Safety of tralokinumab in pediatric patients aged 12–17 years with moderate-to-severe atopic dermatitis: results from the phase 3 ECZTRA 6 trial

Andreas Wollenberg[1,2], Michael Cork[3], Carsten Flohr[4], Anthony Bewley[5], Andrew Blauvelt[6], Chih-ho Hong[7], Shinichi Imafuku[8], Marie L.A. Schuttelaar[9], Eric L. Simpson[10], Weily Soong[11], Petra Amoudruz[12], Katja Wendicke Lophaven[12], Azra Kurbasic[12], Lise Soldbro[12], Natacha Strange Vest[12], Amy Paller[13]

[1]Ludwig Maximilian University of Munich, Department of Dermatology and Allergy, Munich, Germany; [2]Vrije Universiteit Brussel (VUB), Universitair Ziekenhuis Brussel (UZ Brussel), Department of Dermatology, Brussels, Belgium; [3]Sheffield Dermatology Research, Department of Infection, Immunity, and Cardiovascular Disease, The University of Sheffield and Sheffield Teaching Hospitals, NIHR Clinical Research Facility, Sheffield, UK; [4]Department of Paediatric Dermatology, St John's Institute of Dermatology, Guy's & St Thomas' NHS Foundation Trust and King's College London, London, UK; [5]Barts Health NHS Trust, London, UK; [6]Oregon Medical Research Center, Portland, OR, USA; [7]University of British Columbia, Vancouver, BC, Canada; [8]Fukuoka University, Fukuoka, Japan; [9]University Medical Centre Groningen, University of Groningen, Groningen, The Netherlands; [10]Oregon Health & Science University, Portland, OR, USA; [11]Allervie Health-Alabama Allergy & Asthma Center, Birmingham, AL, USA; [12]LEO Pharma, A/S, Ballerup, Denmark; [13]Feinberg School of Medicine, Northwestern University, Chicago, IL, USA

Introduction

- Atopic dermatitis (AD) is a chronic inflammatory skin disease associated with a substantial disease burden; it often develops in early childhood and affects up to 20% of children[1,2]
- There are limited safe and effective treatment options available for long-term use in pediatric patients with moderate-to-severe AD
- Tralokinumab is a fully human, high-affinity, monoclonal antibody that specifically neutralizes interleukin-13, a key driver of inflammation, skin barrier dysfunction and microbial dysbiosis in AD[3–7]
- In the phase 3 ECZTRA 6 monotherapy trial, tralokinumab was effective and well tolerated in patients aged 12–17 years with AD[8]

Objective

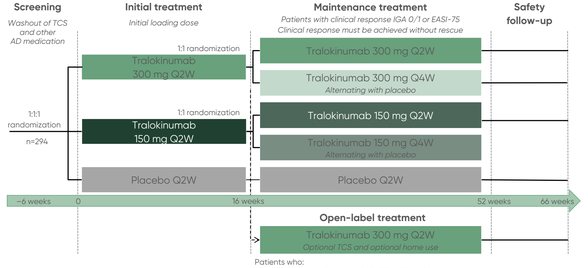
- To present detailed safety data up to 52 weeks for tralokinumab in pediatric patients aged 12–17 years with moderate-to-severe AD enrolled in the ECZTRA 6 trial (NCT03526861)

Materials and Methods

Study design

- Adolescent patients were randomized 1:1:1 to subcutaneous tralokinumab 150 mg or 300 mg every 2 weeks (Q2W), or placebo for an initial treatment period of 16 weeks
- Primary endpoints were Investigator's Global Assessment (IGA) score 0/1 and ≥75% improvement from baseline in Eczema Area and Severity Index (EASI-75) at Week 16
- Patients achieving primary endpoints without rescue treatment were re-randomized to tralokinumab Q2W or every 4 weeks (Q4W), at their same initial tralokinumab dosage for 36 weeks of maintenance treatment as shown in **Figure 1**, while Placebo responders continue in the Placebo Q2W
- Patients not achieving primary endpoints at Week 16, those receiving rescue treatment from Week 2 to Week 16, and those meeting other specific criteria† were transferred to open-label treatment of tralokinumab 300 mg Q2W plus optional mild-to-moderate strength topical corticosteroids (TCS)
- Key secondary endpoints include change in SCORing AD (SCORAD) from baseline to Week 16, reduction of worst daily pruritus numeric rating scale (NRS) (weekly average) of at least 4 from baseline to Week 16, and change in Children's Dermatology Life Quality Index (CDLQI) score from baseline to Week 16

Figure 1. ECZTRA 6 trial design



Patients who:
- Did not achieve IGA 0/1 or EASI-75 at Week 16
- Received rescue treatment between Week 2–16
- Were transferred from maintenance treatment if specific criteria were met

Rescue treatment during initial and maintenance treatment defined as: TCI, TCS or systemic AD treatment.
AD, atopic dermatitis; EASI, Eczema Area and Severity Index; IGA, Investigator's Global Assessment; Q2W, every 2 weeks; Q4W, every 4 weeks; TCS, topical corticosteroids. †Patients not achieving EASI-75 over ≥4 weeks with IGA ≥2 after IGA=0 at Week 16, or with IGA ≥3 after IGA=1 at Week 16, or who had IGA >1 at Week 16; patients who receive rescue treatment after Week 16

Statistical analyses and endpoints

- EASI-75, IGA 0/1, and secondary endpoint ≥4-point improvement in adolescent pruritus NRS were analyzed using Cochran-Mantel-Haenszel test stratified by geographic region and baseline disease severity
  - Patients receiving rescue therapy between Week 2 and 16 or with missing data at Week 16 were considered non-responders
- Secondary endpoints, change from baseline in SCORAD and CDLQI were analyzed using a linear mixed model for repeated measurements
  - Data after use of rescue or discontinuation were disregarded
- A closed testing procedure with hierarchical tests, alpha splitting, and alpha recycling were applied for above efficacy endpoints

Results

Patient characteristics

- Baseline demographic and clinical characteristics were comparable across treatment groups (**Table 1**)

Table 1. Baseline characteristics

Patients	Placebo (n=94)	Tralokinumab 150 mg Q2W (n=98)	Tralokinumab 300 mg Q2W (n=97)
Mean age, years	14.3	14.8	14.6
Age group, n (%) 12–14 15–17	 49 (52.1) 45 (47.9)	 37 (37.8) 61 (62.2)	 45 (46.4) 52 (53.6)
Male sex, n (%)	51 (54.3)	51 (52.0)	47 (48.5)
Mean duration of AD, years (SD)	12.1 (3.5)	12.7 (3.7)	12.1 (3.7)
Severe disease (IGA=4), n (%)	43 (45.7)	44 (44.9)	48 (49.5)
Mean EASI (SD)	31.2 (14.5)	32.1 (12.9)	31.8 (13.9)
Mean SCORAD (SD)	67.4 (14.9)	67.7 (14.4)	68.3 (13.7)
Mean CDLQI (SD)	13.3 (6.0)	12.9 (6.3)	13.4 (7.3)
Mean Weekly Average Peak Pruritus NRS (SD)	7.5 (1.7)	7.5 (1.6)	7.8 (1.5)

AD, Atopic Dermatitis; CDLQI, Children's Dermatology Life Quality Index; EASI, Eczema Area and Severity Index; IGA, Investigator's Global Assessment; n, Number of subjects in analysis set; NRS, Numeric rating scale; Q2W, Every 2 weeks; SCORAD, Scoring Atopic Dermatitis; SD, standard deviation.

Overall Summary of AEs: Weeks 0–16

- Tralokinumab was well-tolerated and rates of adverse events (AEs) were similar in the pooled tralokinumab and placebo arms (majority were mild or moderate in severity) (**Table 2**)
- No patterns were seen in types of serious AEs and none led to any safety concerns (**Table 2**)
- The majority of AEs had resolved within the initial 16-week period; only one AE led to treatment withdrawal and was not considered related to treatment* (**Table 2**)

Table 2. ECZTRA 6 Safety Summary (Weeks 0-16)

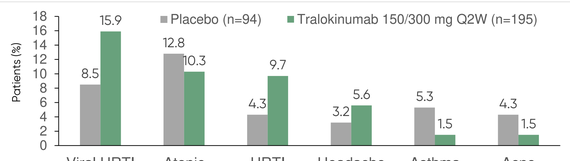
	Placebo (n=94)		Tralokinumab 150/300 mg Q2W (n=195)	
	N (%)	Rate	N (%)	Rate
Patients with ≥1 AEs	58 (61.7)	479.7	129 (66.2)	518.6
Patients with ≥1 Serious AEs	5 (5.3)	17.9	4 (2.1)	6.8
Severity of AEs				
Mild	40 (42.6)	275.7	95 (48.7)	323.1
Moderate	31 (33.0)	179.0	65 (33.3)	171.7
Severe	7 (7.4)	25.1	8 (4.1)	23.8
Related to IMP	20 (21.3)	128.9	51 (26.2)	158.1
Leading to withdrawal	0	0	1 (0.5)*	1.7
Outcome				
Fatal	0	0	0	0
Not recovered/not resolved	7 (7.4)	25.1	11 (5.6)	22.1
Recovering/resolving	2 (2.1)	7.2	5 (2.6)	10.2
Recovered/resolved	55 (58.5)	433.2	122 (62.6)	481.2
Recovered/resolved with sequelae	3 (3.2)	10.7	1 (0.5)	1.7
Unknown	1 (1.1)	3.6	2 (1.0)	3.4

*Cerebrovascular accident, not considered related to treatment by the investigator or study sponsor; The patient had several risk factors for developing cerebrovascular accident. The event was not considered related to treatment with tralokinumab by either investigator or sponsor/LEO. The outcome was reported as recovered with sequelae.
Rate: number of events divided by patient years of exposure x 100
AE, adverse event; IMP, investigational medicinal product; N, number of patients with one or more events.

Frequently Reported AEs: Weeks 0–16

- The most frequently reported AEs in adolescents were similar to those seen in adults (**Figure 2**)

Figure 2. AEs during the initial treatment phase (≥5% of patients in pooled tralokinumab or placebo arms)



Viral URTIs were most commonly reported as the common cold
URTI, Upper respiratory tract infection

Frequency of Conjunctivitis AESI: Weeks 0–16

- The frequency of conjunctivitis was low and similar between the pooled tralokinumab and placebo arms; only 2 cases of conjunctivitis (PT) occurred, both in the tralokinumab 150 mg arm (**Table 3**)

Table 3. Frequency of Conjunctivitis AESI

	Placebo (n=94)		Tralokinumab 150/300 mg Q2W (n=195)	
	N (%)	Rate	N (%)	Rate
Conjunctivitis (AESI)	2 (2.1)	10.7	7 (3.6)	11.9
Conjunctivitis (PT)	0	0	2 (1.0)	3.4
Conjunctivitis bacterial (PT)	0	0	1 (0.5)	1.7
Conjunctivitis allergic (PT)	2 (2.1)	10.7	4 (2.1)	6.8
Conjunctivitis viral (PT)	0	0	0	0

Rate: number of events divided by patient years of exposure x 100
AESI, adverse event of special interest; PT, preferred term

Additional Adverse Events of Relevance: Weeks 0–16

- Eczema herpeticum was reported in 2 patients in the initial treatment phase (1 in placebo and 1 in tralokinumab 150 mg Q2W arm)
  - No patients had eczema herpeticum in the tralokinumab 300 mg Q2W arm
- Herpes simplex infections were reported in 4 patients in the initial treatment phase (2 in placebo and 2 in the tralokinumab 150 mg Q2W arm)
  - No patients had herpes simplex infections in the tralokinumab 300 mg Q2W arm
- There were no reports of swelling related to joints, enthesitis, tenosynovitis, generalized joint pain, or psoriasis
  - There was one case of right hip pain (coded as arthralgia), starting at Day 4 after loading dose, mild, not considered related to treatment, resolved after 3 days without any action taken

Disclosures

Andreas Wollenberg has received grants, personal fees, or nonfinancial support from AbbVie, Alleens, Almirall, Beiersdorf, Bioderma, Chugai, Galapagos, Galderma, GSK, Hans Karrer, LEO Pharma, Lilly, L'Oreal, Maruho, MedImmune, Merck, Novartis, Pfizer, Pierre Fabre, Regeneron, Santen, and Sanofi-Aventis. **Michael Cork** has served as a clinical trial investigator for Astellas, Galapagos, Johnson & Johnson, LEO Pharma, La Roche-Posay, MSD, Novartis, Perrigo, Regeneron, Sanofi Genzyme, and Stiefel; has served as an advisory board member, consultant, and/or invited lecturer for Pfizer Inc., Amgen, Astellas, Bayer, Johnson & Johnson, LEO Pharma, L'Oreal, MSD, Novartis, Regeneron, Sanofi Genzyme, Stiefel, and Unilever; has received honoraria from Astellas, Johnson & Johnson, LEO Pharma, Novartis, Regeneron, Sanofi Genzyme, and Stiefel; and has received research funding from Bayer. **Carsten Flohr** is Chief Investigator of the UK National Institute for Health Research-funded TREAT (ISRCTN15837754) and SOFTER (Clinicaltrials.gov NCT03270566) trials as well as the UK-Irish Atopic eczema Systemic Therapy Register (A-STAR; ISRCTN11210918) and a Principal Investigator in the European Union (EU) Horizon 2020-funded BIOMAP Consortium (http://www.biomap-imi.eu/). He also leads the EU Trans-Foods consortium. His department has received funding from both Sanofi-Genzyme and Pfizer for skin microbiome work. **Anthony Bewley** has been a consultant for and received consultancy fees or travel bursaries from AbbVie, Almiral, Eli Lilly, Galderma, Janssen, LEO Pharma, Novartis, Sanofi, and UCB Pharma. **Andrew Blauvelt** has served as a speaker/received honoraria from AbbVie and UCB, served as a scientific adviser/received honoraria from AbbVie, Abcentra, Aligos, Almirall, Amgen, Anaptysbio, Arcutis, Arena, Asian, Athenex, Boehringer Ingelheim, Bristol-Myers Squibb, Dermavant, EcoRI, Eli Lilly and Company, Evommune, Forte, Galderma, HighlightI Pharma, Incyte, Janssen, Landos, Leo, Merck, Novartis, Pfizer, Rapt, Regeneron, Sanofi Genzyme, Sun Pharma, UCB Pharma, Viblisme, and Xencor, and has acted as a clinical study investigator/institution has received clinical study funds from AbbVie, Amgen, Arcutis, Athenex, Boehringer Ingelheim, Bristol-Myers Squibb, Dermavant, Eli Lilly and Company, Galderma, Incyte, Janssen, Leo, Merck, Novartis, Pfizer, Regeneron, Sun Pharma, and UCB. **Chih-ho Hong** is a researcher, consultant, and/or advisor for AbbVie, Amgen, Arcutis, Bausch Health, Boehringer Ingelheim, Celgene, Dermavant, Dermira, DS Biopharma, Galderma, GlaxoSmithKline, Incyte, Janssen, LEO Pharma, Lilly, MedImmune, Novartis, Pfizer, Regeneron, Roche, Sanofi Genzyme, Sun Pharma, and UCB. **Shinichi Imafuku** is a researcher, consultant, or speaker for AbbVie, Amgen, Boehringer Ingelheim, Celgene, DaiichiSankyo, Eisai, KyowaKirin, Lilly, Taihoyakuhinkogyo, TanabeMitsubishi, Tsumura, Torii, Maruho, Novartis, LEO Pharma, and Janssen. **Marie L.A. Schuttelaar** has served on advisory boards for Sanofi Genzyme, Pfizer, LEO Pharma, Eli Lilly, Galderma, and AbbVie; as an investigator for AbbVie, Novartis, Regeneron Pharmaceuticals, Inc., Sanofi Genzyme, and Galderma; as a consultant for Regeneron Pharmaceuticals, Inc.; has received research grants from Sanofi Genzyme and Novartis. **Eric L. Simpson** is a consultant and investigator for Regeneron/Sanofi, Dermira, Menlo Pharmaceuticals, Lilly, Abbvie, Genentech, Medimmune, GSK, LEO Pharma, Celgene, and Pfizer. **Weily Soong** has served on the advisory board and received research grants from AbbVie, LEO Pharma, Genentech, Inc., Teva, Novartis, and Pfizer; served on the advisory board, received research grants, and was a speaker for Amgen, AstraZeneca, Regeneron, Sanofi, and GlaxoSmithKline; received research grants and was a speaker for Optinose; received research grants from Aimmune, Avillion, Galderma, Gossamer Bio, 3M, and LEO Pharma. **Petra Arlert, Katja Wendicke Lophaven, Azra Kurbasic, Lise Soldbro** and **Natacha Strange Vest** are employees of LEO Pharma A/S. **Amy Paller** has served as an investigator for AbbVie, Anaptysbio, Incyte, Janssen, KrystalBio, LEO Pharma, Regeneron, and UCB, received honorarium for consultancy from AbbVie, Abeona, Almirall, Anaptysbio, Arena, Azitra, BiomX, Boehringer Ingelheim, Castle Biosciences, Catawba, Dermira, Exicure, Forté, Kamari, LEO Pharma, Lilly, LifeMax, Novartis, Pfizer, Regeneron, Sanofi Genzyme, Seanergy, and UCB, and served on a Data Safety Monitory Board for AbbVie, Bausch, Galderma, and Novan.

Acknowledgements

The ECZTRA 6 clinical trial was sponsored by LEO Pharma A/S (Ballerup, Denmark). This poster is an encore of a previous presentation at European Academy of Dermatology and Venereology 31st Annual Meeting, 7–10 September 2022. Editorial support from Alphabet Health (New York, NY, USA) by Juliel Espinosa, PhD and Meredith Whitaker, PhD was funded by LEO Pharma (USA).

Overall Summary of AEs: Weeks 0–52

- During Weeks 16–52, the types and frequencies of AEs were similar to the initial phase, with the majority being non-serious and mild or moderate in severity (**Table 4**)

Table 4. ECZTRA 6 Safety Summary (Weeks 0-52)

	Initial phase (Weeks 0–16)		Maintenance phase (Weeks 16–52)		Open-label phase (Weeks 16–52)	
	Tralokinumab 150/300 mg Q2W (n=195)		Tralokinumab 150/300 mg Q2/4W (n=50)		Tralokinumab 300 mg Q2W plus optional TCS (n=234)	
	N (%)	Rate	N (%)	Rate	N (%)	Rate
Patients with ≥1 AE	129 (66.2)	518.6	28 (56.0)	205.4	158 (67.5)	349.4
Patients with ≥1 SAE	4 (2.1)	6.8	0	0	7 (3.0)	4.63
Severity						
Mild	95 (48.7)	323.1	16 (32.0)	90.83	122 (52.1)	238.9
Moderate	65 (33.3)	171.7	19 (38.0)	110.6	82 (35.0)	107.9
Severe	8 (4.1)	23.8	1 (2.0)	3.95	4 (1.7)	2.7
Related to IMP	51 (26.2)	158.1	10 (20.0)	75.03	65 (27.8)	107.2
Conjunctivitis (AESI)	4 (4.1)	13.6	3 (6.0)	11.85	11 (4.7)	9.3

Rate: number of events divided by patient years of exposure x 100
AE, adverse event; AESI, adverse event of special interest; IMP, investigational medicinal product; n, Number of subjects in analysis set; Q2W, Every 2 weeks; Q4W, Every 4 weeks; SAE, serious adverse event; TCS, topical corticosteroid.

Conclusions

- Tralokinumab was well tolerated in pediatric patients aged 12–17 years with moderate-to-severe AD, with a favorable safety profile seen through 52 weeks of treatment
- The safety profile was similar to that seen in adult phase 3 studies, with the frequency and type of AEs being generally consistent[9,10]
- The frequency of conjunctivitis was low and similar between the tralokinumab and placebo arms at Week 16, with no increase observed up to Week 52
- The frequency of acne was low across tralokinumab and placebo arms, supporting a favorable tolerability profile of tralokinumab in this age group
- The detailed long-term safety data presented here add to the previous findings that tralokinumab is efficacious and well tolerated in this adolescent patient group[8]

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