Safety of tralokinumab in patients with moderate-to-severe atopic dermatitis followed for up to 4.5 years: an integrated analysis of 8 clinical trials

Running head: Integrated safety of up to 4.5 years tralokinumab in patients with AD

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Merck, Novartis, Ortho Dermatologics, Pfizer, Pierre Fabre Dermo Cosmetique, Regeneron, Sanofi, Tioga, and Valeant.

Data availability: Data will be made available, upon request to the study sponsor, following review by the external Patient and Scientific Review Board.

Ethics statement: All trials were conducted in accordance with the ethical principles derived from the Declaration of Helsinki and Good Clinical Practice guidelines and were approved by the local institutional review board or ethics committee of each institution.

Patient consent: All patients provided written informed consent.

What is already known about this topic?

- For patients with chronic, moderate-to-severe atopic dermatitis (AD) who require long-term systemic treatments to control their disease, drug safety is a top priority
- Tralokinumab, a monoclonal antibody that specifically targets interleukin-13, is indicated for the treatment of patients ≥12 years of age with moderate-to-severe AD
- A previous pooled analyses of phase II and III trials showed that tralokinumab was well-tolerated for up to 1 year of treatment

What does this study add?

- Here, a large integrated safety analysis of tralokinumab is reported, including 2693 patients ≥12 years of age with moderate-to-severe AD treated with tralokinumab in 7 placebo-controlled clinical trials and an open-label extension
- No new safety signals were observed through 4.5 years of tralokinumab treatment, and the rates of adverse events (AEs) and AEs of special interest remained consistent or decreased with longer tralokinumab exposure
- Long-term use of tralokinumab was well-tolerated

Abstract

Background: Patients with moderate-to-severe atopic dermatitis (AD) require long-term management, and understanding the long-term safety of new treatments is a top priority for patients and healthcare professionals.

Objectives: To evaluate the safety of tralokinumab in adults and adolescents with moderate-to-severe AD by conducting an integrated safety analysis of 7 placebo-controlled trials and the ongoing, open-label extension study ECZTEND.

Methods: An initial 16-week placebo-controlled (PBO-CTRL) safety set and an all-tralokinumab (ALL-TRALO) safety set combining the placebo-controlled trials and ECZTEND (data cut-off 30 April, 2022) were analyzed. All treatment-emergent adverse events (AEs) were recorded. AEs of special interest (AESIs) were pre-defined. Safety areas of clinical interest for advanced systemic AD treatments were captured retrospectively. Proportions of patients with events and incidence rates (IR) per 100 patient-years of exposure (PYE) were calculated. PYE was defined as the time until the first event or exposure end, whichever came first, and incidence was defined as the first event.

Results: Safety results were similar between the PBO-CTRL safety set and ALL-TRALO safety set. In the latter, 2693 patients received tralokinumab for up to 238.5 weeks (≈4.5 years, PYE=5320.2). Most AEs were nonserious, mild or moderate in severity, and occurred with similar frequencies between tralokinumab and placebo in the PBO-CTRL safety set. The most common AEs that occurred at higher rates for tralokinumab vs. placebo were nasopharyngitis (IR ratio [IRR] comparing tralokinumab vs. placebo=1.26), conjunctivitis (IRR=3.11), and injection site reaction (IRR=19.57). Dermatitis atopic and asthma occurred at lower rates with tralokinumab vs. placebo (IRR=0.51 and 0.57, respectively). AESI eye disorders occurred at higher rates with tralokinumab vs. placebo (IRR=2.43), and 98% were mild to moderate. AESIs that were less frequent with tralokinumab vs. placebo included skin infections requiring systemic treatment (IRR=0.43) and eczema herpeticum (IRR=0.32). Rates of AEs of clinical interest (related to other approved systemic AD treatments) were low and similar between treatment groups. IRs of AEs did not increase with longer exposure in the ALL-TRALO safety set.

Conclusions: Long-term use of tralokinumab in adults and adolescents with moderate-to-severe AD was well-tolerated and consistent with the initial placebo-controlled treatment period, with no new safety signals identified.

Clinical trial registration: ECZTRA 1 (NCT03131648), ECZTRA 2 (NCT03160885), ECZTRA 3 (NCT03363854), ECZTRA 5 (NCT03562377), ECZTRA 6 (NCT03526861), ECZTRA 7 (NCT03761537), ECZTRA 8 (NCT04587453), and ECZTEND (NCT03587805; data cut-off 30 April, 2022).

Introduction

Atopic dermatitis (AD) is a chronic skin disease characterized by dysregulated type 2 immune response, impaired skin-barrier function, itch, and skin microbial dysbiosis with increased *Staphylococcus aureus* colonization.[1] Interleukin (IL)-13 has been identified as a dominant cytokine in AD pathogenesis.[2-4] Of note, improved understanding of AD immunopathogenesis has led to development of new systemic treatment options, such as biologics targeting type 2 cytokines (including IL-13) and small molecules targeting the Janus kinase (JAK) and signal transducer and activator of transcription pathways.[5-7]

Tralokinumab is a fully human, high-affinity, monoclonal antibody that specifically targets IL-13 and is indicated for the treatment of patients ≥12 years of age with moderate-to-severe AD.[8] In phase III clinical trials for up to 1 year, tralokinumab improved signs and symptoms of AD both as monotherapy and in combination with topical corticosteroids (TCS) in adults and adolescents.[6,9-11] Interim analyses of the ongoing long-term tralokinumab extension trial, ECZTEND, showed that clinical improvements were sustained for up to 4 years.[12,13]

Studies assessing patient preferences for the most important attributes of systemic treatments show that safety is a top priority.[14,15] Previous integrated safety analyses of phase II and III placebo-controlled clinical trials demonstrated similar frequency and severity of adverse events (AEs) between tralokinumab and placebo during the initial 16-week treatment period.[16] Common AEs that occurred more frequently with tralokinumab vs. placebo were upper respiratory tract infection (mainly symptoms related to common cold), conjunctivitis, and injection-site reactions. As patients with moderate-to-severe AD often require long-term treatment, it is important to continuously monitor and assess the safety profile of systemic treatments with cumulative exposure over time. Here, updated integrated safety data of tralokinumab treatment from 8 clinical trials in AD are presented, including data from 2693 adolescent and adult patients treated for up to 4.5 years, representing 5320.2 patient-years of exposure (PYE).

Patients and methods

Studies

This integrated safety analysis of tralokinumab included 7 double-blinded, randomized, placebo-controlled clinical trials of up to 52 weeks duration (parent trials): the 2, 52-week phase III monotherapy studies ECZTRA 1 (NCT03131648) and ECZTRA 2 (NCT03160885), the 32-week phase III TCS-combination trial ECZTRA 3 (NCT03363854), the 16-week phase II vaccine response trial ECZTRA 5 (NCT03562377), the 52-week phase III monotherapy trial in adolescents ECZTRA 6 (NCT03526861), the 26-week phase III TCS combination trial in cyclosporin failures ECZTRA 7 (NCT03761537), the 16-week phase III TCS combination study in Japanese patients ECZTRA 8 (NCT04587453), and an ongoing up to 5-year open-label extension study ECZTEND (NCT03587805) with a data cut-off of 30 April, 2022 (Figure 1).

Individual trial designs and eligibility criteria have been previously described[6,9-12,17-19] and are summarized in Appendix S1 (see Supporting Information). All trials were conducted in accordance with the ethical principles derived from the Declaration of Helsinki and Good Clinical Practice guidelines and were approved by the local institutional review board or ethics committee of each institution. All patients, or their legal representatives, provided written informed consent.

Patients

The parent trials ECZTRA 1-3 and ECZTRA 5-8 enrolled adolescent (12-17 years of age) and adult patients (≥18 years of age) with moderate-to-severe AD for whom topical treatment was inadequate or inadvisable (Figure 1 and Appendix S1; see Supporting Information). Patients who completed the 7 parent trials were invited to enroll in ECZTEND.[12] All patients who received at least one dose of subcutaneous tralokinumab or placebo with or without TCS were included in the analyses.

Analysis sets

This analysis examined 2 pooled datasets. A placebo-controlled (PBO-CTRL) safety set assessed the profile of placebo vs. tralokinumab 300 mg (or 150 mg in 98 adolescent patients) every 2 weeks (Q2W) during the initial 16 weeks in the 7 parent trials ECZTRA 1-3 and ECZTRA 5-8. The PBO-CTRL safety set included both monotherapy and combination studies

with TCS. An all-tralokinumab (All-TRALO) safety set assessed the long-term safety profile of tralokinumab and included data for all patients who received at least 1 dose of tralokinumab (300 mg or 150 mg Q2W, or 300 mg or 150 mg every 4 weeks [Q4W]) while on active treatment in any of the 7 placebo-controlled parent trials (ECZTRA 1-3 and ECZTRA 5-8) and the open-label study ECZTEND (tralokinumab 300 mg Q2W) until data cut-off.

Endpoints

All AEs, including serious adverse events (SAEs) and AEs leading to discontinuation of study drug, were treatment-emergent and reported after the first dose of study drug. Investigators recorded AEs during the treatment period, which were coded using the Medical Dictionary for Regulatory Activities (MedDRA®) version 24.0. AEs of special interest (AESIs) were predefined based on areas of safety and regulatory interest for biologics in AD: eye disorders, skin infections requiring systemic treatment, eczema herpeticum, and malignancies diagnosed after dosing (excluding basal cell carcinoma, localized squamous cell carcinoma of the skin, and carcinoma in situ of the cervix). These AEs were captured using an electronic case report form questionnaire.

For other safety areas of clinical interest, the cluster analyses grouped the preferred terms (PTs) and terms associated with related clinical disease presentations retrospectively using Standardized or Customized MedDRA® Queries based on: known adverse drug reactions (ADRs) and precautions listed in the tralokinumab Summary of Product Characteristics/United States Prescribing Information, AEs of interest for targeted immunomodulatory therapies in AD, and inclusion of any system organ classes (SOC) or preferred terms (PTs) reported in the PBO-CTRL safety set (using a flagging nominal *P*-value ≤0.05 between tralokinumab and placebo to avoid potential reporting bias). The clusters are described in Table S1 (see Supporting Information).

Statistical analyses

Statistical analyses were based on pooled safety information from individual trials; no sample size calculation was performed. Incidence was reported as the percentage of patients with at least 1 event. Only AEs occurring while on active treatment were included, and PYE was defined as the sum of the exposure while on active treatment. 'PYE at risk' was defined as PYE or PYE up until an event (whichever came first). Periods of safety follow up were disregarded in both safety sets. Marginal incidence rates (IRs) for AEs were calculated using Poisson

regression and g-computation[20] for both safety sets with incidence rate ratios (IRRs) estimated if at least one patient in both treatment groups experienced an event. The regression was adjusted for treatment (PBO-CTRL safety set only) and parent trial with an offset of log (PYE at risk), and used the HC3 robust covariance matrix ('sandwich' R package).[21] The delta method was used to calculate IRs (log-scale), IRRs (log-scale), and incidence rate differences (IRD). Model assumptions were not checked. Adjustment for parent trials was performed to mitigate potential issues due to differing randomization ratios across parent trials (Simpson's paradox). Further details on the methodology can be found in Appendix S2 (see Supporting Information). Presentations are made using the safety analysis set, which comprised all dosed patients. Estimates used in figures, additional analyses, and corresponding presentations as per the United States Prescribing Information population are provided in Tables S1-S11 and Figures S1-S5 (see Supporting Information).

Results

Patient disposition and baseline characteristics

A total of 2852 patients comprised the PBO-CTRL safety set (tralokinumab, n=1939; placebo, n=913), and 2693 patients comprised the ALL-TRALO safety set (Table 1). In the ALL-TRALO safety set, 30.6% (n=824) of patients had ≥3 years of tralokinumab exposure with a median and maximum treatment exposure of approximately 1.5 years and 4.5 years, respectively (Table S12; see Supporting Information). The frequencies of discontinuations due to treatment failure (AEs or lack of efficacy) were low (5.3% and 9.0%, respectively) (Figure S6; see Supporting Information). Baseline characteristics were similar between the tralokinumab and placebo-treated groups in the PBO-CTRL safety set, and with the ALL-TRALO safety set (Table 1). Additional information on atopy and skin disease history at baseline is included in Tables S13 and S14 (see Supporting Information).

Treatment-Emergent Adverse Events

During Weeks 0-16 in the PBO-CTRL safety set, the overall frequency of patients reporting ≥1 AE was similar between the placebo (68.1%) and tralokinumab (67.5%) groups, and most AEs were mild or moderate in severity (Figure 2). The frequency of SAEs in both groups was low, with lower IR for tralokinumab vs. placebo (IRR=0.60), and the frequencies of AEs leading to drug withdrawal were similar between the tralokinumab and placebo groups in the PBO-CTRL safety set (IRR=0.94) (Figure 2). Among the commonly reported AEs (≥2% in any treatment group of the PBO-CTRL safety set), those with higher IRs for tralokinumab vs. placebo were the PTs nasopharyngitis (IRR=1.26), conjunctivitis (IRR=3.11), and injection site reaction (IRR=19.57) (Figure 3). Common AEs with lower IRs for tralokinumab vs. placebo included the PTs dermatitis atopic (worsening of AD; IRR=0.51) and asthma (IRR=0.57).

The IRs of AEs, SAEs, and AEs leading to drug withdrawal did not increase with increased exposure time in the ALL-TRALO safety set vs. the PBO-CTRL safety set (Figure 2). In the ALL-TRALO safety set, the most common SOC of SAEs were infections and infestations (n=51; IR=0.94); injury, poisoning, and procedural complications (n=26; IR=0.48); and skin and subcutaneous tissue disorders (n=26; IR=0.47). Most SAEs were reported as single events without any clustering. SAEs reported in >0.1% of tralokinumab-treated patients at the PT level were dermatitis atopic (n=18; IR=0.33) and asthma (n=5; IR=0.09). In the ALL-TRALO safety set, the most common AEs leading to drug withdrawal included the PTs dermatitis atopic (n=29; IR=0.57), injection site reaction (n=13; IR=0.25), conjunctivitis (n=5; IR=0.09), eosinophilia (n=5; IR=0.08), conjunctivitis allergic (n=3; IR=0.06), and ulcerative keratitis (n=3; IR=0.05). Consistent results for treatment-emergent AEs (TEAEs) were found in the United States Prescribing Information population (Figures S1 and S2; see Supporting Information).

Overall summary of AESIs

AESI eye disorders–classified by the investigator as conjunctivitis, keratoconjunctivitis, or keratitis–occurred in more patients receiving tralokinumab than placebo (IRR=2.43) in the PBO-CTRL safety set (Figure 4). This difference between tralokinumab and placebo was largely driven by the higher IR for the AESI conjunctivitis category. AESIs with a lower IR for tralokinumab vs. placebo in the PBO-CTRL safety set included AESI skin infections requiring systemic treatment (IRR=0.43) and AESI eczema herpeticum (IRR=0.32). In the ALL-TRALO

safety set 98% of AESI eye disorder events were mild-to-moderate, and only 0.4% lead to permanent discontinuation of study drug. AESI malignancy was reported in 20 patients (0.7%; IR=0.35) in the ALL-TRALO safety set, with the PTs reported by more than one patient being prostate cancer (n=4; IR=0.07), invasive breast carcinoma (n=3; IR=0.05), invasive ductal breast carcinoma (n=2; IR=0.04), and breast cancer (n=2; IR=0.03) (Table S6; see Supporting Information). The rates of all AESIs except for malignancy did not increase over time with tralokinumab treatment in the ALL-TRALO safety set. Consistent results for AESIs were found in the United States Prescribing Information population (Figure S3; see Supporting Information).

Safety areas of interest for targeted immunomodulatory therapies in AD

The known tralokinumab ADRs (other than the above-mentioned AESIs conjunctivitis and keratitis) of injection site reactions, upper respiratory tract infections, and eosinophilia were all reported at higher IRs for tralokinumab vs. placebo in the PBO-CTRL safety set (Figure 5). IRs for all ADRs did not increase over time in the ALL-TRALO safety set. While not an ADR, there is a special warning and precaution for use of tralokinumab in patients with helminth infections, as the influence of tralokinumab on the immune response against helminth infections is unclear;[22] in this analysis there were no cases of helminth infections.

IRs for AEs of interest for targeted immunomodulatory therapies in AD, including serious infections, herpes viral infections, arthralgia, nausea, major adverse cardiovascular events, and malignancies were low and did not differ between tralokinumab and placebo ($P \leq 0.05$) for the PBO-CTRL safety set (Figure 6). Skin infections demonstrated a lower IR for tralokinumab vs. placebo, including the PTs dermatitis infected (IRR=0.29) and staphylococcal skin infection (IRR=0.12). IRs for the majority of the safety areas of interest for targeted immunomodulatory therapies in AD did not increase over time in the ALL-TRALO safety set. Consistent results for ADRs and safety areas of interest for targeted immunomodulatory therapies in AD were found in the United States Prescribing Information population (Figures S4 and S5; see Supporting Information).

Discussion

This analysis represents the largest integrated safety data set published for biologics indicated for the treatment of moderate-to-severe AD to date, including data from 2693 patients ≥12 years of age treated with tralokinumab for up to 4.5 years, with a total of 5320.2 PYE. This analysis expands upon and demonstrates a pattern of AEs generally consistent with previously reported results, with no new safety signals identified.[16] Most AEs for tralokinumab were non-serious and mild or moderate in severity, and the IRs did not increase with increasing duration of treatment (i.e., entire period vs. initial 16-week period). The most commonly reported AE, both here and in previous studies, was related to symptoms of common cold, with specific differences between previous results and the present analysis related to differences between MedDRA® versions used (i.e., AEs related to symptoms of common cold were coded as PT viral upper respiratory tract infection in MedDRA® 20.0 used by Simpson et al. 2022[16] and as PT nasopharyngitis in MedDRA® 24.0 used in the present analysis). The lower IRs for the PTs dermatitis atopic and dermatitis infected for tralokinumab vs. placebo (49% and 71% lower rate, respectively) further support the efficacy of tralokinumab. The most frequently reported AEs in the adolescent ECZTRA 6 study and among adolescents in ECZTEND were consistent with the present integrated data set, with overall lower rates in ECZTEND.[10,23]

Informal comparisons with safety analyses for other oral and biologic medications utilized to treat patients with moderate-to-severe AD suggest a favorable safety profile for tralokinumab. Ocular surface diseases, including various forms of conjunctivitis, are commonly present in patients with AD and have been reported to increase with baseline AD disease severity.[24-26] In the present analysis, frequency of the AESI 'conjunctivitis' during the initial 16 weeks of treatment was 7.4% for tralokinumab Q2W and 3.1% for placebo, i.e., risk ratio of 2.4 (7.4/3.1) comparing tralokinumab to placebo. These results are consistent with a previous analysis of a smaller patient pool in 5 clinical trials characterizing the occurrence of conjunctivitis with up to 16 weeks of tralokinumab treatment,[26] and lower than reported for 16 weeks of dupilumab (9.7% for dupilumab Q2W vs. 2.2% for placebo; risk ratio ≈ 9.3/2.1 = 4.4),[25,27] and lebrikizumab (8.5% for lebrikizumab vs. 2.5% for placebo; risk ratio ≈ 8.5/2.5 = 3.4 or 10.0/2.7 = 3.7).[28,29]

The IRs related to safety areas of interest for targeted immunomodulatory therapies in AD were low. Arthralgia has been added as a listed ADR for dupilumab due to post-marketing

reports.[30] The IR for arthralgia in the present analysis was low and similar between tralokinumab and placebo (IRR=1.02) in the PBO-CTRL safety set and did not increase with additional exposure time. It has been suggested that arthralgia reported in the literature for dupilumab could be explained by the importance of IL-4 for balancing Th2 (IL-4/IL-13) vs. Th17 (IL-17/IL-23) polarization;[31] it remains to be determined whether tralokinumab, which only targets IL-13, will be associated with this rare AE over time in post-marketing data.

In AD, the combination of skin barrier defects, immune dysregulation, and alteration in the skin microbiome results in an increased risk for viral and bacterial skin infections, including eczema herpeticum and *S. aureus*.[32] Additionally, there is a potential increased risk of infections associated with immunomodulating systemics, such as herpes viral infection.[16,27,33-36] In the PBO-CTRL safety set of the present analysis, the rate of serious infections was 58% lower, AESI eczema herpeticum was 68% lower, and herpes zoster was 14% lower with tralokinumab vs. placebo. Similarly, local skin infections were reduced by 58%, mainly driven by an 88% reduction in staphylococcal skin infections. This is consistent with previous studies showing that biologics such as tralokinumab and dupilumab significantly reduce *S. aureus* abundance in patients with moderate-to-severe AD.[2,37-40]

An increased risk of malignancy has been reported in patients treated with immunomodulatory systemics, particularly JAK inhibitors.[33-35] In the present analysis, malignancies (Standardized MedDRA® Query) were reported in 0.4% of both tralokinumab- and placebo-treated patients in the PBO-CTRL safety set, and the IR did not increase with additional exposure time in the ALL-TRALO safety set. Among the 20 AESI malignancies (IR=0.35) reported in the present analysis (diagnosed among 2693 patients over a total exposure time of 5320 PYE), the occurrence of 4 prostate cancer events and 7 events related to breast cancer was consistent with previous data. Both are common forms of cancer occurring with a rate of 0.2-0.3 events per 100 PYE in adult men and women with AD.[41]

A limitation of the study is that the short 16-week placebo-controlled period limits the assessment of AEs with tralokinumab vs. the underlying disease, especially for uncommon or rare events. When comparing the IRs between the PBO-CTRL and ALL-TRALO safety sets, it is important to consider that risk over time may not be constant and can change for reasons other than treatment exposure. For example, disease severity improves over time due to treatment effect, thus leading some AEs to become less frequent (e.g., eczema herpeticum). Additionally, selection and survival biases may have been possible, as patients with more AEs may not have

elected to, or been eligible for, participation in ECZTEND. Potential observational biases due to the lower visit frequency in ECZTEND compared with the parent trials may have resulted in patients not accurately remembering safety concerns, causing lower rates of AEs. These biases are likely smaller for the pre-defined AESIs, severe AEs, and SAEs due to the special focus and remembrance of these events as compared to, for example, headache and symptoms of common cold. Comparisons of AE frequencies from this study with the current literature are for context only.

In summary, this integrated safety analysis in adolescent and adult patients with moderate-to-severe AD is consistent with the previously published safety profile of tralokinumab and demonstrates that long-term use of tralokinumab for up to 4.5 years was well-tolerated with no new safety signals.

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Figure legends

Figure 1 Integrated safety analysis study design. Patients with AD who had an Eczema Area and Severity Index (EASI) of ≥16, Investigator's Global Assessment (IGA) score of ≥3, ≥10% of the total body surface area affected, a history of chronic AD for ≥1 year, and for whom topical treatment was inadequate or inadvisable were eligible for enrollment into the parent trials. Patients who completed the parent trials were invited to enroll in ECZTEND.
AD, atopic dermatitis; JP, Japan; n, number of included patients from the indicated trial; N, number of patients in indicated treatment set; PBO, placebo; Q2W, every 2 weeks; Q4W, every 4 weeks; TCS, topical corticosteroids; TRALO, tralokinumab.

Figure 2 Overall summary of TEAEs. Details on represented data in the figures are provided in Tables S2 and S3 (see Supporting Information). [a]Study size–adjusted % and IR; [b]All Safety Sets Adj IR plot: X-axis transformed to a pseudo-log10 scale in two segments. Dotted line represents the breakpoint of the X-axis segments. Error bars represent 95% CI; [c]PBO-CTRL Safety Set IRR plot: IRR only calculated if at least one patient in both treatment groups experienced the event(s). X-axis transformed to a log10 scale. **P*-value ≤0.05. Error bars represent 95% CI. [d]The reported death occurred after the patient discontinued treatment in the initial period of the vaccine study (ECZTRA 5) trial. The cause of death was noted as due to septic shock and respiratory failure, caused by suppurative pneumonia, as well as pulmonary embolism, caused by underlying emphysema with liver disease and malnutrition as contributing factors. These were assessed by the investigator as not related to study drug (tralokinumab and vaccines).[18]
%, percentage of patients; Adj, adjusted; AE, adverse event; CI, confidence interval; IR, Incidence rate (n/100PYE), for IR calculations, patient exposure was censored at the time of first event; IRR, incidence rate ratio; n, number of patients achieving the indicated metric, or with ≥1 event; N, number of patients with recorded observation; PBO-CTRL, placebo-controlled; PYE, patient-years of exposure; TEAE, treatment-emergent AE; TRALO, tralokinumab.

Figure 3 Most frequently reported TEAEs (≥2% in any treatment group of the placebo-controlled safety set). Details on represented data in the figures are provided in Tables S4 and S5 (see Supporting Information). [a]Study size–adjusted % and IR; [b]All Safety Sets Adj IR plot: X-axis transformed to a pseudo-log10 scale in two segments. Dotted line represents the breakpoint of the X-axis segments. Error bars represent 95% CI; [c]PBO-CTRL Safety Set IRR plot: IRR only

calculated if at least one patient in both treatment groups experienced the event(s). X-axis transformed to a log10 scale. *P-value ≤0.05. Error bars represent 95% CI.
%, percentage of patients; Adj, adjusted; AE, adverse event; CI, confidence interval; IR, incidence rate (n/100PYE), for IR calculations; IRR, incidence rate ratio; patient exposure was censored at the time of first event; n, number of patients achieving the indicated metric, or with ≥1 event; N, number of patients with recorded observation; PBO-CTRL, placebo-controlled; PYE, patient-years of exposure; TEAE, treatment-emergent AE; TRALO, tralokinumab.

Figure 4 Overall summary of AESIs. Definitions of Customized MedDRA® Queries, Standardized MedDRA® Queries, and other cluster terms used are provided in Table S1; details on represented data in the figures are provided in Tables S6 and S7 (see Supporting Information). [a]Study size–adjusted % and IR; [b]All Safety Sets Adj IR plot: X-axis transformed to a pseudo-log10 scale in two segments. Dotted line represents the breakpoint of the X-axis segments. Error bars represent 95% CI; [c]PBO-CTRL Safety Set IRR plot: IRR only calculated if at least one patient in both treatment groups experienced the event(s). X-axis transformed to a log10 scale. *P-value ≤0.05. Error bars represent 95% CI; [d]Conjunctivitis category includes several PTs, such as conjunctivitis, conjunctivitis allergic, conjunctivitis bacterial, and conjunctivitis viral; [e]Keratitis category includes several PTs, such as keratitis, keratitis viral, and ulcerative keratitis; [f]Keratoconjunctivitis category includes the LLT atopic keratoconjunctivitis, and PT keratitis or vernal keratoconjunctivitis; [g]Eczema herpeticum category includes PTs such as eczema herpeticum and Kaposi's varicelliform eruption; [h]Malignancies diagnosed after dosing, excluding basal cell carcinoma, localized squamous cell carcinoma of the skin, and carcinoma in situ of the cervix; the malignancies diagnosed after randomization in the ALL-TRALO safety analysis set include prostate cancer (n=4), invasive breast carcinoma (n=3), breast cancer (n=2), invasive ductal breast carcinoma (n=2), adenoid cystic carcinoma, angiosarcoma, cutaneous T-cell lymphoma, keratoacanthoma, malignant melanoma in situ, malignant melanoma, ovarian cancer, papillary thyroid cancer, and tonsil cancer.
%, percentage of patients; Adj, adjusted; AE, adverse event; AESI, adverse event of special interest; CI, confidence interval; IR, incidence rate (n/100PYE), for IR calculations, patient exposure was censored at the time of first event; IRR, incidence rate ratio; LLT, low level term; n, number of patients achieving the indicated metric, or with ≥1 event; N, number of patients with recorded observation; PBO-CTRL, placebo-controlled; PT, preferred term; PYE, patient-years of exposure; TRALO, tralokinumab.

Figure 5 Overall summary of ADRs. Definitions of Customized MedDRA® Queries, Standardized MedDRA® Queries, and other cluster terms used are provided in Table S1; details on represented data in the figures are provided in Tables S8 and S9 (see Supporting Information). [a]Study size–adjusted % and IR; [b]All Safety Sets Adj IR plot: X-axis transformed to a pseudo-log10 scale in two segments. Dotted line represents the breakpoint of the X-axis segments. Error bars represent 95% CI; [c]PBO-CTRL Safety Set IRR plot: IRR only calculated if at least one patient in both treatment groups experienced the event(s). X-axis transformed to a log10 scale. **P*-value ≤0.05. Error bars represent 95% CI; [d]ADR eosinophilia category includes eosinophilia and eosinophil count increased; [e]ADR upper respiratory tract infections category includes upper respiratory tract infection, pharyngitis, and nasopharyngitis.
%, percentage of patients; Adj, adjusted; ADR, adverse drug reaction; AE, adverse event; CI, confidence interval; CMQ, Customized MedDRA® Query; HLT, high level term; IR, incidence rate (n/100PYE), for IR calculations, patient exposure was censored at the time of first event; IRR, incidence rate ratio; n, number of patients achieving the indicated metric, or with ≥1 event; N, number of patients with recorded observation; NEC, not elsewhere classified; PBO-CTRL, placebo-controlled; PYE, patient-years of exposure; TRALO, tralokinumab.

Figure 6 Safety areas of interest for targeted immunomodulatory therapies in AD. Definitions of Customized MedDRA® Queries, Standardized MedDRA® Queries, and other cluster terms used are provided in Table S1; details on represented data in the figures are provided in Tables S10 and S11 (see Supporting Information). [a]Study size–adjusted % and IR; [b]All Safety Sets Adj IR plot: X-axis transformed to a pseudo-log10 scale in two segments. Dotted line represents the breakpoint of the X-axis segments. Error bars represent 95% CI; [c]PBO-CTRL Safety Set IRR plot: IRR only calculated if at least one patient in both treatment groups experienced the event(s). X-axis transformed to a log10 scale. **P*-value ≤0.05. Error bars represent 95% CI; [d]SOC: Infections and Infestations + Serious AE = Yes. [e]CMQ for skin infections involves selecting relevant preferred terms related to skin infections to accurately identify and classify instances of skin infections within the dataset. [f]Defined as the SMQ: 'Malignant or unspecified tumors (narrow scope)'. [g]Non-melanoma skin cancer identified by HLT = "Skin neoplasms malignant and unspecified (excl melanoma)."
%, percentage of patients; Adj, adjusted; AE, adverse event; CI, confidence interval; CMQ, Customized MedDRA® Query; HLT, high level term; IR, incidence rate (n/100PYE), for IR calculations, patient exposure was censored at the time of first event; IRR, incidence rate ratio; MACE, major adverse cardiovascular event; n, number of patients achieving the indicated metric, or with ≥1 event; N, number of patients with recorded observation; NMSC, non-

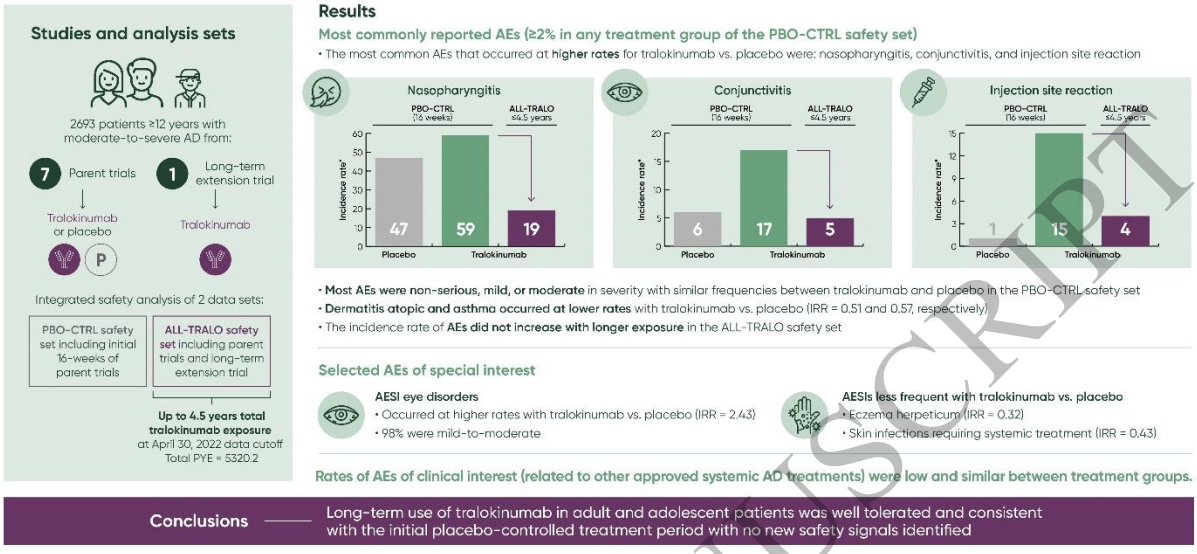
melanoma skin cancer; PBO-CTRL, placebo-controlled; PYE, patient-years of exposure; SMQ, Standardized MedDRA® Query; SOC, system organ class; TRALO, tralokinumab.

Table 1 Baseline parent trial demographics and characteristics

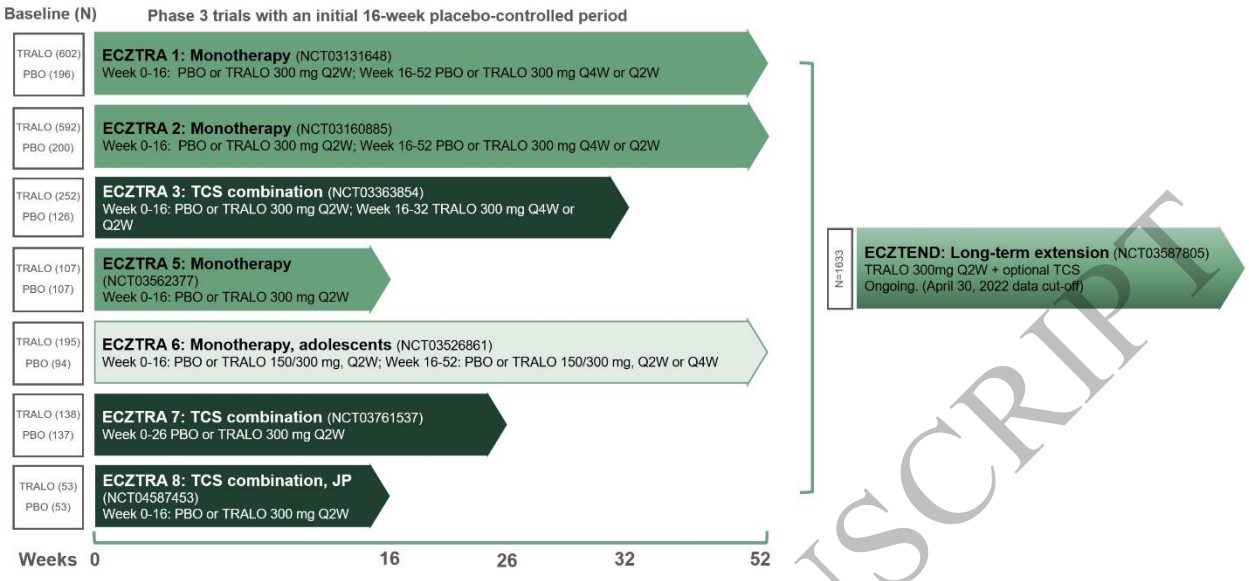
	PBO-CTRL Safety Set (Week 0-16)		ALL-TRALO Safety Set
	Tralokinumab N=1939, PYE=587.2	**Placebo** N=913, PYE=271.3	N=2693 PYE=5320.2
Median age, years (min; max)	33.0 (12.0 ; 92.0)	32.0 (12.0 ; 82.0)	33.0 (12.0 ; 92.0)
Age group, n (%)			
12-17	195 (10.1)	94 (10.3)	280 (10.4)
≥18	1744 (89.9)	819 (89.7)	2413 (89.6)
Female, n (%)	836 (43.1)	395 (43.3)	1155 (42.9)
Race, n (%)			
White	1307 (67.4)	587 (64.3)	1802 (66.9)
Asian	409 (21.1)	210 (23.0)	588 (21.8)
Black or African American	153 (7.9)	84 (9.2)	211 (7.8)
BMI (kg/m^2), N	1934	910	2687
Median (Q1 ; Q3)	24.8 (21.8 ; 29.0)	25.2 (21.9 ; 29.1)	24.9 (21.8 ; 29.0)
Current medical history, n (%)			
Asthma	769 (39.7)	368 (40.3)	1085 (40.3)
Allergic conjunctivitis	401 (20.7)	207 (22.7)	583 (21.6)
Atopic keratoconjunctivitis	60 (3.1)	26 (2.8)	84 (3.1)
Median duration of AD, years (min ; max)	24.0 (1.0 ; 77.0)	23.0 (1.0 ; 77.0)	24.0 (1.0 ; 77.0)
Median BSA, % (Q1 ; Q3)	49.0 (31.0 ; 70.0)	50.0 (31.0 ; 72.0)	50.0 (32.0 ; 70.0)
Median EASI (Q1 ; Q3)[a]	27.6 (20.6 ; 39.3)	27.9 (20.8 ; 40.0)	27.8 (20.8 ; 39.5)
Median SCORAD score (Q1 ; Q3)[a]	68.3 (60.0 ; 78.5)	68.9 (60.6 ; 79.2)	68.5 (60.2 ; 78.7)
IGA, n (%)[a]			
3	1005 (51.8)	475 (52.0)	1391 (51.7)
4	934 (48.2)	438 (48.0)	1302 (48.3)

[a]Full analysis set.

%, percentage of patients; AD, atopic dermatitis; BMI, body mass index; BSA, body surface area; EASI, Eczema Area and Severity Index; IGA, Investigator's Global Assessment; n, number of patients with recorded observation; N, number of patients in indicated data set; PBO-CTRL, placebo-controlled; PYE, patient-years of exposure; Q1, first quartile (25th percentile); Q3, third quartile (75th percentile); SCORAD, SCORing Atopic Dermatitis; TRALO, tralokinumab.



Graphical Abstract



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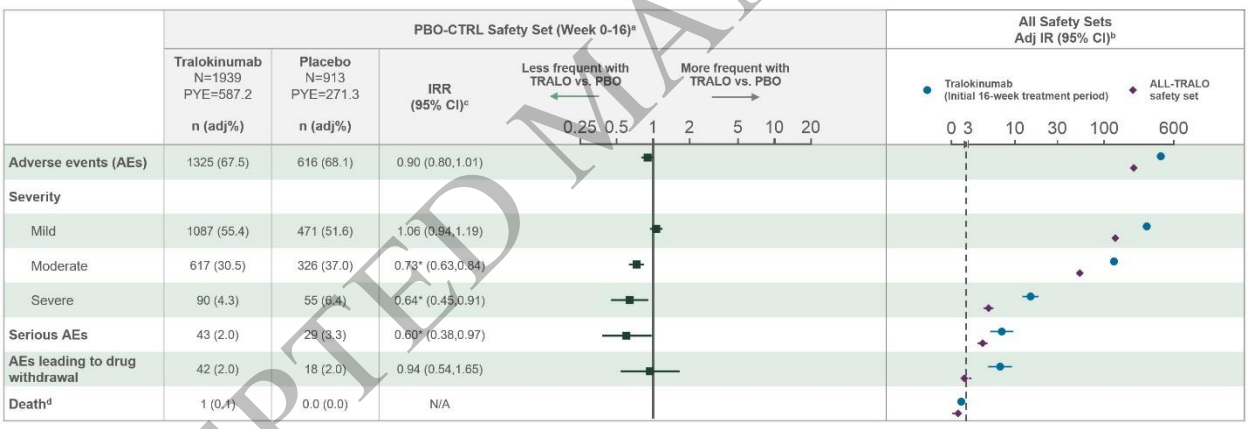

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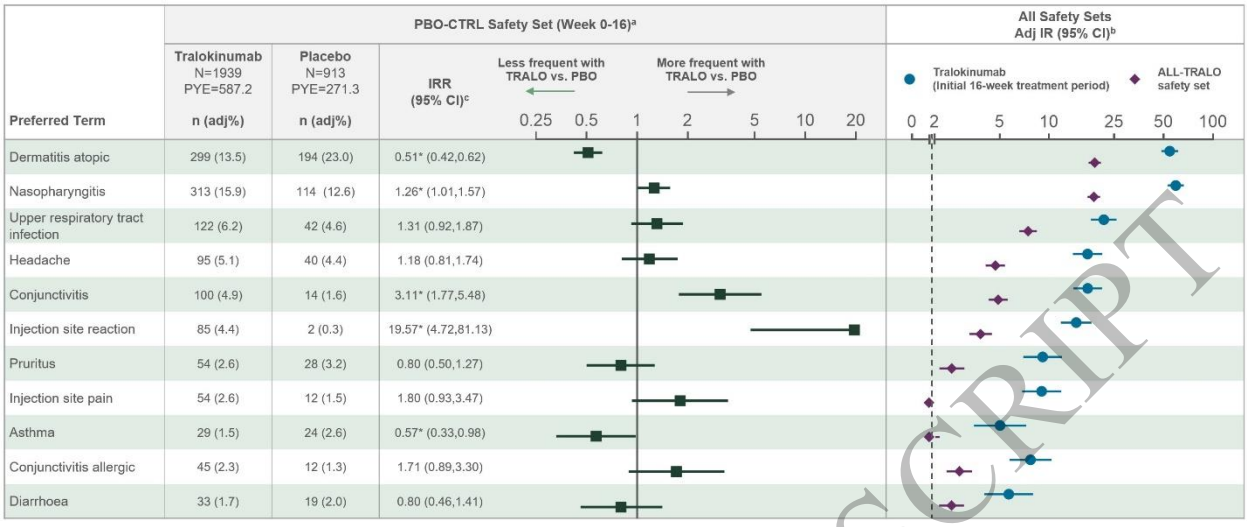

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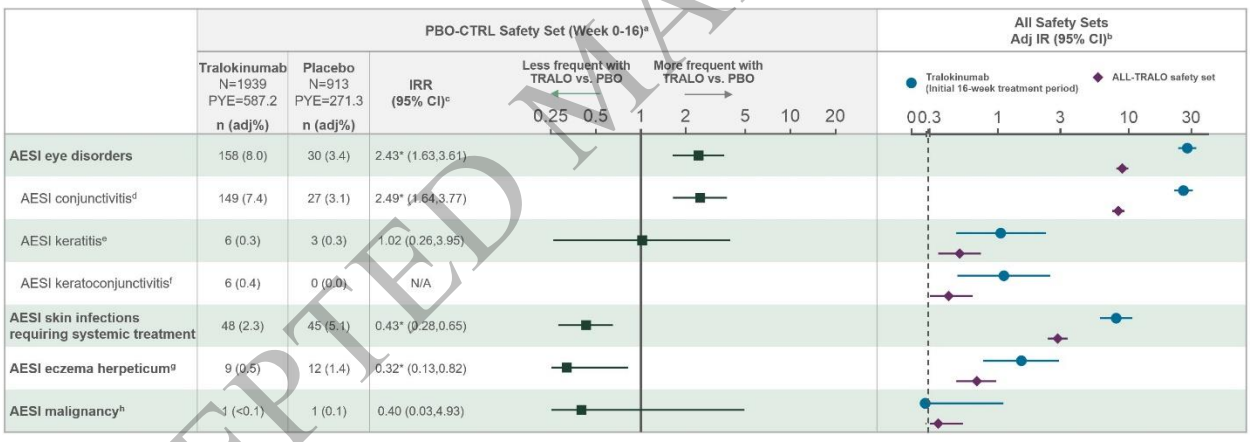

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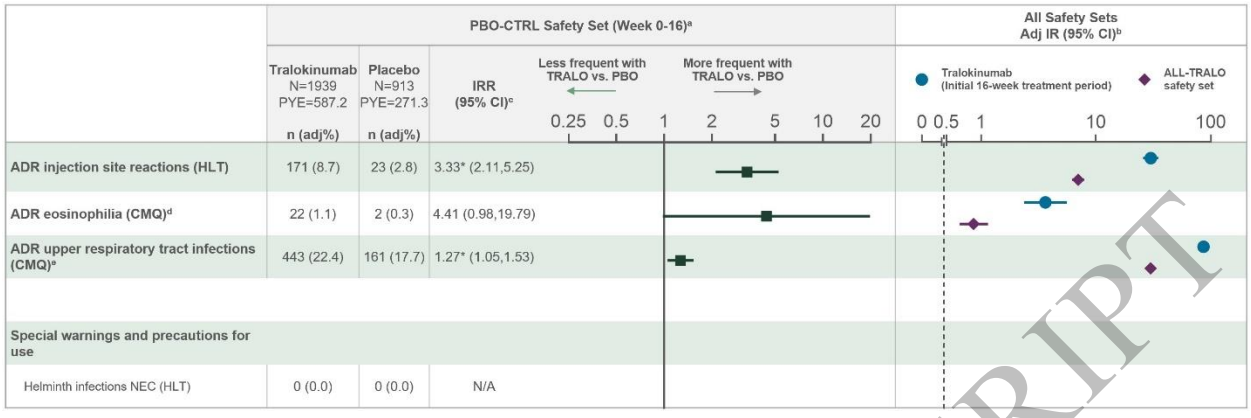

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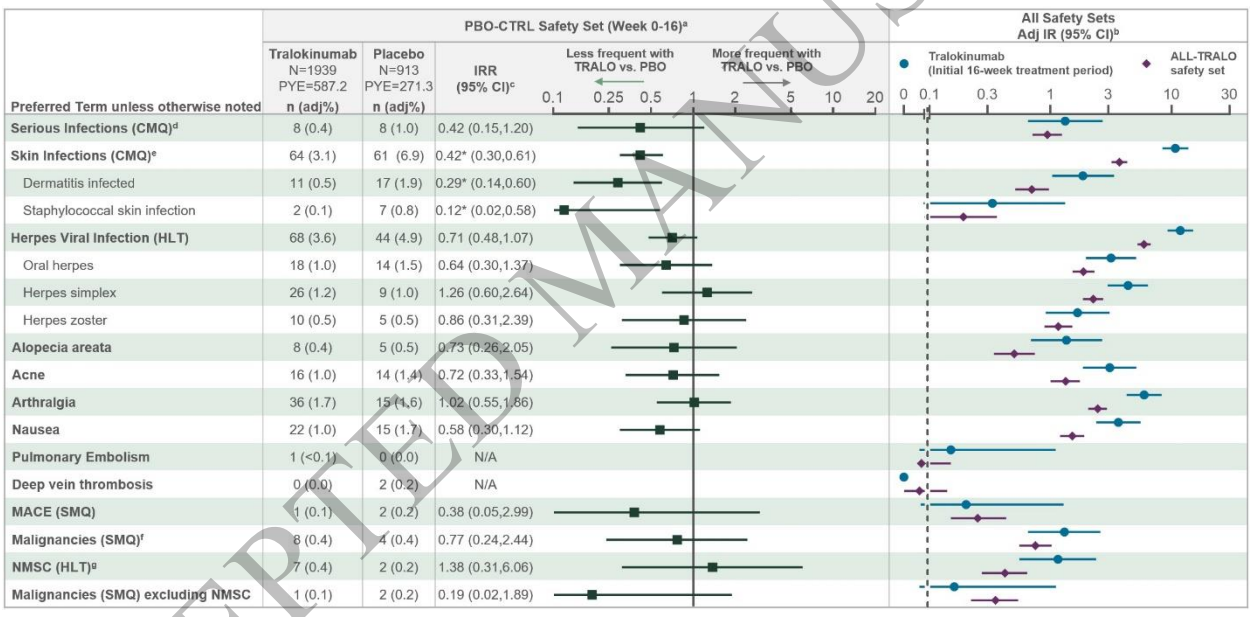

Figure 7
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