Report ADTRALZA® Tralokinumab

Product & Mechanism of action

Substance: Tralokinumab

Brand Name: Adtralza®

Originator/licensee: Leo Pharma A/S

Classification: NCE

ATC code: D11AH07

Orphan Status:
Eu: No
Us: No

Mechanism of action:
Tralokinumab is an IL-13-neutralising human IgG4 monoclonal antibody; IL-13 is over expressed locally and has a significant impact on skin biology, including the recruitment of inflammatory cells, the alteration of the skin microbiome, and the decrease in the epidermal barrier function. Tralokinumab binds to IL-13 helices A and D, thus preventing IL-13 from interacting with IL-13Rα1 and IL-13Rα2. [1]

Authorized indications Licensing status

Authorized Indication:
EMA: tralokinumab is indicated for the treatment of MSAD in adults who are candidates for systemic therapy. [2]

Route of administration: SC

Licensing status
EU CHMP P.O. date: 22/04/2021
FDA M.A. date: -

EU Speed Approval Pathway: No

FDA Speed Approval Pathway: -

ABBREVIATIONS:
AD: Atopic Dermatitis
AE: adverse event
CHMP: Committee for Medicinal Products for Human Use
DLQI: Dermatology Life Quality Index
EASI: Eczema Area and Severity Index
EASI 50 75 90: 50% 75% 90% improvement in Eczema Area and Severity Index
IGA: Investigator's Global Assessment
IL-13: Interleukin 13
M.A.: Marketing Authorization
MSAD: Moderate-to-Severe Atopic Dermatitis
NRS: Numerical Rating Scale
P.O.: Positive Opinion
pts: patients
Q2W: every 2 weeks
Q4W: every 4 weeks
SAE: Serious Adverse Event
sc: subcutaneous
TCS: Topical Corticosteroids
w: week

Essential therapeutic features

Summary of clinical EFFICACY:
ECZTRA 1 (NCT03131648) and ECZTRA 2 (NCT03160885): were identically designed 52-week, multinational, randomized, double-blind, placebo-controlled, phase III studies. Pts ≥ 18 years of age, with a diagnosis of AD for ≥ 1 year, candidates for systemic therapy due to inadequate response to topical treatment were recruited. Pts were randomized 3:1 to subcutaneous Tralokinumab 300 mg Q2W, after a 600-mg loading dose on day 0, or placebo for 16 weeks. Pts achieving an IGA score of 0 or 1 and/or EASI reduction ≥75% with Tralokinumab at week 16 were re-randomized 2:2:1 to Tralokinumab Q2W or Q4W or placebo, for 36 weeks (maintenance treatment period).
Primary endpoints were IGA score of 0 or 1 and at least 75% reduction in EASI at week 16 and at week 52 (maintenance end point). [3]
ECZTRA 3 (NCT03363854): is a 32-week, multinational, randomized, double-blind, placebo-controlled, phase III study. The inclusion criteria of study population are the same as in the ECZTRA 1 and ECZTRA 2. The primary endpoints were IGA score of 0 or 1 and at least 75% reduction in EASI at week 16. Pts were randomized 2:1 to sc Tralokinumab. 300 mg with TCS or placebo with TCS Q2W, after a 600-mg loading dose on day 0, over 16 weeks. Pts achieving an IGA score of 0 or 1 and/or EASI reduction ≥75% with Tralokinumab. at week 16 were re-randomized 1:1 to T. Q2W or Q4W or placebo with TCS, for another 16 weeks. [4]

Efficacy outcome of ECZTRA 1. Results are expressed as difference vs. placebo (95% CI):

	At 16 W	At 52 W
IGA score	8.6% (CI 4.1-13.1)**	Q2W and Q4W were not statistically significant for both primary endpoints
EASI 75	12.1% (CI 6.5-17.7)***	

Efficacy outcome of ECZTRA 2. Results are expressed as difference vs. placebo (95% CI):

	At 16 W	At 52 W Q2W	At 52 W Q4W
IGA score	11.1% (CI 5.8-16.4)***	34.1% (CI 13.4-54.9)**	19.9% (CI 1.2-40.9) ns
EASI 75	21.6% (CI 15.8-27.3)***	33.7% (CI 17.3-50.0)***	30.0% (CI 13.7-46.4)***

Efficacy outcome of ECZTRA 3. Results at 16 W are expressed as difference vs. placebo (95% CI), while results at 32 W are expressed as % of pts that achieve IGA score 0/1 and EASI 75:

	At 16 W	At 32 W Q2W	At 32 W Q4W
IGA score	12.4% (CI 2.9-21.9)*	89.6% (CI 77.8-95.5) nr	77.6% (CI 64.1–87.0) nr
EASI 75	20.2% (CI 9.8-30.6)***	92.5% (CI 83.7–96.8) nr	90.8% (CI 81.3–95.7) nr

*p<0.05; **P<0.01; ***P<0.001; ns = not significant nr = not reported

Summary of clinical SAFETY:
In ECZTRA 1, AEs were reported in 76.4% of pts treated with Tralokinumab and 77% of pts receiving placebo; in ECZTRA 2, 61.5% of pts receiving Tralokinumab vs. 77% of pts treated with placebo experienced AEs; in ECZTRA 3, 71.4% of subjects with Tralokinumab and 66.7% with placebo showed AEs.
The most frequently reported AEs in ECZTRA 1, 2 and 3 were: viral upper respiratory tract infection (23.1%, 8.3% and 19.4%, respectively) conjunctivitis (10%, 5.2% and 13.1%, respectively) eye disorders (10.3%, 5.6% and 13.5%, respectively). In ECZTRA 3 only headache (8.7%) was reported; six pts (2.4%) receiving Tralokinumab had AEs leading to permanent discontinuation vs. one pt (0.8%) in the placebo arm. No fatal AEs were reported. [3,4]
SAEs were reported in a lower percentage of pts treated with Tralokinumab compared with those treated with placebo in all the three trials considered (ECZTRA 1: 3.8% with Tralokinumab vs. 4.1% with placebo; ECZTRA 2: 1,7% with Tralokinumab vs. 2.5% with placebo; ECZTRA 3: 0,8% with Tralokinumab vs. 3.2% with placebo).

Ongoing studies:
- ***For the same indication:*** Yes [5,6]
- ***For other indications:*** Yes

[Phase III, but if it is an O/OE drug, also Phase II]
Discontinued studies (for the same indication): No

NHS impact

Cost of therapy:
In US a single dose of Tralukinumab costs $1,601.70 (300 mg Q2W), while the yearly price is $31,131.56. [5]

Epidemiology:
Among adults AD has a prevalence of 2%–10% in Europe and 6.6% in Italy. [6,7]

POSSIBLE PLACE IN THERAPY
Emollients and topical corticosteroids are 1st-line therapies; topical calcineurin inhibitors are 2nd-line options, while phototherapy and ciclosporin are considered as 3rd and 4th-line options, respectively.
Dupilumab and Baricitinib are recommended if the pt has not responded at least to one systemic therapy (5th-line) [6,8]

OTHER INDICATIONS IN DEVELOPMENT
Asthma, Idiopathic Pulmonary Fibrosis asthma, alopecia areata [9,10]

SAME INDICATION IN EARLIER LINE(S) OF TREATMENT: No

OTHER DRUGS IN DEVELOPMENT for the SAME INDICATION:
Yes: Nemolizumab, Ruxolitinib, Benralizumab, Lebrikizumab, Bermekimab, Upadacitinib, rizankizumab, Mepolizumab, Secukinumab, Etrasimod. [1,9]

*Service reorganization Y/N: No
*Possible off label use Y/N: Yes

References:
1 https://adisinsight.springer.com/drugs/800019573
2 https://www.ema.europa.eu/en/medicines/human/summaries-opinion/adtralza
3 Wollenberg A, 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; 437-449.
4 Silverberg JI, 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; 450-463.
5 Atlas SJ, et al., JAK Inhibitors and Monoclonal Antibodies for the Treatment of Atopic Dermatitis: Effectiveness and Value; Draft Evidence Report. Institute for Clinical and Economic Review, May 14, 2021. https://icer.org/assessment/atopic-dermatitis-2021/#timeline
6 Wollenberg A, et al. European Task Force on Atopic Dermatitis/EADV Eczema Task Force. ETFAD/EADV Eczema task force 2020 position paper on diagnosis and treatment of atopic dermatitis in adults and children. J Eur Acad Dermatol Venereol. 2020 Dec;34(12):2717-2744. doi: 10.1111/jdv.16892. Epub 2020 Nov 17. PMID: 33205485.
7 Kowalska-Olędzka E, et al., Epidemiology of atopic dermatitis in Europe. J Drug Assess. 2019 Jun 12;8(1):126-128.
8 nice.org.uk/guidance/ta681
9 https://clinicaltrials.gov/
10.http://www.io.nihr.ac.uk/wp-content/uploads/2019/12/10753-TSID_9983-Tralokinumab-for-Atopic-Dermatitis-V.1.0-NOV2019-NON-CONF.pdf