Efficacy and safety of tralokinumab treatment in adults of different racial subgroups with moderate-to-severe atopic dermatitis in three randomized, placebo-controlled phase 3 trials

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Introduction

- Atopic dermatitis (AD) is a chronic inflammatory skin disease associated with significant disease burden
- Although AD is highly prevalent in patients with skin of color, data on the efficacy and safety of AD therapies in these patients is limited since most clinical trials enroll predominately White patients[1]
  - Several standard measures, including EASI, can underestimate AD severity in dark skin[1]
- Tralokinumab, a specific, high-affinity interleukin-13 inhibitor, is approved in Europe, Canada, and the United States for the treatment of adults with moderate-to-severe AD
- ECZTRA 1 (NCT03131648), ECZTRA 2 (NCT03160885), and ECZTRA 3 (NCT03363854) were randomized phase 3 trials assessing the safety and efficacy of tralokinumab or tralokinumab + TCS, as needed.
  - ECZTRA 1 and 2 were placebo-controlled trials and ECZTRA 3 was placebo + TCS controlled

Objective

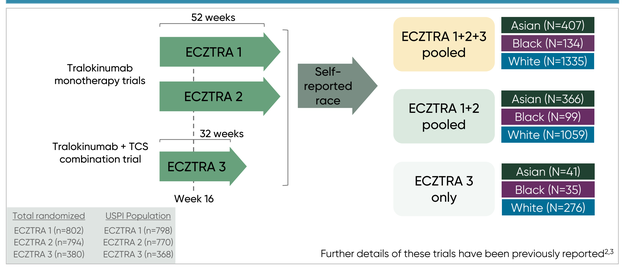
To evaluate the efficacy and safety of tralokinumab +/- TCS versus placebo +/- TCS, by self-identified racial subgroup (Asian, Black, White) in adults with moderate-to-severe AD across three phase 3 trials

Materials and Methods

Patients and treatment

- ECZTRA 1 and 2 were two identically designed, multinational, double-blind, randomized, placebo-controlled, 52-week trials (**Figure 1**)
  - Patients were randomized 3:1 to subcutaneous tralokinumab 300 mg or placebo every 2 weeks (Q2W) for an initial 16 weeks following a 600 mg loading dose
  - Patients who achieved IGA 0/1 or EASI-75 at Week 16 with tralokinumab were rerandomized to tralokinumab Q2W or every 4 weeks or placebo, for an additional 36 weeks
  - Rescue treatment could be used at the discretion of the investigator to control intolerable symptoms
- In ECZTRA 3, patients were randomized 2:1 to subcutaneous tralokinumab 300 mg + TCS as needed or placebo + TCS as needed Q2W for an initial treatment period of 16 weeks following a 600 mg loading dose
  - Patients who achieved IGA 0/1 or EASI-75 at Week 16 with tralokinumab were rerandomized to tralokinumab Q2W or every 4 weeks, with TCS as need, for an additional 16 weeks
- Patients self-reported their racial subgroup

Figure 1. Summary of tralokinumab ECZTRA trials included in these analyses



Further details of these trials have been previously reported[2,3]

Analyses

- As shown in **Figure 1**, data are presented as:
  - pooled from ECZTRA 1/2/3
  - pooled from ECZTRA 1/2
  - ECZTRA 3
- Efficacy outcomes assessed were:
  - Proportion of patients achieving EASI-75, IGA 0/1
  - Change from baseline in EASI, Peak Pruritus NRS, DLQI, and POEM
- Data are presented at Week 16 (ECZTRA 1/2/3) and Week 52 (ECZTRA 1/2)
- Data are presented as observed regardless of rescue medication use. Multiple imputation was used for missing data
- Data were used as per Food and Drug Administration (FDA) label and United States Prescribing Information (USPI; i.e., data from 2 sites were excluded as per FDA guidance)

Results

Patients, Demographics, and Clinical Characteristics

- This post hoc analysis included 1876 patients (USPI population) across ECZTRA 1, 2, and 3 who self-reported their race as Asian, Black, or White (**Figure 1, Table 1**)
- Baseline demographic and disease characteristics were largely balanced between treatment groups and across racial subgroups (**Table 1**)
  - AD severity was more moderate in the Black subgroup

Table 1. Baseline demographic and disease characteristics of patients by racial subgroup in pooled E1/2/3

	Asian N=407		Black N=134		White N=1335	
	Tralokinumab (n=291)	Placebo (n=116)	Tralokinumab (n=95)	Placebo (n=39)	Tralokinumab (n=992)	Placebo (n=343)
Mean age, y (SD)	35.2 (12.3)	32.4 (13.2)	39.3 (14.1)	38.6 (16.8)	39.0 (14.8)	38.7 (14.6)
Male, n (%)	176 (60.5)	76 (65.5)	38 (40.0)	20 (51.3)	578 (58.3)	209 (60.9)
Ethnicity, n (%) Hispanic or Latino	2 (0.7)	3 (2.6)	3 (3.2)	0	68 (6.9)	26 (7.6)
Region, n (%) North America Europe Australia Japan Asia	100 (34.4) 20 (6.9) 17 (5.8) 96 (33.0) 58 (19.9)	48 (41.4) 10 (8.6) 7 (6.0) 31 (26.7) 20 (17.2)	86 (90.5) 8 (8.4) 1 (1.1) – –	36 (92.3) 3 (7.7) – – –	284 (28.6) 640 (64.5) 68 (6.9) – –	89 (25.9) 233 (67.9) 21 (6.1) – –
Country, n (%) United States Canada Japan	43 (14.8) 57 (19.6) 96 (33.0)	23 (19.8) 25 (21.6) 31 (26.7)	82 (86.3) 4 (4.2) –	35 (89.7) 1 (2.6) –	178 (17.9) 106 (10.7) –	52 (15.2) 37 (10.8) –
Patients with IGA 3, n (%)	138 (47.4)	53 (45.7)	61 (64.2)	23 (59.0)	507/1001 (50.6)	169/346 (48.8)
Patients with IGA 4, n (%)	153 (52.6)	63 (54.3)	33 (34.7)	15 (38.5)	490/1001 (49.0)	175/346 (50.6)
Mean EASI (SD), n	33.2 (15.1)	34.1 (14.2)	29.2 (13.0), 94	33.1 (15.8), 38	31.5 (13.4), 997	31.9 (13.3), 344
Mean SCORAD score (SD)	70.7 (14.7)	71.4 (12.4)	66.4 (12.4), 94	67.6 (12.7), 38	69.7 (12.8), 997	70.8 (12.8), 344
Mean DLQI (SD), n	17.5 (7.1), 289	18.0 (6.6), 114	16.9 (7.1), 94	17.2 (9.7), 37	17.3 (7.0), 984	17.4 (6.9), 342
Mean Worst Pruritus NRS (SD), n	7.8 (1.4), 288	7.8 (1.4), 116	8.1 (1.6), 94	7.7 (1.7), 37	7.7 (1.5), 991	7.9 (1.4), 342

Tralokinumab improved signs and symptoms of AD across racial subgroups at Week 16

- Across three pooled trials at Week 16, tralokinumab significantly improved efficacy outcomes in the Asian and White subgroups relative to placebo. Similar results were found in the smaller Black subgroup, although statistical significance was not reached for all endpoints vs placebo (**Figures 2-3**)
- Lower efficacy was observed for the Black subgroup relative to Asian and White subgroups when the monotherapy trials were pooled, driven by higher placebo response rates. In contrast, higher efficacy was observed for the Black subgroup relative to Asian and White subgroups in the TCS combination trial

Figure 2. Percentage of patients achieving EASI-75 and IGA 0/1 by racial subgroup at Week 16

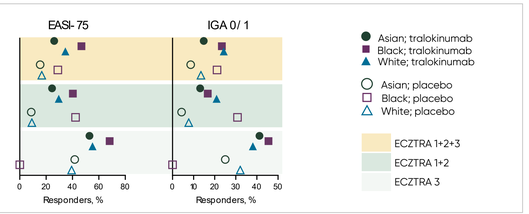
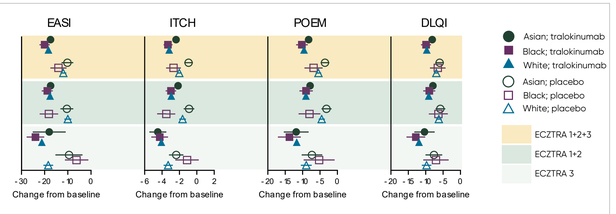


Figure 3. Change from baseline in EASI, ITCH, POEM, and DLQI by racial subgroup at Week 16

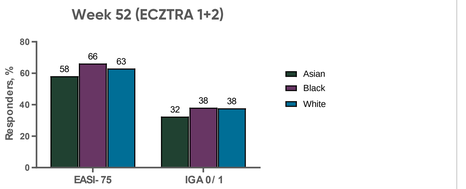


Error bars show standard error.

Improvements in efficacy outcomes beyond Week 16 were consistent across racial subgroups

- At Week 52 (pooled monotherapy trials), EASI-75 was achieved in 58% of Asian patients, 66% of Black patients, and 63% of White patients (**Figure 4**)
  - IGA 0/1 was achieved in 32% of Asian patients, 38% of Black patients, and 38% of White patients (**Figure 4**)
- Improvements in efficacy outcomes after Week 16 were also observed across racial subgroups in ECZTRA 3 (TCS combination trial)

Figure 4. Percentage of patients achieving EASI-75 and IGA 0/1 by racial subgroup at Week 52 (pooled monotherapy trials)



The safety profile of tralokinumab treatment was consistent across racial subgroups

- Tralokinumab was generally well-tolerated, with a safety profile comparable to placebo and largely consistent across racial subgroups (**Table 2**)
- Rates of adverse events (AEs), serious AEs, and AEs leading to drug withdrawal were low in all treatment groups
- Conjunctivitis rates were lower in the Asian and Black relative to White subgroup (**Table 3**)

Table 2. Summary of AEs through Week 16 in ECZTRA 1/2/3 by racial subgroup

	Asian				Black				White			
	Tralokinumab (n=292)		Placebo (n=115)		Tralokinumab (n=94)		Placebo (n=38)		Tralokinumab (n=989)		Placebo (n=340)	
PYE	86.93		33.60		26.92		10.74		294.47		99.54	
	n (%)	Rate (nE/100 PYE)	N (%)	Rate (nE/100 PYE)	N (%)	Rate (nE/100 PYE)	N (%)	Rate (nE/100 PYE)	N (%)	Rate (nE/100 PYE)	N (%)	Rate (nE/100 PYE)
All AEs	197 (67.5)	570.5	79 (68.7)	633.9	52 (55.3)	542.3	25 (65.8)	512.1	713 (72.1)	753.2	243 (71.5)	772.5
Serious AEs	6 (2.1)	6.9	1 (0.9)	2.9	2 (2.1)	7.4	3 (7.9)	27.9	25 (2.5)	8.8	13 (3.8)	17.0
Severity												
Mild	161 (55.1)	424.4	61 (53.0)	455.3	45 (47.9)	408.6	17 (44.7)	316.5	590 (59.7)	500.9	181 (53.2)	412.9
Moderate	76 (26.0)	132.2	42 (36.5)	157.7	19 (20.2)	122.5	13 (34.2)	167.6	362 (36.6)	224.4	149 (43.8)	311.4
Severe	11 (3.8)	13.8	5 (4.3)	20.8	3 (3.2)	11.1	2 (5.3)	27.9	56 (5.7)	27.8	31 (9.1)	48.2
Leading to withdrawal from trial	7 (2.4)	8.0	5 (4.3)	17.8	5 (5.3)	26.0	1 (2.6)	9.3	20 (2.0)	8.1	8 (2.4)	11.0
Outcome												
Not Recovered/Not Resolved	39 (13.4)	65.5	18 (15.7)	65.4	14 (14.9)	55.7	7 (18.4)	74.4	156 (15.8)	70.3	43 (12.6)	60.2
Recovering/Resolving	16 (5.5)	18.4	8 (7.0)	23.8	7 (7.4)	26.0	–	–	41 (4.1)	15.6	21 (6.2)	26.1
Recovered/Resolved	179 (61.3)	483.1	68 (59.1)	544.6	49 (52.1)	445.7	22 (57.9)	428.3	668 (67.5)	655.4	233 (68.5)	680.1
Recovered/Resolved with Sequelae	3 (1.0)	3.4	-	-	1 (1.1)	3.7	-	-	14 (1.4)	4.7	2 (0.6)	3.0
Unknown	–	–	–	–	2 (2.1)	11.1	1 (2.6)	9.3	20 (2.0)	7.1	3 (0.9)	3.0

Table 3. Summary of selected AEs by SOC and preferred term through Week 16 in ECZTRA 1/2/3 by racial subgroup

	Asian				Black				White			
	Tralokinumab Q2W (n=292)		Placebo (n=115)		Tralokinumab Q2W (n=94)		Placebo (n=38)		Tralokinumab Q2W (n=989)		Placebo (n=340)	
	N (%)	Rate (nE/100 PYE)	N (%)	Rate (nE/100 PYE)	N (%)	Rate (nE/100 PYE)	N (%)	Rate (nE/100 PYE)	N (%)	Rate (nE/100 PYE)	N (%)	Rate (nE/100 PYE)
All AEs	197 (67.5)	570.59	79 (68.7)	633.90	52 (55.3)	542.36	25 (65.8)	512.12	713 (72.1)	753.21	243 (71.5)	772.59
Infections and infestations	87 (29.8)	141.50	40 (34.8)	196.42	27 (28.7)	133.73	12 (31.6)	139.67	446 (45.1)	237.71	145 (42.6)	232.08
Viral upper respiratory tract infection	28 (9.6)	35.66	9 (7.8)	29.76	8 (8.5)	37.15	4 (10.5)	46.56	191 (19.3)	80.14	55 (16.2)	72.34
Conjunctivitis	5 (1.7)	5.75	1 (0.9)	2.98	3 (3.2)	14.86	1 (2.6)	9.31	79 (8.0)	31.24	9 (2.6)	9.04
Upper respiratory tract infection	17 (5.8)	21.86	6 (5.2)	20.83	3 (3.2)	11.14	2 (5.3)	18.62	60 (6.1)	22.07	15 (4.4)	15.07
Skin infection	2 (0.7)	3.45	2 (1.7)	5.95	1 (1.1)	3.71	1 (2.6)	9.31	14 (1.4)	5.09	10 (2.9)	10.05
Herpes simplex	5 (1.7)	8.05	1 (0.9)	2.98	1 (1.1)	3.71	–	–	17 (1.7)	6.45	4 (1.2)	5.02

Conclusions

- In this post hoc analysis, tralokinumab was well-tolerated and improved the signs and symptoms of moderate-to-severe AD, regardless of race, with further improvements up to 52 weeks of treatment
- Limitations of this analysis include disparate sample sizes across racial subgroups

Abbreviations

adj., adjusted; AE, adverse event; AD, atopic dermatitis; DLQI, dermatology life quality index; E, number of adverse events; EASI, Eczema Area and Severity Index; IGA, Investigator's Global Assessment; n, number of patients achieving the indicated metric, or with ≥1 event; nE, number of events; nPY, number of patients, N, number of patients with recorded observation; NRS, numerical rating scale; PYE, patient-years of exposure; Q2W, every 2 weeks; SD, standard deviation; TCS, topical corticosteroids

References

1. Kaufman B, et al. *Exp Dermatol* 2018; 27: 340-357. **2.** Wollenberg A, et al. *Br J Dermatol.* 2021; 184(3)437-449. **3.** Silverberg J, et al. *Br J Dermatol.* 2021; 184(3)450-463

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