Risk of anaphylaxis and conjunctivitis with tralokinumab in atopic dermatitis

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Introduction

- Biologics, including human monoclonal antibodies (mAbs), are currently approved for the therapy of numerous diseases, including inflammatory skin diseases such as psoriasis[1] and atopic dermatitis (AD).[2]
- Potential safety concerns regarding the immunogenicity of biologics remain, including development of anti-drug antibodies (ADAs) and adverse events (AEs) such as anaphylaxis and/or severe hypersensitivity reactions.[3]
- A specific concern for the use of biologics in AD is the possibility of unexplained conjunctivitis with treatment, as AEs of conjunctivitis were more frequently reported in patients treated with biologics targeting interleukin (IL)-13 and IL-[4,4,5]
- Tralokinumab is an IgG_4 fully human mAb that works by specifically blocking the effects of IL-13[6] and has been evaluated in a Phase 2b, randomised, double-blind, placebo-controlled study (NCT02347176) in adults with moderate to severe AD.
  - Results of the study showed improvements in the Eczema Area and Severity Index (EASI), Investigator's Global Assessment (IGA) and SCORing Atopic Dermatitis (SCORAD) scores with tralokinumab on a background of topical corticosteroids (TCS), with a favourable overall safety and tolerability profile.[7]

Objectives

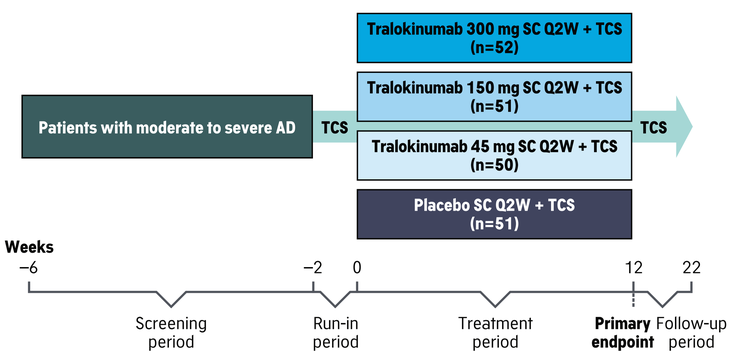
- To evaluate the risk of developing ADAs with tralokinumab treatment in the Phase 2b study.
- To investigate reports of anaphylaxis, or other severe hypersensitivity reactions, and compare the incidence of eye disorders, including conjunctivitis, between the placebo and tralokinumab treatment groups.

Methods

Study design

- Patients were randomised 1:1:1:1 to receive subcutaneous tralokinumab (45 mg, 150 mg or 300 mg) or placebo every 2 weeks for 12 weeks on a TCS background (**Figure 1**).
- Concomitant Class 3 (World Health Organisation) TCS were administered at least once daily during the 2-week run-in and as needed throughout the treatment and follow-up periods.

Figure 1. Study design



AD, atopic dermatitis; Q2W, every 2 weeks; SC, subcutaneous; TCS, topical corticosteroids.

Patients

- Eligible patients were aged 18–75 years with physician-confirmed diagnosis of AD for ≥1 year (according to Hanifin and Rajka criteria[8]) and with AD body surface area involvement of ≥10%, EASI score of ≥12, SCORAD of ≥25 and IGA of ≥3.
- Key exclusion criteria included: active dermatological conditions that may confound AD diagnosis, allergic or irritant contact dermatitis and history of anaphylaxis following any biologic therapy.

Measurement of anti-drug antibodies

- ADAs were measured using a validated electrochemiluminescence method (Meso Scale Discovery SECTOR Imager 6000). Samples for ADA response were taken at day 1 (prior to treatment) and weeks 4, 12 and 22.

Capture of anaphylaxis/serious hypersensitivity reactions

- AEs associated with anaphylaxis/serious hypersensitivity were captured using the following standardised Medical Dictionary for Regulatory Activities queries: hypersensitivity, anaphylactic reaction and anaphylactic/anaphylactoid shock conditions.[9]

Eye disorders

- Eye disorders, including but not limited to conjunctivitis, were extracted from the AEs occurring during treatment for all subjects in each treatment arm: placebo: n=51, tralokinumab 45 mg: n=50, tralokinumab 150 mg: n=51 and tralokinumab 300 mg: n=52.

—All events were included regardless of seriousness, causality or any other parameter of the AEs.

- Cases of eye disorders were compared between placebo and tralokinumab arms.

Statistical analysis

- Safety data were summarised descriptively according to the highest dosage received by each participant measured in the as-treated population.

Figure 2. Frequency of patients with one or more eye disorders in the placebo and pooled tralokinumab treatment groups

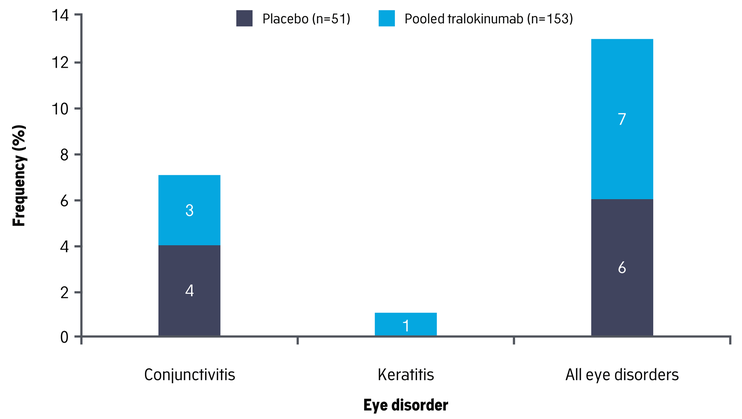


Table 1. Incidence of eye disorders (including conjunctivitis) for placebo and tralokinumab treatment groups

		Tralokinumab			
Frequency of eye disorder events, n (%)	Placebo (n=51)	45 mg (n=50)	150 mg (n=51)	300 mg (n=52)	Pooled (n=153)
Conjunctivitis	2 (4)	1 (2)	3 (6)†	0	4 (3)
Allergic conjunctivitis	0	0	1 (2)†	0	1 (1)
Episcleritis	0	0	1 (2)†	0	1 (1)
Eye infection	1 (2)*	0	1 (2)‡	0	1 (1)
Eye pruritus	0	1 (2)	0	0	1 (1)
Eye swelling	0	0	1 (2)†	0	1 (1)
Herpes ophthalmic	0	1 (2)	0	0	1 (1)
Hordeolum	0	0	1 (2)†	0	1 (1)
Iridocyclitis	1 (2)*	0	0	0	0
Keratitis	0	0	1 (2)	0	1 (1)
Increased lacrimation	0	0	1 (2)†	0	1 (1)
Macular edema	0	0	1 (2)†	0	1 (1)
Periorbital rash	0	0	1 (2)†	0	1 (1)
Patients with ⩾1 eye event, n (%)	**3 (6)**	**3 (6)**	**7 (14)**	**0**	**10 (7)**

*Eye infection and iridocyclitis were reported by the same patient in the placebo group.

†Three patients in the tralokinumab 150-mg group reported >1 event: 1) episcleritis and hordeolum; 2) conjunctivitis and macular edema; and 3) periorbital rash, eye swelling, increased lacrimation and allergic conjunctivitis.

‡Staphylococcal eye infection.

Results

Patient characteristics

- Overall, 204 patients were randomised in the Phase 2b study and included in the as-treated population: 153 tralokinumab-treated patients and 51 placebo-treated patients.
- Baseline demographics and disease characteristics were similar between treatment groups.[7]

Anti-drug antibodies

- Three patients in the tralokinumab 45-mg group had pre-existing ADAs at baseline. These are likely to be the result of the 'cut point' for the ADA assay, which is typically set expecting some positive results.
- Only one tralokinumab-treated patient (300-mg group) had ADA formation, which was measured at week 22. The titre was low and had no impact on the observed pharmacokinetics of tralokinumab.

— No AEs were reported for this patient.

- No positive cases of ADAs were identified in the placebo group.

Anaphylaxis/severe hypersensitivity reactions

- No cases of anaphylasxis or severe hypersensitivity were identified in this study.

Eye disorders

- Overall, there was no difference in the frequency of patients reporting conjunctivitis, keratitis or all eye disorders between the placebo and pooled tralokinumab groups (**Figure 2**).
  - No dose-related trend was observed, as the greatest frequency of one or more eye disorders was reported for the tralokinumab 150-mg treatment group.
- The number of patients with ≥1 eye disorder was 6%, 6%, 14% and 0% in the placebo and tralokinumab 45-mg, 150-mg and 300-mg treatment groups, respectively, and 7% in the pooled tralokinumab group (**Table 1**).
- Four patients experienced more than one eye event:
  - Eye infection and iridocyclitis were reported by the same patient in the placebo group.
  - In the tralokinumab 150-mg group, three patients reported more than one eye event. Two patients each reported two events: episcleritis and hordeolum, and conjunctivitis and macular edema. A third patient reported four events: periorbital rash, eye swelling, increased lacrimation and allergic conjunctivitis.
- No events of blepharitis were reported. Events of conjunctivitis and keratitis were infrequent: event rates were 4%, 2%, 6% and 0% for conjunctivitis in the placebo and tralokinumab 45-mg, 150-mg and 300-mg groups, respectively, and were 2% for keratitis in the tralokinumab 150-mg group.
- All eye disorders were non-serious, mild or moderate in severity and reported as not related to treatment.
- Two patients discontinued treatment due to eye disorders: one patient in the placebo group (iridocyclitis) and one patient in the tralokinumab 150-mg group (keratitis).

Limitations

- Hypersensitivity reactions are rare; therefore, they are not expected to be observed in such a small sample.
- Conjunctivitis was not pre-defined as an AE of special interest in the Phase 2b study
- Due to small numbers of patients in the treatment groups and low incidences of eye disorders, between-group statistical comparisons were not performed.

Conclusions

- No safety concerns were identified for tralokinumab on background of TCS in this Phase 2b study in patients with moderate to severe AD with respect to ADA development or anaphylaxis/hypersensitivity.
- No difference in the incidence of conjunctivitis or eye disorders was observed between the placebo and pooled tralokinumab groups in this study.
  - Conjunctivitis was infrequently reported, with no incidences considered to be study drug related.[7]
- There was no apparent dose response in the frequency of eye disorder events. The second-largest frequency was observed in the placebo group, while the largest frequency was seen in the tralokinumab 150-mg group, compared to zero events in the tralokinumab 300-mg group.
- The safety (and efficacy) profile of tralokinumab 300 mg is currently being further investigated in large Phase 3 studies as monotherapy (NCT03131648 and NCT03160885) and in combination with TCS (NCT03363854) in adults with moderate to severe AD.

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