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IL-13 Inhibition in the Treatment of Atopic Dermatitis – New and Emerging Biologic Agents

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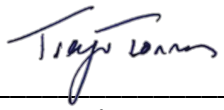

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Resumo

A Dermatite Atópica é uma doença inflamatória cutânea, crónica e prevalente, afetando até 25% das crianças e entre 2 a 10% dos adultos, que se manifesta por placas eritematosas e pruriginosas.

O desenvolvimento da Dermatite Atópica envolve quer fatores ambientais, quer fatores genéticos que causam inflamação, disbiose e desregulação imunológica na epiderme, aumentando a perda transepidérmica de água e permitindo a penetração de irritantes, microorganismos e alergénios. Estes antigénios desencadeiam uma resposta imunológica do tipo 2, resultando num aumento da produção de citocinas como IL-4, IL-5, IL-13 e IL-31. A IL-13 tem sido estudado pelo seu papel fundamental na patogénese da Dermatite Atópica, com variantes genéticas associadas a um maior risco. O recetor da IL-13 é um complexo heterodimérico composto pelo IL-4Rα e pelo IL-13Rα1. Após heterodimerização, este complexo ativa a sinalização STAT6, crucial para iniciar respostas imunológicas do tipo 2.

Tendo em conta o elevado impacto na qualidade de vida destes pacientes, é crucial a procura por novos tratamentos mais seletivos para o uso na Dermatite Atópica moderada a grave. O Dupilumab foi o primeiro agente biológico aprovado para a Dermatite Atópica, em 2017. Ao ligar-se ao IL-4Rα, bloqueia tanto a via de sinalização da IL-13 através do recetor tipo 1, como a via da IL-4 através dos recetores tipo 1 e tipo 2. Este artigo tem como objetivo apresentar o estado atual do conhecimento sobre a eficácia e segurança dos quatro agentes biológicos que sinalizam a IL-13: Tralokinumab, Lebrikizumab, Cendakimab e Eblasakimab, além de explorar o papel do IL-13 na patogénese da Dermatite Atópica.

Tralokinumab e Lebrikizumab são inibidores seletivos da IL-13 que demonstraram segurança e eficácia como opções de tratamento para a Dermatite Atópica em ensaios de fase III. O Tralokinumab está aprovado para o tratamento da Dermatite Atópica na Europa e nos Estados Unidos da América, enquanto o Lebrikizumab está aprovado para uso na Europa. O Cendakimab, também inibidor seletivo da IL-13, mostrou resultados promissores ao apresentar-se como uma opção segura e eficaz em ensaios de fase II. O Eblasakimab, que bloqueia tanto a via de sinalização da IL-13 como da IL-4, está atualmente em ensaios de fase II, após a sua segurança ter sido comprovada em ensaios de fase I.

Para estabelecer o papel da inibição da IL-13 na gestão da Dermatite Atópica, são necessários estudos diretos entre os inibidores da IL-13 entre si e com o Dupilumab para uma melhor compreensão das vantagens desta abordagem.

Palavras-chave: Dermatite Atópica, Anticorpos monoclonais, IL-13, Tralokinumab, Lebrikizumab, Cendakimab, Eblasakimab.

Abstract

Atopic Dermatitis is a prevalent, chronic and recurrent inflammatory skin disease, affecting up to 25% of children and 2-10% of adults, manifested by itchy, dry and erythematous plaques.

Atopic Dermatitis development involves both environmental and genetic factors causing inflammation, dysbiosis and immune dysregulation in the epidermis, enhancing transepidermal water loss, allowing penetration of irritants, microbes and allergens. These antigens trigger a type 2 immune response, resulting in an excessive production of cytokines as IL-4, IL-5, IL-13 and IL-31. IL-13 has been studied for its key role in Atopic Dermatitis pathogenesis, with gene variants linked to higher risk. IL-13 receptor is a heterodimeric complex comprising IL-4Rα and IL-13Rα1. Upon heterodimerization, this complex activates STAT6 signaling, crucial for initiating type 2 allergic responses.

Since there's a high impact in the quality of life of these patients, it is important the search for new and more selective treatments for use in moderate-to-severe Atopic Dermatitis. Dupilumab was the first biologic agent for Atopic Dermatitis, approved in 2017. By targeting the IL- 4Rα, it blocks both the IL-13 pathway through the type 1 receptor and the IL-4 pathway through the type 1 and type 2 receptors. This article aims to outline the current state of knowledge concerning the effectiveness and safety of the four biologic agents targeting IL-13 signaling: Tralokinumab, Lebrikizumab, Cendakimab and Eblasakimab, while also exploring the role of IL-13 in the pathogenesis of AD.

Tralokinumab and Lebrikizumab are selective IL-13 inhibitors who demonstrated safety and efficacy as treatment options for Atopic Dermatitis in phase III trials. Tralokinumab is approved for use for the treatment of Atopic Dermatitis in Europe and United States of America, while Lebrikizumab is approved only in Europe. Cendakimab, another IL-13 selective inhibitor, showed promising results by providing safe and effective outcomes in phase II trials. Eblasakimab, which disrupts both the IL-13 and IL-4 signaling pathways, is currently on phase II trials, following well-tolerated administration in phase I studies.

To establish the role of IL-13 inhibition in AD management, head-to-head studies comparing IL-13 inhibitors with each other and with Dupilumab are needed to understand the advantages of this approach.

Keywords: Atopic Dermatitis, monoclonal antibodies, IL-13, Tralokinumab, Lebrikizumab, Cendakimab, Eblasakimab.

List of Abbreviations

AEs	Adverse Events
AD	Atopic Dermatitis
$AUC_{(0-t)}$	Area under serum concentration-time curve from time 0 to the last measurable time point
$AUC_{(0-inf)}$	Area under serum concentration-time curve from time 0 to infinity
BSA	Body Surface Area
C_{max}	Maximum concentration
CyA	Ciclosporin A
CYP	Cytochrome P450
DLQI	Dermatology Life Quality Index
EASI	Eczema Area and Severity Index
EMA	European Medicines Agency
EU	European Union
FDA	Food and Drug Administration
IGA	Investigator Global Assessment
IgE	Imunoglobulin E
IL-4	Interleukin-14
IL-4Rα	IL-4 receptor α
IL-13	Interleukin-13
IL-13Rα1	IL-13 receptor α1
IL-13Rα2	IL-13 receptor α2
ILC2	Type 2 innate lymphoid cells
IV	Intravenous
LD	Loading Dose
PNRS	Pruritus Numeric Rating Scale
POEM	Patient Oriented Eczema Measure
Q2W	Every 2 weeks
Q4W	Every 4 weeks
QW	Once weekly
SC	Subcutaneous
SCORAD	Scoring AD
SD	Single dose
Tdap	Tetanus, Diphtheria and Pertussis
TCS	Topical corticosteroids
Th2	Type 2 T helper cells
TNF	Tumor necrosis factor
US	United States

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Introduction

Atopic Dermatitis (AD), also known as atopic eczema, is a prevalent, chronic and recurrent inflammatory skin disease. While frequently manifesting in childhood, it can endure into adulthood, affecting up to 25% of children and 2-10% of adults. [1,2] Until the age of 6, both males and females are equally affected, while females show higher prevalence of AD thereafter.[3] A family history of atopy stands out as the most important risk factor for AD. It is estimated to increase a child risk of developing AD by 1.5-fold. This risk increases to approximately 3-fold if one parent has AD and up to 5-fold if both parents are affected by AD. [4]

Itchy, dry and erythematous plaques are the main manifestations of AD. These symptoms often lead to sleep disturbances, decreased productivity, lower self-esteem, social withdrawal and, in severe cases, can contribute to depression and suicidal thoughts. [5,6] AD is linked with various other atopic conditions like asthma, allergic rhinitis, food allergies and eosinophilic esophagitis. Moreover, individuals with AD appear to have higher susceptibility to cardiovascular issues and infections, attributed to factors such as compromised skin barrier function, immune dysregulation, reduced levels of antimicrobial peptides, enhanced bacterial colonization and skin infection, and the use of immunosuppressive medications. [7]

AD is an immune-mediated disorder, driven by the aberrant activation of type 2 T helper cells (Th2) and type 2 innate lymphoid cells (ILC2), accompanied by elevated levels of inflammatory cytokines, notably interleukin-4 (IL-4) and interleukin-13 (IL-13). [8] In the past few years, the introduction of targeted biologic and small molecule therapies has significantly expanded the treatment choices for individuals with moderate-to-severe AD. Dupilumab became the first biologic agent approved for the treatment of moderate-to-severe AD since 2017, acting as an inhibitor of the IL-4 receptor α (IL-4Rα), effectively hindering IL-4 and IL-13 signaling pathways and inhibiting inflammatory processes downstream. [9]

Even though both IL-4 and IL-13 are implicated in the pathogenesis of AD, IL-13 has been suggested as the primary cytokine involved, leading to its focus in research as a potential therapeutic target.

Objectives

This article aims to outline the current state of knowledge concerning the effectiveness and safety of the four biologic agents targeting IL-13 signaling: Tralokinumab, Lebrikizumab, Cendakimab and Eblasakimab, while also exploring the role of IL-13 in the pathogenesis of AD.

Methods

A comprehensive literature search was conducted from 2011 until 30st November of 2023 to investigate the pathogenic role of interleukin-13 and the efficacy of IL-13 inhibitors in treating AD.

The search was executed on the PubMed, Google Scholar, Science Direct and clinicaltrials.gov databases using the following search terms, alone or in combination: "Atopic Dermatitis", "monoclonal antibodies", "IL-13", "Tralokinumab", "Lebrikizumab", "Cendakimab" and "Eblasakimab" with a focus on titles, abstracts and article bodies.

Inclusion criteria encompassed original and review articles published in English, with a specific emphasis on relevance to the pathogenic mechanisms of IL-13 and the therapeutic applications of monoclonal antibodies against IL-13 in the context of AD. The bibliographic references of included articles were scrutinized to identify additional pertinent studies.

This search yielded a total of 47 articles and 21 clinical trials in clinicaltrials.gov.

The role of IL-13 in Atopic Dermatitis Pathogenesis

The development of AD involves both environmental and genetic factors, interacting to induce inflammation, dysbiosis and immune dysregulation within the epidermis, thus enhancing transepidermal water loss and promoting the penetration of irritants, microbes and allergens into the skin. [8,10] These antigens trigger an abnormal type 2 immune response, prompting naïve T cells to commit to the Th2 lineage. This results in an excessive production of cytokines crucial to the atopic manifestations of AD and itching, specifically IL-4, IL-5, IL-13 and IL-31. IL-4 and IL-13 contribute to dysfunction in the epidermal barrier by inducing the production of immunoglobulin E (IgE), attracting eosinophils, enhancing Th2 cell differentiation and reducing filaggrin expression. [8]

IL-13 plays a significant role in the pathogenesis of AD, with gene polymorphisms associated with higher risk of AD. [11,12] IL-13 is a cytokine produced by Th2 cells, natural killer cells, mast cells, basophils, eosinophils and ILC2 cells, that shares structural similarities with IL-4, although their sequence homology is only 25%. The receptor for IL-13 is a heterodimeric complex comprising IL-4Rα and IL-13 receptor α1 (IL-13Rα1). Upon heterodimerization, this complex activates STAT6 signaling, crucial for initiating type 2 allergic responses. Additionally, IL-13 binds to IL-13 receptor α2 (IL-13Rα2), which lacks a significant cytoplasmic domain and functions as a decoy receptor, without mediating signaling. The expression of IL-13Rα2 can be induced by various pro-inflammatory cytokines, including IL-13, IL-4 and tumor necrosis factor (TNF), suggesting a negative feedback mechanism. [12,13]

Overexpression of IL-13 has been shown to compromise the integrity of the epithelial barrier by down-regulating crucial components, including lipids and proteins such as filaggrin, loricrin and involucrin. Skin biopsy samples from patients with AD exhibit notable overexpression of IL-13 in both lesion and non-lesion skin, whereas only a mild overexpression of IL-4 is detectable in 40% of AD lesions. [14–16]

Treatment of Atopic Dermatitis

Targeting IL-13 to treat Atopic Dermatitis

IL-13 stands out as a promising therapeutic target for effectively managing AD due to its substantial efficacy potential and minimal toxicity concerns. [6,16]

Dupilumab was the first biologic agent for AD, first approved in 2017. By targeting the IL-4Rα, it blocks both the IL-13 pathway through the type 1 receptor and the IL-4 pathway through the type 1 and type 2 receptors.[8] Randomized controlled trials and real-world studies have

demonstrated the efficacy and safety of subcutaneous (SC) Dupilumab for the treatment of AD. Its safety profile is well studied, with the most relevant adverse events (AEs) being conjunctivitis, facial redness, arthralgia and immunological shift towards Th1/Th17.[17–20]

Four other distinct monoclonal antibodies targeting IL-13 signaling are being developed or have been already approved. Tralokinumab, having obtained approval from Health Canada, the Food and Drug Administration (FDA) and the European Medicines Agency (EMA), is now available for individuals with moderate-to-severe AD. Lebrikizumab has received approval from the EMA for its use in treating AD; however, it is yet to receive approval from the FDA. Cendakimab and Eblasakimab are currently undergoing investigation in phase II trials. [21–23]

Tralokinumab

Tralokinumab, a fully human IgG4 monoclonal antibody originating from a human phage display library, was the first biologic approved in the European Union (EU) and United States (US) with the mechanism of targeting and neutralizing selectively IL-13. It effectively prevents IL-13 from binding to both IL-13Rα1 and IL-13Rα2 receptors. The latter receptor, characterized by a short cytoplasmic tail lacking signaling motifs, serves as a decoy with an anti-inflammatory function by internalizing excess IL-13. By blocking IL-13-mediated signaling downstream of IL-4Rα/IL-13Rα1 heterodimerization, Tralokinumab not only inhibits IL-13 activity but also potentially disrupts the endogenous regulation of IL-13 mediated by IL-13Rα2. [8,23,24]

A phase I trial involving 30 healthy Japanese adults, a single-blind, randomized controlled study examined the effects of SC Tralokinumab at doses of 150, 300 or 600 mg. The study revealed dose-dependent increases in the observed maximum concentration (C_{max}), area under serum concentration-time curve from time 0 to the last measurable time point ($AUC_{(0-t)}$) and area under serum concentration-time curve from time 0 to infinity ($AUC_{(0-inf)}$) with Tralokinumab administration. The incidence and nature of AEs were consistent across all dosage levels and injection-site pain was the predominant treatment-related AE, reported by 83–100% of individuals across all treatment groups. This trial concluded that a single SC dose of Tralokinumab ranging from 150 to 600 mg demonstrated a favorable safety and pharmacokinetic profile among healthy adults.[23,25] In a phase IIb trial, a cohort of 204 healthy adults with moderate-to-severe AD received treatment comprising 45, 150 or 300 mg of SC Tralokinumab or placebo, administered every 2 weeks (q2w) over a span of 12 weeks with topical corticosteroids (TCS). Individuals in the 300 mg Tralokinumab group exhibited notable enhancements in EASI (Eczema Area and Severity Index) scores, a higher proportion of patients achieving an Investigator Global Assessment (IGA) score of 0 or 1 and marked improvements in the Scoring AD (SCORAD),

Dermatology Life Quality Index (DLQI) and Pruritus Numeric Rating Scale (PNRS) scores relative to those on placebo. The most significant clinical improvement was observed within the 300 mg cohort, with the most frequently reported AE being upper respiratory infections. Tralokinumab showed favorable safety and tolerability profiles, along with demonstrating early and sustained improvements in disease symptoms among patients with moderate-to-severe AD. [23,26]

In the ECZTRA 1 (802 patients enrolled) and ECZTRA 2 (794 patients enrolled) trials, two extensive 52-week-long randomized, double-blind, placebo-controlled, phase III studies were conducted to assess the safety and efficacy of Tralokinumab. Within these trials, patients received either SC Tralokinumab 300 mg q2w or a placebo. Only the patients who achieved an IGA score of 0 or 1 and/or EASI 75 with Tralokinumab by week 16 underwent rerandomization to receive Tralokinumab q2w, every 4 weeks (q4w), or placebo for an additional 36 weeks. In both clinical trials, patients receiving Tralokinumab exhibited higher rates of achieving an IGA score of 0/1 and EASI 75 at week 16 compared to those receiving placebo. Also, patients treated with Tralokinumab experienced improvements in pruritus, sleep, DLQI and SCORAD, with positive responses maintained up to week 52. [23,27]

In the ECZTRA 3 study, a phase III trial designed to evaluate the effectiveness and safety of Tralokinumab in combination with TCS for patients diagnosed with moderate-to-severe AD who required systemic therapy, a double-blind methodology was employed. Patients were allocated randomly in a 2:1 ratio to receive either SC Tralokinumab at a dosage of 300 mg or a placebo q2w, alongside TCS as needed, over 16 weeks. Results revealed a notable increase in the proportion of patients achieving an IGA score of 0 or 1 and a EASI 75 at the end of the 16 week treatment period among those administered Tralokinumab compared to the placebo group. Following the initial treatment phase, a subset of patients from both arms of the study underwent rerandomization to receive SC Tralokinumab either q2w or q4w, for an additional 16 weeks. A high percentage of patients maintained their positive response to treatment, with 89.6% and 92.5% of those receiving Tralokinumab q2w and 77.6% and 90.8% of those receiving Tralokinumab q4w, sustaining their IGA and EASI 75 responses at the 32-week mark, respectively. [23,28]

ECZTRA 7, a phase III trial, evaluated Tralokinumab combined with TCS in adults with severe AD who have contraindications for cyclosporin A (CyA) treatment or previously failed CyA treatment. In this multicentered, randomized, double-blind study, 277 adults received either Tralokinumab or placebo injections q2w for 26 weeks and TCS as needed. A significantly higher number of patients treated with Tralokinumab plus TCS attained the primary efficacy target of EASI 75 by week 16 in comparison to those receiving placebo plus TCS. This study revealed that

combining Tralokinumab with TCS on an as-needed basis notably enhances both the signs and symptoms of AD in adults with severe disease refractory to CyA treatment. [23,29]

ECZTRA 8 was a randomized, double-blind, placebo-controlled trial involving 106 participants. Its primary endpoints were the percentage of patients achieving IGA score of 0 or 1 and EASI 75 at week 16. The participants received either a SC 500mg LD of Tralokinumab followed by SC 300mg q2w with TCS as needed or placebo. This study proved the efficacy of Tralokinumab with higher percentage of achieving an IGA score of 0 or 1 (32,1% vs 26,4% on placebo) and EASI 75 (71,7% vs 56,6% on placebo). [30]

ECZTRA 6, a recent phase III trial, evaluated Tralokinumab monotherapy versus placebo in adolescents with moderate-to-severe AD who required systemic treatment. The trial included 301 adolescents aged 12–17, receiving SC Tralokinumab 150 mg, 300 mg, or placebo q2w for 16 weeks. Tralokinumab demonstrated significant improvements in various patient-reported outcomes such as eczema-related sleep, hospital anxiety, depression and PNRS compared to placebo. Overall, Tralokinumab was well-tolerated and its efficacy and safety profiles in adolescents were similar to those observed in phase III trials involving adults. [31] Another phase III clinical trial is evaluating the effectiveness of Tralokinumab among adolescents. This trial involves a single-arm design and focuses on individuals aged 12 years and above. Participants received an initial SC dose of 600 mg of Tralokinumab, followed by self-administered doses of 300 mg q2w for a total duration of 14 weeks. The trial aims to assess both the safety and efficacy of Tralokinumab in this age group. [32] Although Tralokinumab has already been approved by the FDA and EMA for the treatment of AD in adults, it is not yet approved for use in adolescents. [23]

ECZTRA 5 trial, a randomized, double-blind, placebo-controlled phase II study, aimed to investigate the potential impact of Tralokinumab on the immune response to vaccines. Over a 16-week period, 107 adult patients were administered Tralokinumab 300 mg, while 108 received a placebo q2w. At week 12, all participants received Tdap (Tetanus, Diphtheria and Pertussis) and meningococcal vaccines, with the primary endpoints focusing on positive immune responses to either vaccine during weeks 12 and 16. This study revealed that both the Tralokinumab and placebo groups exhibited similar immune responses at week 16 to both the Tdap (91.9% vs. 96.1%) and meningococcal (86.0% vs. 84.2%) vaccines. Tralokinumab-treated adults with moderate-to-severe AD can continue their treatment without interruption, as standard non-live vaccines have proven effective and safe in this population. [23,33]

Some retrospective analyses underscore the efficacy of Tralokinumab in treating AD among patients who previously failed other systemic treatments. One study involving 12 adults who did not achieve EASI 50 with 16-week Dupilumab treatment found that Tralokinumab led to rapid improvements, reaching EASI 75 within 8 weeks, with notable reductions in itch and sleep

disturbances. [34] Another analysis of 10 patients who received Tralokinumab for at least 26 weeks, after unsuccessful CyA and Dupilumab trials, demonstrated superior outcomes compared to Tralokinumab phase III trials, including greater itch reduction and higher rates of EASI 75 and IGA 0/1 achievement. [35] Additionally, in a multicenter retrospective study involving 85 adult patients with severe AD, Tralokinumab treatment for 16 weeks yielded significant improvements in EASI score, SCORAD and Peak PNRS, with systemic treatment-naive patients exhibiting higher rates of EASI 75 achievement compared to those with prior systemic therapy experience. [36] These findings highlight Tralokinumab real-world effectiveness in providing short-term relief for AD symptoms among patients unresponsive to other systemic treatments. [23]

ECZTRA 4 is a trial designed to explore whether Tralokinumab alters the metabolism of specific Cytochrome P450 (CYP) substrates in adults diagnosed with moderate-to-severe AD. A 14-week treatment period with Tralokinumab, involving the administration of a single dose (SD), is conducted. This trial is an open-label, multi-center drug-drug interaction study aimed at investigating the effects of Tralokinumab on the pharmacokinetics of selected CYP substrates in adult subjects with moderate-to-severe AD. [37] TraSki is a phase II trial with 16 patients receiving a SC 600mg loading dose (LD) of Tralokinumab followed by 300mg q2w to study the skin barrier function, with the primary outcome being the change in transepidermal water loss at one non-lesional and one lesional marker skin at week 16. As of the date of the bibliographic review search, no results from this two trials had been posted. [38]

Overall, Tralokinumab has demonstrated a favorable safety profile across all studies with no important life-threatening AEs. The most frequent systemic AEs observed include upper respiratory tract infection, headache, somnolence, toothache, conjunctivitis, pruritus, pyrexia, nasopharyngitis and acne. Locally, cases of injection site reaction with pain erythema were reported. [25–31,33]

Ongoing clinical trials studying Tralokinumab for the treatment of AD are listed in Table II.

Lebrikizumab

Lebrikizumab, a humanized monoclonal antibody, exhibits high affinity for soluble IL-13 by binding to its non-receptor binding domain. When IL-13 is bound, it retains the capacity to form a complex with IL-13Rα1 but impedes its heterodimerization with IL-4Rα and blocks signal transduction. Consequently, Lebrikizumab effectively inhibits the formation of the IL-4Rα/IL-13Rα1 signaling complex, while concurrently modulating endogenous IL-13 through the stimulation of IL-13Rα2. [8,39]

There were two phase II trials that studied the safety and efficacy of Lebrikizumab for the treatment of moderate-to-severe AD. [40–42] TREBLE evaluated the efficacy and safety of Lebrikizumab as an adjunct therapy to TCS in 209 adults with AD demonstrating that Lebrikizumab 125 mg administered q4w for 12 weeks significantly improved the primary endpoint of achieving a 50% reduction in EASI score compared to placebo (82.4% vs 62.3%). Additionally, Lebrikizumab group showed significant improvements in secondary endpoints, including EASI 75, SCORAD 50 and IGA score of 0/1. While single-dose groups did not show significant responses at week 12, the results on the 250 mg single-dose group suggested a potential dose-response relationship. [40,41] A phase IIb trial investigated the efficacy, dose-response relationship and safety of Lebrikizumab monotherapy using TCS if necessary, in 280 adults with AD unresponsive to standard topical treatment. The patients were randomized into four arms: Lebrikizumab LD of 250 mg followed by 125 mg q4w, Lebrikizumab LD of 500 mg followed by 250 mg q4w, Lebrikizumab LD of 500 mg at baseline and at week 2 followed by 250 mg q2w and placebo q2w. The primary endpoint revealed dose-dependent reductions in EASI scores at week 16 across all Lebrikizumab groups compared to placebo, with significant differences observed as early as week 4. Specifically, the Lebrikizumab 250 mg groups exhibited superior response rates in secondary endpoints, including IGA 0/1 response, EASI 50, EASI 75 and EASI 90. Furthermore, placebo-treated patients required approximately three times more rescue TCS use, initiated earlier and sustained for a longer duration than Lebrikizumab treated patients. [41,42]

Four major phase III trials have been completed to thoroughly assess the efficacy and safety profile of Lebrikizumab: ADhere, Advocate 1, ADvocate 2 and ADdore. [41,43–46]

ADhere trial is a multicenter, double-blind, placebo-controlled study that involved 211 adolescents aged 12–16 years and adults that were randomized to receive either SC Lebrikizumab LD of 500 mg at baseline and week 2, followed by 250 mg q2w or placebo. Both groups received treatment in combination with a low- to mid-potency TCS. The primary endpoints included achieving an IGA score of 0 or 1 with a reduction of at least 2 points from baseline and EASI 75 at 16 weeks. Secondary endpoints included improvements in EASI score, PNRS score, sleep loss due to pruritus and DLQI. At week 16, significant improvements were observed in the Lebrikizumab plus TCS group compared to the placebo group. Specifically, 41.2% of patients achieved an IGA score of 0 or 1 with a reduction of at least 2 points from baseline, compared to 22.1% in the placebo group. Additionally, 69.5% of patients in the Lebrikizumab group achieved EASI 75, compared to 42.2% in the placebo group. Clinically meaningful improvements across all key secondary endpoints were also observed in the Lebrikizumab group as early as 4 weeks. [43]

In ADvocate 1 and ADvocate 2 trials, Lebrikizumab administered q2w demonstrated significant improvements compared to placebo in primary and secondary endpoints, including skin clearance, pruritus, sleep interference and quality of life. At week 16, a higher proportion of Lebrikizumab treated patients achieved an IGA score of 0 or 1 with a reduction of at least 2 points from baseline compared to placebo. Similarly, more Lebrikizumab treated patients achieved EASI 75 and EASI 90 responses at week 16 compared to placebo. During the maintenance period, patients maintaining response to Lebrikizumab q2w or q4w had sustained improvements in IGA scores, EASI 75 and EASI 90 responses and PNRS scores compared to those in the withdrawal arm. [44,45]

ADore study was a single-arm trial that evaluated the safety and efficacy of Lebrikizumab in adolescents with moderate-to-severe AD with patients receiving two doses of Lebrikizumab of 250 mg initially and at week 2, followed by a single injection q4w from week 4 to week 52. Throughout the 52-week treatment period, Lebrikizumab demonstrated clinically meaningful improvements in skin clearance, noticeable as early as the first assessment at week 4, with an increasing number of patients experiencing improvement over time. The positive results of the study indicate that treating moderate-to-severe AD in adolescents targeting IL-13 with Lebrikizumab is a promising approach. [46]

Clinically significant improvements were observed across all primary and secondary endpoints in the four mentioned studies.

ADopt trial is a phase III randomized, double-blind, placebo-controlled study with a cohort of 254 participants designed to investigate the impact of Lebrikizumab on vaccine immune responses in adults diagnosed with moderate-to-severe AD. The primary endpoints were a positive anti-tetanus response and a positive ani-meningococcal response at week 16. This study demonstrated that the immune response was comparable in both groups, with 73,6% of participants on Lebrikizumab achieving a positive anti-tetanus response compared to 73,4% of participants receiving the placebo. A positive anti-meningococcal immune response was achieved by 86,9% of participants on Lebrikizumab and 75,0% of participants on placebo. [47]

ADhere-J is a randomized, double-blind, placebo-controlled trial designed to assess the efficacy and safety of Lebrikizumab combined with TCS in Japanese individuals with moderate-to-severe AD. In the Lebrikizumab treatment groups, a higher percentage of patients achieved significant improvements compared to the placebo group across all the measures. A greater proportion of patients achieved EASI 75, with 33.4% in the 250mg q2w group and 29.1% in the 250mg q4w group, compared to only 6.1% in the placebo group. Also, a higher percentage of patients in the Lebrikizumab groups achieved IGA scores of 0 or 1 with at least a 2-point

reduction. 51.2% of patients in the 250mg q2w group and 47.2% in the 250mg q4w group achieved IGA 0/1 compared to 13.4% in the placebo group. [48]

ADjoin is an ongoing phase III study focusing on evaluating the long-term efficacy and safety of Lebrikizumab. With a participant pool of 1000 individuals, the study spans 110 weeks. Its primary aim is to assess how well Lebrikizumab works over an extended period and to monitor any safety concerns that may arise. This long-term extension study encompasses patients who have completed their involvement in a previous Lebrikizumab trial. [49]

Overall, Lebrikizumab has shown a favorable safety profile across all studies with no significant life-threatening AEs. The most frequent systemic AEs observed include upper respiratory tract infections, nasopharyngitis, headache, COVID-19, oral herpes and conjunctivitis. Locally, injection site reactions were reported, with frequencies ranging from 1.3% to 5.7% in Lebrikizumab groups. [40,42–48]

Although Lebrikizumab was approved by the EMA for use in AD in EU in September 2023, it has not been approved by the FDA for use in the US. [21,22] Ongoing clinical trials evaluating the role of Lebrikizumab in the treatment of AD are listed in Table IV.

Cendakimab

Cendakimab (RPC-4046), a recombinant humanized anti-IL-13 monoclonal antibody, binds to IL-13 at an epitope that overlaps with the binding site of receptors IL-13Rα1 subunit and IL-13Rα2 subunit, thereby preventing its interaction and blocking further signaling.[50]

A phase II multicenter, randomized, double-blind, parallel-group, placebo-controlled trial (NCT04800315) evaluated the effectiveness and safety of 3 dose regimen of Cendakimab in adult participants with moderate-to-severe AD. The study consisted of four experimental groups. In group 1, participants received a high dose of Cendakimab SC once weekly (qw) for 16 weeks. In group 2, participants were administered a high dose of Cendakimab SC q2w, with placebo given alternately q2w. Participants in group 3 received a low dose of Cendakimab SC q2w, with placebo administered SC weekly. Participants in the placebo group received placebo SC qw. The primary outcome of the study was the mean percentage change in EASI score from baseline to week 16, with a higher decrease in the Cendakimab high dose qw (-84,41%), compared to high dose Cendakimab q2w (-76,03%), low dose Cendakimab q2w (-78,93%) and placebo (-62,25%). The greatest proportion of patients achieving an IGA score of 0 or 1 was noticed on the low dose Cendakimab q2w group (38,2%), compared to 33,3% in the group 1 and 24,4% on group 2. In this study, the most reported AEs were upper respiratory tract infection, allergic conjunctivitis, Covid-19 and headache. [51]

Eblasakimab

Eblasakimab is a monoclonal antibody designed to specifically bind with high affinity to IL-13Rα1. Unlike the previously mentioned ones, its mechanism involves disrupting the signaling pathways of both IL-13 and IL-4. [52,53]

The phase Ia study featuring an open-label, single ascending dose design delved into the mechanistic actions of Eblasakimab and its impact on IL-13Rα1 signaling. 44 healthy male volunteers of Asian descent received single ascending doses of Eblasakimab via either intravenous (IV) or SC injection. The data obtained from this open-label study reveal that the human IL-13Rα1 specific monoclonal antibody, Eblasakimab, was safe and well tolerated regardless of the route of administration. Notably, Eblasakimab exhibited a capacity to effectively block IL-13Rα1 and impede IL-13 induced activation of STAT6 (at SD of 3 mg/kg IV and 300 mg SC), a pivotal transcription factor responsible for the expression of Th2 effector cytokines. In the IV cohorts, the most frequent AEs were upper respiratory tract infection, decreased appetite, headache, oropharyngeal pain and pyrexia. In the SC cohorts, headache, elevated C-reactive protein and pruritus at the injection site were the most related AEs. [53]

A phase Ib randomized, double-blinded study evaluated the efficacy of Eblasakimab in patients with AD. The preliminary data included 52 patients randomized to receive Eblasakimab at doses of 200 mg, 400 mg or 600 mg, compared to a placebo group. After 8 weeks of treatment, significant improvements were observed in the Eblasakimab groups compared to placebo. The reductions in EASI scores were notable across all dose groups: 50% in the 200 mg group, 63% in the 400 mg group and 61% in the 600 mg group, compared to 32% in the placebo group. Similarly, EASI 50 and EASI 75 responses were higher in the Eblasakimab groups compared to placebo. The peak PNRS showed a significant decrease in the 600 mg Eblasakimab group compared to placebo. Further analysis indicated that the 400 mg and 600 mg doses of Eblasakimab produced greater clinical responses than the 200 mg dose. At week 8, Eblasakimab 600 mg demonstrated significant improvements in mean percentage change in EASI, proportion of patients achieving EASI 50 and EASI 75 compared to placebo. The study also noted improvements in PNRS, Patient Oriented Eczema Measure (POEM) scores and sleep disturbance with Eblasakimab treatment compared to placebo. The most reported AEs were pruritus, injection site erythema and injection site swelling. [54]

Overall, the phase I studies concluded that the administration of Eblasakimab to adults with moderate-to-severe AD was well-tolerated. The data from these trials demonstrate significant clinical enhancements compared to placebo, as evidenced by both physician- and patient-reported outcomes. These findings highlight the promising therapeutic potential of

Eblasakimab in the management of AD. Consequently, further investigation through phase II trials is warranted to better understand its efficacy and safety profile in larger patient populations and to determine its potential as a treatment option for this inflammatory skin condition.

NCT05694884 is an undergoing phase II multicenter, randomized, double-blind, placebo-controlled, parallel-arm clinical trial aimed at assessing the effectiveness and safety of Eblasakimab in individuals with moderate-to-severe AD who stopped Dupilumab treatment due to non-response, intolerance or AEs. The trial spans a 16-week treatment period followed by an 8-week follow-up period, totaling 24 weeks. Approximately 75 participants are estimated to be enrolled in the study. The study officially began on December 2022 and is expected to reach its primary completion by December 2024.[55]

Discussion

As a chronic disease with significant implications for patients' quality of life, there is a continuous need for the development of new, more effective and targeted therapies for AD. Opting for selective IL-13 inhibitors in AD treatment seems to offer advantages over broadly targeting both IL-4 and IL-13. By specifically inhibiting IL-13, these medications can potentially avoid interfering with the functions of IL-4, which plays a role in a range of immune and non-immune cells. This specificity allows for a more refined approach to modulating the immune response, potentially reducing the risk of AEs associated with broader cytokine inhibition.

Among the selective IL-13 inhibitors, Tralokinumab, Lebrikizumab and Cendakimab exhibit distinct mechanisms of action. Tralokinumab, a fully human IgG4 monoclonal antibody, selectively binds with IL-13, neutralizing its signaling activity by preventing its binding to IL-13Rα1 and IL-13Rα2, while Lebrikizumab, a high-affinity monoclonal antibody, targets IL-13 by binding to a different epitope that prevents IL-4Rα/IL-13Rα1 heterodimerization, thus blocking downstream signaling pathways. However, unlike Tralokinumab, Lebrikizumab does not inhibit the binding of IL-13 to IL-13Rα2, not interfering with the IL-13 endogenous regulation. Similarly, Cendakimab, a selective, high-affinity monoclonal antibody, blocks IL-13 binding to both IL-13 receptors (IL-13Rα1 and IL-13Rα2) with potent efficacy, thereby inhibiting downstream signaling pathways involved in AD pathogenesis. [8,39,50]

A study compared the *in vitro* binding affinities and cell-based functional activities of clinical IL-13 monoclonal antibodies, Lebrikizumab, Tralokinumab and Cendakimab. Lebrikizumab demonstrated higher binding affinity to both glycosylated and aglycosylated forms of IL-13 compared to Tralokinumab and Cendakimab. This stronger binding affinity is driven by a slower dissociation rate. In cell-based neutralization assays, Lebrikizumab showed higher potency in inhibiting IL-13 induced effects compared to Tralokinumab and Cendakimab. Furthermore,

Lebrikizumab binds to a distinct epitope on IL-13 that does not impede the natural clearance of IL-13 through the IL-13Rα2 receptor, in contrast to Tralokinumab and Cendakimab. These *in vitro* findings offer support for molecular and mechanistic distinctions among Lebrikizumab, Tralokinumab and Cendakimab, potentially leading to differences in clinical efficacy for patients with AD. [12]

Although both Eblasakimab and Dupilumab block IL-13 and IL-4 pathways, there are differences in their mechanisms of action. Eblasakimab selectively binds to the IL-13 receptor α1 subunit of the type 2 receptor, preventing the formation of the IL-13Rα1/IL-4Rα heterodimer receptor signaling complex, thus exclusively blocking IL-4 and IL-13 signaling via the type 2 receptor, while sparing the type 1 receptor. This targeted approach potentially reduces unwanted effects associated with broad cytokine inhibition. In contrast, Dupilumab, a fully human IgG4κ monoclonal antibody, targets the α subunit in the IL-4 receptor, blocking both IL-4 and IL-13 signaling through the type 2 receptor (IL-4Rα/IL-13Rα1). Dupilumab also inhibits IL-4 signaling via the type 1 receptor (IL-4Rα/common γ chain). This broader inhibition may lead to more widespread effects on the immune response. Eblasakimab selective targeting of the type 2 receptor may offer advantages in modulating Th2 cytokines without inducing an increase in Th1 cytokines, compared to blocking the IL-4 receptor entirely. [8,17,52,53]

Conjunctivitis is an important AE associated with the use of Dupilumab, reported in up to 25% of patients, in clinical trials and real-world studies. The exact mechanism behind this occurrence is not fully understood, but it is suggested that Dupilumab, by targeting IL-4, induces a Th1 response, leading to interferon γ-mediated goblet cell apoptosis and reduced mucin production, resulting in eye dryness and conjunctivitis. [56] In fact, the prevalence of conjunctivitis with IL-13 selective inhibitors is lower compared to Dupilumab, which affects both IL-4 and IL-13 signaling pathways. In clinical trials of Tralokinumab, the prevalence of conjunctivitis was 11.1% in ECZTRA 3 and less than 10% in all other studies. [25–33] Lebrikizumab showed a prevalence of conjunctivitis as an AE of only up to 9.76%. [40–48] Additionally, up to 12.73% of patients treated with Cendakimab experienced conjunctivitis. [51] In all three selective IL-13 inhibitors, the prevalence of conjunctivitis as an AE was slightly higher in the treatment groups compared to the placebo groups. [41]

Direct comparisons between different IL-13 inhibitors with each other or with other therapies, such as Dupilumab and JAK inhibitors, are difficult because no head-to-head studies have been carried out and individual studies have different designs. This gap needs to be addressed in future trials and network meta-analyses to establish the place-in-therapy of selective IL-13 inhibitors in the management of AD.

Conclusion

AD represents an important health issue with profound implications for patients' quality of life. The pivotal role of IL-13 in AD pathogenesis has been underscored by the clinical success of therapies targeting this cytokine.

Tralokinumab and Lebrikizumab have emerged as effective and safe treatment options for individuals with moderate-to-severe AD, demonstrating notable efficacy and safety in clinical settings. Two other selective IL-13 inhibitors, each with slightly different mechanisms of action are currently under study. Further investigations are warranted to elucidate the therapeutic efficacy of Eblasakimab and Cendakimab. Hence, given the scarcity of sustainable therapeutic options for severe and refractory AD, the outcomes achieved through selective IL-13 inhibition illuminate the path forward in managing the disease.

Appendix

Tables

Table I: Completed clinical trials investigating Tralokinumab for the treatment of Atopic Dermatitis.

Trial	Study Design	Endpoints	Main results disclosed	Main adverse events
Phase I trial [25]	Single-blind, randomized controlled trial. N= 30 (20-55 years old) SC Tralokinumab (150, 300 or 600 mg)	Primary: safety and tolerability of Tralokinumab (monitoring the incidence of AEs and physical examinations, vital signs, electrocardiograms and laboratory parameters).	SC Tralokinumab 150mg, 300mg and 600 mg was well-tolerated; As the dosage of Tralokinumab increased, there was a corresponding increase in Cmax, AUC(0-t) and AUC(0-inf).	Injection-site pain (95,8% in the treatment groups vs 83,3% in placebo group), upper respiratory tract infection (16,7% vs 0%), headache (8,3% vs 0%), somnolence (8,3% vs 0%), toothache (8,3% vs 0%).
Phase IIb trial [26]	Randomized 1:1:1, double-blind placebo-controlled trial. N= 204 (≥ 18 years old) SC Tralokinumab (45, 150 or 300 mg) or placebo q2w for 12 weeks with TCS	Primary: change EASI and % of participants with an IGA response (0/1 and reduction of ≥2) at week 12. Secondary: change in EASI and SCORAD to week 22, % of participants with a reduction of ≥50% in EASI and reduction of ≥ 50% in SCORAD at week 12; % of participants achieving an IGA response at week 22; change in PNRS and DLQI at week 12.	Higher improvement in EASI score in the 300mg Tralokinumab group vs placebo (-15,72 vs -7,81); Higher % of patients achieving IGA score of 0/1 and higher improvements in SCORAD, DLQI and PNRS compared with placebo group.	Upper respiratory tract infection (3,9% in the treatment groups vs 3,9% in placebo), headache (2,0% vs 2,0%).
ECZTRA 1 [27] (phase III)	Randomized 3:1, double-blind, placebo-controlled trial. N= 802 (≥ 18 years old) SC Tralokinumab 300mg q2w after a LD of 600mg or placebo q2w	Primary: IGA 0/1 and EASI 75 at week 16. Secondary: ≥ 4 points reduction of weekly average worst daily PNRS, change in SCORAD and in DLQI at week 16. Maintenance endpoints: IGA 0/1 at week 52 in patients randomized to Tralokinumab with IGA 0/1 at week 16 without rescue TCS; EASI 75 at week 52 in patients randomized to Tralokinumab with EASI 75 at week 16 without rescue TCS.	Higher % of patients achieving IGA score of 0/1 at week 16 in Tralokinumab group vs placebo (15,8% vs 7,1%); Higher % of patients achieving EASI 75 vs placebo (25,0% vs 12,7%); Higher improvements in PNRS, DLQI and SCORAD in the Tralokinumab group; Positive responses maintained up to week 52.	Viral upper respiratory tract infection (23,1% in treatment group vs 20,9% in placebo group), conjunctivitis (7,1% vs 2,0%), pruritus (5,3% vs 5,1%).
ECZTRA 2 [27] (phase III)	Randomized 3:1, Double-blind, Placebo-controlled trial. N= 794 (≥ 18 years old) SC Tralokinumab 300mg q2w after a LD of 600mg or placebo q2w	Primary: IGA 0/1 and EASI 75 at week 16. Secondary: ≥ 4 points, reduction of weekly average worst daily PNRS, change in SCORAD and in DLQI at week 16. Maintenance endpoints: IGA 0/1 at week 52 in patients randomized to Tralokinumab with IGA 0/1 at week 16 without rescue TCS; EASI 75 at week 52 in patients randomized to Tralokinumab with EASI 75 at week 16 without rescue TCS.	Higher % of patients achieving IGA score of 0/1 at week 16 in Tralokinumab group vs placebo (22,2% vs 10,9%); Higher % of patients achieving EASI 75 vs placebo (33,2% vs 11,4%); Higher improvements in PNRS, DLQI and SCORAD in the Tralokinumab group; Positive responses maintained up to week 52.	Viral upper respiratory tract infection (8,3% in treatment group vs 8,5% in placebo group), upper respiratory tract infection (10,0% vs 8,5%), conjunctivitis (3,0% vs 1,5%).

ECZTRA 3 [28] (phase III)	Randomized 2:1, Double-blind, Placebo-controlled trial. N= 380 (≥ 18 years old) SC Tralokinumab 300 mg q2w or placebo q2w over 16 weeks with TCS as needed	Primary: % of patients achieving IGA 0/1 and EASI 75 at week 16. Secondary: SCORAD, change ≥ 4 weekly average of worst daily PNRS and DLQI scores at week 16; % of patients achieving EASI 50 and EASI 90 or ≥ 4 points improvement of DLQI and change in EASI, POEM, worst daily pruritus and TCS use. Maintenance endpoints: IGA 0/1 at week 32 in patients with IGA 0/1 at week 16 and EASI 75 at week 32 in patients with EASI 75 at week 16.	Higher % of patients achieving IGA 0/1 in the Tralokinumab group vs placebo group at week 16 (38,9% vs 26,2%); Higher % of patients achieving EASI 75 in the Tralokinumab group vs placebo group (56,0% vs 35,7%); Higher improvements in PNRS, DLQI and POEM in the Tralokinumab group; Positive responses maintained up to week 32.	Viral upper respiratory tract infection (19,4% in Tralokinumab group vs 11,1% in placebo group), conjunctivitis (11,1% vs 3,2%), headache (8,7% vs 4,8%), upper respiratory tract infection (7,5% vs 4,8%).
ECZTRA 7 [29] (phase III)	Randomized 1:1, Double-blind, Parallel-group, Placebo-controlled trial. N= 277 (≥ 18 years old) SC Tralokinumab 300 mg q2w or placebo q2w with TCS as needed over 16 weeks	Primary: EASI 75 at week 16. Secondary: ≥ 4 points reduction of worst daily PNRS (weekly average), change in SCORAD and DLQI at weeks 16 and 26; EASI 75 at week 26. EASI 90 and change in EASI, POEM, eczema-related sleep, amount of TCS used and number of days without TCS use, at weeks 16 and 26.	Higher % of patients achieving EASI 75 in the Tralokinumab group vs placebo group at week 16 (64,2% vs 50,5%); Higher improvements in PNRS, DLQI and POEM in the Tralokinumab group; Positive responses maintained up to week 26.	Viral upper respiratory tract infection (26,8% in Tralokinumab group vs 25,5% in placebo group), headache (15,2% vs 9,5%), upper respiratory tract infection (7,2% 7,3%).
ECZTRA 8 [30] (phase III)	Randomized, Double-blind, Placebo-controlled trial. N= 106 (≥ 18 years old) SC LD 600mg Tralokinumab followed by SC 300mg q2w Tralokinumab + TCS as needed or SC LD placebo followed by SC placebo q2w + TCS as needed over 26 weeks	Primary: IGA 0/1 and EASI 75 at week 16. Secondary: change in SCORAD and DLQI at week 16; ≥ 4 points reduction of Worst PNRS at week 16; EASI 50 and EASI 90 at week 16; % change in EASI, change in PNRS, change in Eczema-related Sleep Numerical Rating Scare and change in POEM at week 16; number of AEs at week 16; number of subjects with presence of treatment-emergent anti-drug antibodies.	Higher % of patients achieving IGA 0/1 in the Tralokinumab group vs placebo group at week 16 (32,1% vs 26,4%); Higher % of patients achieving EASI 75 in the Tralokinumab group vs placebo group (71,7% vs 56,6%); Higher improvements in SCORAD (-44,1 vs -39,0) and DLQI (-10,0 vs -8,8) at week 16 in the Tralokinumab group; Higher % of patients achieving EASI 50 and EASI 90; Higher improvements in EASI, PNRS, Eczema-related Sleep Numerical Rating Scale and POEM in the Tralokinumab group at week 16.	Injection site reaction (9,43% in Tralokinumab group vs 0,0% in placebo group), injection site erythema (5,66% vs 0,0%), pyrexia (5,66% vs 0,0%), nasopharyngitis (5,66% vs 9,43%), acne (11,32% vs 7,55%).
ECZTRA 6 [31] (phase III)	Randomized 1:1:1, Double-blind, Parallel-group, Placebo-controlled trial. N= 301 (12 to 17 years old) SC Tralokinumab (150mg or 300mg) q2w or placebo q2w over 16 weeks	Primary: IGA 0/1 and EASI 75 at week 16. Secondary: ≥ 4 points reduction of Adolescent Worst PNRS, change in SCORAD and in Children's DLQI at week 16.	Higher % of patients achieving IGA 0/1 in the Tralokinumab group vs placebo group at week 16 (21,4% in Tralokinumab 150mg vs 17,5% in Tralokinumab 300mg group vs 4,3% in placebo group); Higher % of patients achieving EASI 75 in the Tralokinumab group vs placebo (28,6% vs 27,8% vs 6,4%); Higher % of patients with ≥ 4 reduction in Adolescent Worst PNRS with Tralokinumab 150mg (23.2%) and Tralokinumab 300 (25.0%) vs placebo (3.3%); Higher improvements in SCORAD and in Children's DLQI in the Tralokinumab group. Positive responses maintained up to week 52.	Viral upper respiratory tract infection (19,44% in Tralokinumab 150mg vs 12,4% in Tralokinumab 300mg group vs 8,5% in placebo group), upper respiratory tract infection (8,2% vs 11,3% vs 4,3), headache (5,1% vs 6,2% vs 3,2%), conjunctivitis (4,1% vs 3,1% vs 2,1%).

ECZTRA 5 [33] (phase III)	Randomized 1:1, Double-blind, Placebo-controlled trial. N= 215 (≥ 18 years old) SC Tralokinumab 300mg q2w or placebo q2w for 16 weeks. Tdap and meningococcal vaccines at week 12	Primary: positive anti-tetanus response at week 16; positive anti-meningococcal response at week 16. Secondary: IGA 0/1 and EASI 75 at week 16; number of AEs; presence of anti-drug antibodies.	Similar immune responses: 91.9% of the patients in the Tralokinumab group had positive antitetanus response at week 16 vs 96.1% in the placebo group; 86,0% of the patients in the Tralokinumab group had positive antimeningococcal response at week 16 vs 84,2% in the placebo group; Higher % of patients achieving IGA 0/1 in the Tralokinumab group vs placebo group at week 16 (31,1% vs 19,4%); Higher % of patients achieving EASI 75 in the Tralokinumab group vs placebo group at week 16 (49,1% vs 36,1%).	Viral upper respiratory tract infection (9,3% in Tralokinumab group vs 1,9% in placebo group), AD (9,3% vs 12,1%).

Table II: Ongoing clinical trials investigating Tralokinumab for the treatment of Atopic Dermatitis.

ClinicalTrials.gov identifier	Title	Phase	Enrollment (n)	Status	Estimated study completion date
NCT05194540 [32]	Tralokinumab Administered With Device A in Adults and Adolescents With Moderate-to-severe Atopic Dermatitis (INJECZTRA)	III	136 (actual)	Completed (waiting for results)	June 2023
NCT03556592 [37]	Drug-drug Interaction Trial With Tralokinumab in Moderate to Severe Atopic Dermatitis - ECZTRA 4	III	40 (actual)	Completed (waiting for results)	June 2020
NCT04556461 [38]	Effects of Tralokinumab Treatment of Atopic Dermatitis on Skin Barrier Function (TraSki)	II	16 (actual)	Completed (waiting for results)	March 2023
NCT03587805 [57]	Long-term Extension Trial in Subjects With Atopic Dermatitis Who Participated in Previous Tralokinumab Trials – ECZTEND	III	1672 (actual)	Active, Not Recruiting	July 2027
NCT05388760 [58]	Tralokinumab Monotherapy for Children With Moderate-to-severe Atopic Dermatitis - TRAPEDS 1 (TRAlokinumab PEDiatric Trial no. 1)	III	53 (estimated)	Active, Not Recruiting	September 2025
NCT05958407 [59]	A 32-week Trial to Evaluate the Efficacy and Safety of Tralokinumab in Subjects With Moderate-to-severe Atopic Hand Eczema Who Are Candidates for Systemic Therapy (ADHAND)	III	402 (estimated)	Recruiting	March 2026
NCT05938478 [60]	Monitoring Pregnancy and Infant Outcomes Following Tralokinumab Exposure During Pregnancy in the US and Canada - PROTECT (PROTECT)	III	900 (estimated)	Recruiting	September 2035
NCT05378698 [61]	Effects of Tralokinumab in the Skin: an Immunologic and Molecular Investigation (TRALIS)	III	25 (estimated)	Not yet recruiting	June 2025
NCT05682976 [62]	Ophthalmological Adverse Events of Tralokinumab in AD (TRALO-Oeil)	III	100 (estimated)	Not yet recruiting	March 2026

Table III: Completed clinical trials investigating Lebrikizumab for the treatment of Atopic Dermatitis.

Trial	Study Design	Endpoints	Main results disclosed	Main adverse events
TREBLE (Phase II) [40]	Randomized 1:1:1:1, Double-blind, Placebo-controlled trial. N= 209 (≥ 18 years old) 125 mg SD or 250 mg SD or 125 mg q4w or placebo q4w over 12 weeks with concomitant use of TCS	Primary: % of patients achieving EASI 50 at week 12. Secondary: % of patients achieving EASI 75, IGA 0/1 and SCORAD 50 at week 12.	Higher % of patients achieving EASI 50 on 125mg q4w vs placebo at week 12 (82,4% vs 62,3%); Higher % of patients achieving EASI 75 on 125mg q4w vs placebo at week 12 (54,9% vs 34,0%); Higher % of patients achieving IGA 0/1 on 125mg q4w vs placebo at week 12 (33,3% vs 18,9%); Higher % of patients achieving SCORAD 50 in 120mg q4w (47,2%) and 250mg SD (51%) vs placebo (26,4%)	Conjunctivitis (9.6% in Lebrikizumab groups vs 7,5% in placebo), herpes infections (3.8% vs 0%), peripheral eosinophilia (3.2%), injection-site reactions (1.3% vs 1,9%).
Phase IIb [42]	Randomized 3:3:3:2, Double-blind, Parallel-group, Placebo-controlled trial. N= 280 (≥ 18 years old) 250mg LD plus 125mg q4w or 500mg LD plus 250mg q4w or 500mg LD plus 500mg at week 2 plus 250mg q2w or placebo q2w, over 16 weeks with TCS as needed	Primary: % change in EASI at week 16. Secondary: % patients with EASI 75, EASI 50, EASI 90 and ≥ 2 points reduction in IGA and % change in PNRS.	Higher % change in EASI in Lebrikizumab groups (−62.3% in 125mg q4w, −69.2% in 250mg q4w, −72.1% in 250 mg q2w) vs placebo (−41.1%); Superior response in IGA 0/1, EASI 50, EASI 75 and EASI 90 in Lebrikizumab 250mg groups vs placebo; Higher improvement in PNRS (35.9% in 125mg q4w, 49.6% in 250mg q4w, 60.6% in 250mg q2w) vs placebo (-4.3%).	Upper respiratory tract infections (7.5% in Lebrikizumab groups vs 5,8% in the placebo group), nasopharyngitis (6.6% vs 3,8%), injection-site reactions (5.7% vs 1.9%), herpesvirus infections (3,5% vs 3,8%), conjunctivitis (2.6% vs 0%).
ADhere [43]	Randomized 2:1, Double-blind, Parallel-group, Placebo-controlled trial. N=211 (≥ 12 years old) 50mg LD plus 500mg at week 2, then 250mg q2w + TCS vs placebo q2w + TCS, over 16 weeks	Primary: % of patients achieving EASI 75 and IGA 0/1 with ≥ 2 points reduction at week 16. Secondary: EASI 90; improvement in PNRS, DLQI and Sleep-Loss Scale Score at week 16.	Higher % of patients on Lebrikizumab + TCS achieving IGA 0/1 (41,4%) vs placebo (22,7%) at week 16; Higher % of patients on Lebrikizumab + TCS achieving EASI 75 (69,7%) vs placebo (42,4%) at week 16; Higher % of patients on Lebrikizumab + TCS vs placebo + TCS with improvements in PNRS (51% vs 36%), DLQI (79% vs 57%) and Sleep-Loss Scale Score (35% vs 17%) at week 16.	Conjunctivitis (4,8% in Lebrikizumab group vs 0,0% in the placebo group), headache (4,8% vs 1,5%), herpes infection (3.4% vs 1,5%), injection site reactions (2.8% vs 1,5%).
ADvocate 1 and Advocate 2 [44,45]	Randomized 2:1, Double-blind, Parallel-group, Placebo-controlled trial. N (ADv1) = 424 (≥12 years old)	Primary: % of patients achieving EASI 75 and IGA 0/1 with ≥ 2 points reduction at week 16. Secondary: % of patients achieving IGA/01 with ≥ 2 points reduction at weeks 2 and 4; % of patients achieving EASI	Higher % of patients on Lebrikizumab achieved IGA 0/1 with ≥ 2 points vs placebo (ADv1: 43,1% vs 12,7%; ADv2: 33,2% vs 10,8%); Higher % of patients on Lebrikizumab achieved EASI 75 vs placebo (ADv1: 58,8% vs 16,2%; ADv2: 52,1% vs 18,1%);	Conjunctivitis (8,3% in ADv1 and 8,1% in ADv2), nasopharyngitis (6,8% in ADv1 and 9,6% in ADv2) headache (3,3% in ADv1 and 5,7% in ADv2), herpes infection

	N (ADv2) = 445 (≥12 years old) Induction period (16 weeks): 500 mg LD + 500mg at week 2 + 250 mg q2w or placebo q2w Maintenance period (36 weeks) - re-randomization 2:2:1 of responders: 250mg q2w or 250mg q4w or placebo q2w (rescue medication as needed)	90; ≥ 4 points reduction in PNRS at weeks 1, 2, 4 and 16; change in Sleep-Loss Scale Score and DLQI; Maintenance of IGA 0/1, EASI 75 and ≥ 4 points reduction in PNRS at week 52.	Higher % of patients on Lebrikizumab achieved EASI 75 vs placebo (ADv1: 38,3% vs 9,0%; ADv2: 30,7% vs 9,5%); Higher % of patients on Lebrikizumab maintained an IGA 0/1 compared to those in the withdrawal arm (65 to 81% vs 47 to 50%); Higher % of patients on Lebrikizumab maintained an EASI 75 compared to those in the withdrawal arm (77 to 85% vs 61 to 72%); Higher % of patients on Lebrikizumab maintained ≥ 4 points reduction in PNRS at week 52 compared to those in the withdrawal arm (80 to 90% vs 65 to 68%).	(5,0% in ADv1 and 4,9% in ADv2), injection site reactions (1,8% in ADv1 and 2,9% in ADv2), eosinophilia (1,3% in ADv1 and 1,7% in ADv2).
Adore [46]	Open-label, Single-arm trial. N= 206 (≥12 to <18 years old) SC LD Lebrikizumab 500 mg + SC 500mg at week 2 + 250 mg q2w, 52 weeks	Primary: % of patients who discontinued treatment because of AEs. Secondary: % of patients achieving IGA 0/1 with ≥ 2 points improvement; % of patients achieving EASI 75, EASI 50 and EASI 90; % change in EASI; change in Body Surface Area (BSA), Patient-Reported Outcomes Measurement Information System measures of anxiety and depression, DLQI and Children's DLQI.	172 patients completed the treatment (83,5%) while 34 discontinued treatment (16,5%); 62,6% of patients achieved IGA 0/1 with ≥ 2 points improvement; 73,2% of patients achieving EASI 75 at week 16 and 81.9% at week 52; EASI mean % improvement was 86,0% by week 52; BSA decreased from 45.4% at baseline to 8.4% by week 52; Improvements reported in Patient-Reported Outcomes Measurement Information System measures of anxiety and depression, DLQI and Children's DLQI.	Atopic dermatitis (13,1%), nasopharyngitis (9,7%), COVID-19 (8,7%), upper respiratory tract infection (6,3%), headache (5,8%), oral herpes (5,3%), conjunctivitis (4,9%).
Adopt-VA [47]	Randomized, Double-Blind, Parallel- Group, Placebo-Controlled trial. N= 254 (≥18 years old) SC LD Lebrikizumab 500 mg + SC 500mg at week 2 + 250 mg q2w from week 4 to week 14	Primary: positive anti-tetanus response at week 16; positive anti-meningococcal response at week 16. Secondary: IGA 0/1 with ≥ 2 points improvement, EASI 75 and EASI 90 at week 16; % of patients with ≥ 4 points improvement in PNRS; change from baseline in BSA and Sleep-Loss Score.	73,6% of the patients in the Lebrikizumab group had positive antitetanus response at week 16 vs 73,4% in the placebo group; 86,9% of the patients in the Lebrikizumab group had positive antimeningococcal response at week 16 vs 75,0% in the placebo group; Higher % of patients achieving IGA 0/1 with ≥ 2 points improvement in the Lebrikizumab group vs placebo group at week 16 (40,6% vs 18,9%); Higher % of patients achieving EASI 75 in the Lebrikizumab group vs placebo group at week 16 (58,0% vs 32,7%); Higher % of patients with ≥ 4 points improvement in PNRS in Lebikizumab group (51,7% vs 33,2% in placebo); Higher changes from baseline in BSA and Sleep-Loss Score in patients on Lebrikizumab.	Atopic Dermatitis (4,72% in Lebrikizumab group vs 6,3% in the placebo group), COVID-19 (5,51% vs 3,94%), headache (3,15% vs 0,79%), nasopharyngitis (3.15% vs 2,36%), conjunctivitis (2,36% vs 0,0%).
ADhere-j [48]	Randomized, Double-Blind, Placebo-Controlled trial. N= 286 (≥12 years old) SC LD Lebrikizumab 500 mg + 250 mg q4w + TCS	Primary: % of patients achieving EASI 75 and IGA 0/1 with ≥ 2 points reduction at week 16. Secondary: % change in EASI at week 16; % of patients achieving EASI 90 at week 16; % of patients with an Itch	Higher % of patients achieving EASI 75 in Lebrikizumab groups (33,4% on 250mg q2w group and 29,1% on 250mg q4w group) vs placebo (6,1%); Higher % of patients achieving IGA 0/1 with ≥ 2 points reduction in Lebrikizumab groups (51,2% and 47,2) vs placebo (13,4%) Higher % change in EASI in Lebrikizumab groups (-64,23% and -59,74%) vs placebo (-25,25%);	Conjunctivitis allergic (17,07% in Lebrikizumab 250mg q2w group vs 12,35% in Lebrikizumab 250mg q2w group vs 4,88% in placebo), pyrexia (20,33% vs 18,52% vs 15,85%), vaccination site pain

	until week 14 or SC LD Lebrikizumab 500 mg + 250 mg q2w + TCS until week 14 or LD of placebo + placebo q2w + TCS until week 14 Week 16 responders: randomly 1:1 allocated to 250 mg Lebrikizumab q2w or 250 mg Lebrikizumab q2w. Non responders: escape arm, Lebrikizumab 250 mg q2w until week 68	Numeric Rating Scale score of ≥4 points at baseline achieving ≥4 reduction at weeks 1, 2, 4 and 16.	Higher % of patients with an Itch Numeric Rating Scale score of ≥4 points at baseline achieving ≥4 reduction in Lebrikizumab groups vs placebo.	(3,25% vs 3,70% vs 4,88%), conjunctivitis (9,76% vs 6,17% vs 2,44%), folliculitis (5,69% vs 6,17% vs 9,76%), nasopharyngitis (5,69% vs 6,17% vs 2,44%), headache (3,25% vs 3,70% vs 10,98%).

Table IV: Ongoing clinical trials investigating Lebrikizumab for the treatment of Atopic Dermatitis.

ClinicalTrials.gov identifier	Title	Phase	Enrollment (n)	Status	Estimated study completion date
ADjoin [49]	Long-term Safety and Efficacy Study of Lebrikizumab (LY3650150) in Participants With Moderate-to-Severe Atopic Dermatitis (ADjoin)	III	1188 (actual)	Active, Not Recruiting	April 2025
NCT05369403 [63]	A Study of Lebrikizumab in Adult and Adolescent Participants with Moderate-to-Severe Atopic Dermatitis Previously Treated with Dupilumab	III	120 (estimated)	Active, Not Recruiting	December 2024
NCT05149313 [64]	A Study of Lebrikizumab in Combination with Topical Corticosteroids in Participants Having Atopic Dermatitis (AD) that Are Not Adequately Controlled or Non-eligible for Cyclosporine	III	331 (actual)	Active, Not Recruiting	April 2024
NCT05372419 [65]	A Study of Lebrikizumab to Assess the Safety and Efficacy of Adult and Adolescent Participants with Moderate-to-Severe Atopic Dermatitis and Skin of Color	III	80 (estimated)	Recruiting	December 2024
NCT05559359 [66]	A Study of Lebrikizumab (LY3650150) in Participants 6 Months to < 18 Years of Age with Moderate-to-Severe Atopic Dermatitis	III	300 (estimated)	Recruiting	June 2025
NCT05916365 [67]	Long-term Safety and Efficacy of Lebrikizumab in Adult and Adolescent Participant With Moderate-to-Severe Atopic Dermatitis (ADlong)	III	200 (estimated)	Recruiting	April 2026
NCT05990725 [68]	Effectiveness and Safety of Lebrikizumab Treatment in Adults and Adolescents With Moderate-to-Severe Atopic Dermatitis (ADhope)	III	240 (estimated)	Not yet recruiting	May 2025

Table V: Completed clinical trials investigating Cendakimab for the treatment of Atopic Dermatitis.

Trial	Study Design	Endpoints	Main results disclosed	Main adverse events
NCT04800315 (Phase 2) [51]	Randomized, Placebo-controlled, Parallel-group, Double-blind trial. N= 221 Dose 1: High dose Cendakimab SC qw, over 16 weeks Dose 2: High dose Cendakimab SC q2w and placebo q2w, over 16 weeks Dose 3: Low dose Cendakimab SC q2w and placebo qw, over 16 weeks Placebo group: Placebo SC qw, over 16 weeks	Primary: % change in EASI at Week 16. Secondary: % patients with IGA 0/1 with reduction of ≥ 2 points at week 16; % patients with EASI 75 and EASI 90 at week 16; % change in Mean SCORAD and PNRS at week 16; % of participants PNRS Change of ≥ 4 Points; Time to Achieve at Least 4 Points of Improvement in the Severity of PNRS; % change in BSA at week 16; number of participants with AEs; Number of participants with the presence of serum antibodies to Cendakimab; Serum trough concentration at week 16; number of participants with clinically significant laboratory abnormalities.	Higher decrease in EASI at week 16 in the Cendakimab groups vs placebo (-84.41% in the high dose qw group vs -76,03% in the high dose q2w group vs -78,93% in the low dose q2w group vs -62,25% in the placebo group); Higher % of participants achieving IGA 0/1 (33,3% vs 24,4% vs 38,2% vs 9,4%); Higher % of participants achieving EASI 75 and EASI 90 at week 16 (50,0%/31,5% vs 48,2%/24,0% vs 52,7%/29,1% vs 26,3%/13,4%); Higher change in SCORAD at week 16 (-69,28% vs -55,47% vs -60,19% vs -41,11%); Higher % change in PNRS at week 16 (-55,48% vs -46,15% vs -49,30% vs -32,98%); Higher % of Participants with a response and PNRS ≥ 4 Points change (33,3% vs 34,5% vs 32,7% vs 14,8%); Less days to achieve at least 4 Points of Improvement in PNRS (54 vs 76 vs 50 vs 123).	Upper respiratory tract infection (7,41% in the high dose qw group vs 10,91% in the high dose q2w group vs 9,09% in the low dose q2w group vs 8,93% in the placebo group),conjunctivitis allergic (7,41% vs 12,73% vs 9,09% vs 3,57%), Covid-19 (7,41% vs 7,27% vs 5,45% vs 16,07%), headache (3,70% vs 7,27% vs 3,64% vs 3,57%), blood creatine phosphokinase increased (5,56% vs 5,45% vs 1,82% vs 0,00%).

Table VI: Completed clinical trials investigating Eblasakimab for the treatment of Atopic Dermatitis.

Trial	Study Design	Endpoints	Main results disclosed	Main adverse events
Phase Ia trial [53]	Open-Label, Single Ascending Dose trial. N= 44 (healthy male adults) 2 parts: A – SD mg/kg IV Eblasakimab, 5 cohorts B- single fixed SC Eblasakimab, 4 cohorts	Primary: Safety of Eblasakimab (monitoring the incidence of AEs from day 1 to the study completion). Secondary: $AUC_{(0-t)}$, volume of distribution at steady state, SC bioavailability, dose-normalized C_{max} and $AUC_{(0-inf)}$/dose.	Well tolerated to doses up to 10mg/kg IV and 600mg SC; No serious AEs.	IV cohorts: upper respiratory tract infection (20%), decreased appetite (15%), headache (15%), oropharyngeal pain (15%), pyrexia (15%). SC cohorts: headache (8,3%), elevated C-reactive protein (8,3%), pruritus at the injection site (4,2%).
Phase Ib trial [54]	Double-blind, Randomized 3:1 controlled trial. N= 52 (≥18 years old) SC 200 mg Eblasakimab qw or SC 400 mg Eblasakimab or SC 600 mg Eblasakimab mg or placebo, over 8 weeks	Primary: incidence of AEs. Secondary: % change in EASI from baseline; % of patients achieving EASI 75, EASI 50 and EASI 90; % of patients achieving IGA 0/1; % change in BSA; % change in the peak-PNRS from baseline; % of patients with ≥4 points improvement in PNRS; improvements in POEM score.	AEs in 47% of patients on placebo and 71% of Eblasakimab patients; Most AEs were mild or moderate; % of change in EASI score was statistically significant in the 600 mg SC Eblasakimab group vs placebo (-65% vs -27%).	Pruritus (20,8% in Eblasakimab groups vs 7,7% in placebo group), injection site erythema (14,8% vs 7,7), injection site swelling (14,8% vs 0%), eye pruritus 11,1% vs 7,7%), rhinorrhea (11,1% vs 7,7%), injection site pruritus (11,1% vs 0%), headache (11,1% vs 0%), lethargy (11,1% vs 0%).

Table VII: Ongoing clinical trials investigating Eblasakimab for the treatment of Atopic Dermatitis.

ClinicalTrials.gov identifier	Title	Phase	Enrollment (n)	Status	Estimated study completion date
NCT05694884 [55]	Study of Eblasakimab in Male or Female Moderate-to-Severe Atopic Dermatitis Patients Previously Treated With Dupilumab	II	75 (estimated)	Recruiting	February 2025

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