderate-to-severe atopic dermatitis. J Am Acad Dermatol 2021; 85:71–8.

24 Agnihotri G, Shi K, Lio PA. A clinician’s guide to the recognition and management of dupilumab-associated conjunctivitis. Drugs R D 2019; 19:311–8.

25 Wollenberg A, Ariens L, Thuraus S et al. Conjunctivitis occurring in atopic dermatitis patients treated with dupilumab—clinical characteristics and treatment. J Allergy Clin Immunol Pract 2018; 6:1778–80.

26 Thyszen JP, Heegaard S, Ivert L et al. Management of ocular manifestations of atopic dermatitis: a consensus meeting using a modified Delphi process. Acta Derm Venereol 2020; 100:adv00264.

27 Ferreira S, Torres T. Conjunctivitis in patients with atopic dermatitis treated with dupilumab. Drugs in Context 2020; 9:2020–2.3.

28 Wollenberg A, Beck LA, Blauvelt A et al. Laboratory safety of dupilumab in moderate-to-severe atopic dermatitis: results from three phase III trials (LIBERTY AD SOLO 1, LIBERTY AD SOLO 2, LIBERTY AD CHRONOS). Br J Dermatol 2020; 182:1120–35.

29 Bakker DS, Ariens LF, van Luijk C et al. Goblet cell scarcity and conjunctival inflammation during treatment with dupilumab in patients with atopic dermatitis. Br J Dermatol 2019; 180:1248–9.

30 Voorberg AN, den Dunnen WFA, Wijdhi RJH et al. Letter to the Editor: Recurrence of conjunctival goblet cells after discontinuation of dupilumab in a patient with dupilumab-related conjunctivitis. J Eur Acad Dermatol Venereol 2020; 34:e64–6.

31 Yokoi K, Yokoi N, Kinoshita S. Impairment of ocular surface epithelium barrier function in patients with atopic dermatitis. Br J Dermatol 1998; 139:797–800.

32 Dogru M, Katakami C, Nakagawa N et al. Impression cytology in atopic dermatitis. Ophthalmology 1998; 105:1478–84.

33 Utine CA, Li G, Ashbell P et al. Ocular surface disease associated with dupilumab treatment for atopic diseases. Ocul Surf 2020; 19:151–6.

34 Brogger P, Blom LH, Simonsen S et al. Antagonism of the interleukin 4 receptor α promotes TGF-β-signalling among T cells from patients with atopic dermatitis after stimulation. Scand J Immunol 2019; 91:e12835.

35 Thyszen JP. Could conjunctivitis in patients with atopic dermatitis treated with dupilumab be caused by colonization with Demodex and increased interleukin-17 levels? Br J Dermatol 2018; 178:1220.

36 Stern ME, Siemasko K, Gao J et al. Role of interferon-γ in a mouse model of allergic conjunctivitis. Invest Ophthalmol Vis Sci 2005; 46:3239–46.

37 Reyes N, Blanco T, Mathew R et al. Novel mouse model of severe ocular allergy reveals a key role for pathogenic Th17 cells. Invest Ophthalmol Vis Sci 2014; 55:4058.

38 Utine CA, Stern M, Apek EK. Immunopathological features of severe chronic atopic keratoconjunctivitis and effects of topical cyclopentolate treatment. Ocul Immunol Inflamm 2019; 27:1184–93.

39 Thyszen JP, de Bruijn-Weller MS, Paller AS et al. Conjunctivitis in atopic dermatitis patients with and without dupilumab therapy – International Eczema Council survey and opinion. J Eur Acad Dermatol Venereol 2019; 33:1224–31.

40 Aszodi N, Thuraus S, Seegräber M et al. Management of dupilumab-associated conjunctivitis in atopic dermatitis. J Dtsch Dermatol Ges 2019; 17:488–91.

41 Gooderham M, McDonald J, Papp K. Diagnosis and management of conjunctivitis for the dermatologist. J Cutan Med Surg 2017; 22:200–6.

42 Faiz S, Giovannielli J, Podevin C et al. Effectiveness and safety of dupilumab for the treatment of atopic dermatitis in a real-life French multicenter adult cohort. J Am Acad Dermatol 2019; 81:143–51.

43 Simpson E, Merola JF, Silverberg J et al. Safety of specifically targeting interleukin-13 with tralokinumab in adult patients with moderate-to-severe atopic dermatitis: pooled analysis of five randomised, double-blind, placebo-controlled phase 3 and phase 2 trials. Skin 2021; 5:s1.

Supporting Information

Additional Supporting Information may be found in the online version of this article at the publisher’s website:

Appendix S1 Conflicts of interest.

Table S1 Design overview of studies included in the safety analyses of the AD pool.

Table S2 Proportion and exposure-adjusted number of conjunctivitis AESI during the initial treatment period, including HR with 95% CI for tralokinumab vs. placebo.
Table S3 Summary of conjunctivitis events confirmed by an ophthalmologist during the initial treatment period.
Table S4 Severity of all conjunctivitis AESI in the initial treatment period.
Table S5 Mean and median time to the first conjunctivitis AESI.
Table S6 Duration of conjunctivitis AESI.
Table S7 Prior systemic AD treatment in patients with and without conjunctivitis.
Figure S1 Study design of the five studies included in the conjunctivitis analyses.