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Nemolizumab for the Treatment of Atopic Dermatitis

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Nemolizumab for the Treatment of Atopic Dermatitis

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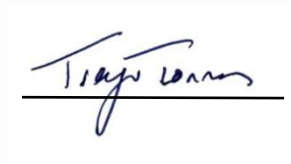
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(Erica de Jesus Rodrigues)

Dedication

To my parents, for the unwavering support, patience, and encouragement over the last six years.

To my best friends Erica, Leandro, Luis, Mónica and Petra, for all your motivation and company throughout this long journey, even in the most challenging moments.

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Resumo

A dermatite atópica é uma doença inflamatória da pele comum e heterogénea, caracterizada por um curso crónico ou recidivante de prurido intenso e lesões eczematosas. Os doentes frequentemente experienciam um impacto significativo na sua qualidade de vida, apresentando um risco acrescido de desenvolver perturbações psiquiátricas. Atualmente, a dermatite atópica permanece incurável e o tratamento das formas moderadas a graves representa um desafio terapêutico. As opções terapêuticas clássicas têm demonstrado uma eficácia limitada e efeitos adversos indesejáveis com a sua utilização a longo prazo, sublinhando a necessidade de terapêuticas inovadoras. Nas últimas décadas, uma compreensão mais aprofundada dos mecanismos subjacentes à dermatite atópica levou ao desenvolvimento de terapêuticas alvo inovadoras. A interleucina 31 desempenha um papel fundamental na patogénese da dermatite atópica, contribuindo para a indução do prurido, disfunção da barreira cutânea, inflamação mediada por células T *helper* 2, remodelação tecidular e fibrose. Assim, o nemolizumab, um anticorpo monoclonal humanizado anti-cadeia α do recetor da interleucina 31, surgiu como uma potencial opção terapêutica para a dermatite atópica. Os resultados de ensaios clínicos de fase II e fase III parecem corroborar a eficácia do nemolizumab no tratamento da dermatite atópica moderada a grave, demonstrando uma melhoria significativa e sustentada dos índices de prurido e gravidade. Além disso, o nemolizumab apresentou um perfil de segurança favorável, sem acontecimentos adversos graves reportados pela maioria dos doentes. Estudos adicionais, incluindo uma análise mais detalhada da interação completa do eixo da interleucina 31 na doença e evidência a longo prazo em contexto real e em estudos comparativos, serão essenciais para melhor definir o seu papel no tratamento da dermatite atópica.

Esta revisão fornece uma visão geral da dermatite atópica e do conhecimento atual sobre o papel da interleucina 31 na fisiopatologia da doença. Além disso, pretende sintetizar os dados mais recentes e relevantes resultantes de ensaios clínicos sobre a eficácia e segurança do nemolizumab no tratamento da dermatite atópica.

Palavras-chave: **“**atopic dermatitis”, “CIM331”, “eczema”, “interleukin-31”, “nemolizumab”

Abstract

Atopic dermatitis (AD) is a common, heterogenous, inflammatory skin disorder, characterized by a chronic or relapsing course of intense pruritus and eczematous lesions. Patients frequently experience a significant impact on their quality of life, facing an increased risk of developing mental health disorders. Currently, AD remains incurable and the management of moderate-to-severe AD forms poses a therapeutic challenge. Classical therapeutic options have demonstrated limited efficacy and undesirable adverse effects with long-term use, underscoring the need for innovative therapies. Over the past few decades, a deeper understanding of the underlying mechanisms of AD has led to the development of novel targeted therapies. Interleukin (IL)-31 plays a key role in AD pathogenesis, contributing to pruritus induction, skin barrier dysfunction, T-helper 2 cell (Th2)-mediated inflammation, tissue remodeling, and fibrosis. Therefore, nemolizumab, a humanized anti-IL-31 receptor α-chain (IL-31RA) monoclonal antibody, has emerged as a potential treatment option for AD. Findings from phase II and phase III clinical trials seem to corroborate efficacy of nemolizumab in the treatment of moderate-to-severe AD, demonstrating a significant and sustained improvement of pruritus and severity scores. Additionally, nemolizumab has shown a favorable safety profile, with most patients experiencing non-serious adverse events (AEs). Further research, including a more detailed analysis of the full interplay of the IL-31 axis in the disease, as well as long-term real-world and comparative evidence, will be essential to better define its role in AD treatment.

This review provides an overview of AD and the current available knowledge regarding the role of IL-31 in the disease´s pathophysiology. It also aims to summarize the most recent and relevant data from clinical trials on the efficacy and safety of nemolizumab in the management of AD.

Keywords: **“**atopic dermatitis”, “CIM331”, “eczema”, “interleukin-31”, “nemolizumab”

List of abbreviations

AD	Atopic dermatitis
AE	Adverse event
AKT	Protein kinase B
BSA	Body surface area
CCL	C-C motif chemokine ligand
CXCL	C-X-C motif chemokine ligand
DLQI	Dermatology Life Quality Index
DRG	Dorsal root ganglia
EASI	Eczema Area and Severity Index
EASI-75	≥ 75% improvement in Eczema Area and Severity Index
EASI-90	≥ 90% improvement in Eczema Area and Severity Index
EMA	European Medicines Agency
FDA	Food and Drug Administration
IGA 0/1	Investigator's Global Assessment score of 0 (clear) or 1 (almost clear)
IGA	Investigator's Global Assessment
IL	Interleukin
IL-31RA	Interleukin-31 receptor α-chain
IL-4Rα	Interleukin-4 α subunit receptor
JAK	Janus kinase
MAPK	Mitogen-activated protein kinase
OSMR	Oncostatin Mβ receptor
PI3K	Phosphoinositide 3-kinase
PP-NRS	Peak Pruritus Numeric Rating Scale
Q4W	Every 4 weeks
Q8W	Every 8 weeks
SD-NRS	Sleep Disturbance Numerical Rating Scale
sIGA	static Investigator's Global Assessment
STAT	Signal transducer and activator of transcription
TCI	Topical calcineurin inhibitors
TCS	Topical corticosteroids
Th1	T helper 1 cells
Th2	T helper 2 cells
VAS	Visual analogue scale

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Table II Summary of phase III trial results evaluating nemolizumab in the treatment of AD

Table III Ongoing clinical trials investigating nemolizumab for the treatment of AD

Introduction

Atopic dermatitis (AD), also known as eczema, represents the most common chronic inflammatory skin disease, affecting 2.1%-4.9% of adults and up to 20.1% of children,[1,2] with a rising global prevalence.[3] Most cases emerge in early childhood, typically between 3 and 6 months of age, as a part of the "atopic march", being frequently associated with other allergic disorders (such as asthma, rhinitis, conjunctivitis, and food allergy).[3-5] However, AD can have heterogeneous trajectory patterns, with active disease commencing in adulthood in approximately a quarter of cases (adult-onset AD) or persisting beyond childhood (persistent AD).[3,6]

A family history of atopic diseases, particularly AD, represents the strongest known risk factor for disease development.[4] While several environmental risk factors have been proposed, only a few - such as a small family size, living in an urban setting or in regions with dry climatic conditions or low ultraviolet light exposure - are supported by strong epidemiological evidence.[3,4]

AD is classically a clinical diagnosis, characterized by a wide spectrum of clinical characteristics that vary depending on ethnicity, age, and disease severity.[4,5] The clinical hallmarks are severe pruritus, eczematous skin lesions, and a chronic or relapsing disease course.[3-5] Eczematous lesions typically show age-related morphology and distribution, with acute inflammatory lesions (characterized by erythema, oedema, and exudation) predominantly affecting the face, cheeks, trunk, and extensor surfaces in infants and young children, and chronic lichenified lesions frequently involving flexural areas in adults.[3-5]

AD poses the highest disease burden among skin disorders, significantly impairing the quality of life of the patients and their caretakers.[7] Individuals with moderate-to-severe AD often experience significant impairment in daily activities, work or school performance, self-esteem and social functioning and frequently develop mental health disorders, including anxiety and depression.[3-5] Furthermore, chronic pruritus, considered to be the most common and distressing symptom in AD,[8] is closely related to sleep disturbances, perpetuation of the itch-scratch cycle, and an increased risk of suicidal ideation, particularly among adolescents.[5,9]

The pathogenesis of AD is multifactorial, with a complex interplay between genetic susceptibility, environmental factors, epidermal barrier dysfunction, T helper 2 (Th2)-skewed immune dysregulation, microbial dysbiosis, an abnormal pruritus response, and environmental triggers (such as stress, sweating, and skin allergens).[3-5] Interleukin (IL)-31, a neuroimmune cytokine implicated in itch, inflammation, and barrier disruption, plays a pivotal role in the disease pathophysiology.[10,11]

AD remains a therapeutic challenge. The chronic-relapsing course of the disorder often demands a long-term management, which aims to achieve clinical remission or minimal levels of disease activity, enhancing the quality of life of the patients. In mild-to-moderate AD, topical therapies – including corticosteroids (TCS), calcineurin inhibitors (TCI), phosphodiesterase-4 inhibitors, and Janus kinase (JAK)

inhibitors – are the mainstay of treatment, alongside allergens avoidance and emollients.[8] Patients with moderate-to-severe AD or those inadequately controlled with topical therapy are candidates for systemic treatment. For many years, conventional immunosuppressant agents (cyclosporine A, azathioprine, methotrexate, and mycophenolate mofetil), phototherapy, and systemic corticosteroids were the only systemic treatment options available for difficult-to-treat AD. However, their suboptimal efficacy and significant long-term toxicity raised the need for the development of new AD therapies.[12]

Advancements in the molecular understanding of AD pathophysiology have led to a transformative shift in the therapeutic landscape of the disease, with the emergence of biologic and small molecule therapies. These innovative treatments, which act specifically on cytokines implicated in AD pathogenesis, their receptors, or associated intracellular signaling pathways, have shown promising results, particularly for individuals with more severe subforms of the disease.[13] Six new systemic therapies have been approved for the treatment of moderate-to-severe AD, including the biologics dupilumab (anti-IL-4 α subunit receptor (IL-4Rα)), tralokinumab and lebrikizumab (both anti-IL-13), and the oral JAK inhibitors baricitinib (targeting JAK1 and JAK2), upadacitinib, and abrocitinib (both targeting JAK1).[14] Despite therapeutic advancements with these newly approved agents, a considerable proportion of AD patients demonstrate either no response or only a partial response to existing therapies.[15] There is thus a large need for further innovative therapeutic approaches that can serve as effective alternatives for these individuals.

Given the central role of pruritus in AD pathogenesis and reduced quality of life, therapies aimed at disrupting the itch-scratch cycle have garnered increasing interest. Nemolizumab (formerly known as CIM331), a subcutaneously injected humanized anti-IL-31 receptor α-chain (IL-31RA) monoclonal antibody, has demonstrated efficacy in alleviating pruritus, reducing inflammation, and promoting skin barrier repair in AD patients.[16] Initially approved in Japan in 2022 for patients aged ≥13 years with refractory AD-related pruritus, nemolizumab was recently approved by the Food and Drug Administration (FDA) and European Medicines Agency (EMA) for the treatment of moderate-to-severe AD inadequately controlled with topical therapy in adolescents and adults.[17,18]

This article will review the role of IL-31 in AD pathogenesis and the latest clinical data on nemolizumab in the disease management. A bibliographic search was conducted (up until February 2025) using the PubMed and ScienceDirect databases, using the aforementioned keywords, individually or in association. The search included original and review articles published in 2016 or later, written exclusively in English. The articles were selected based on the relevance of their abstract, established objectives and subsequent comprehensive analysis of their full texts. Relevant bibliographic references from the selected articles were also included when pertinent. Further data concerning the clinical trials was obtained from the ClinicalTrials.gov platform.

Pathogenesis of AD and the role of IL-31

The complex pathogenesis of AD involves an intricate network of interrelated and multidirectional mechanisms, influenced by gene-gene and gene-environment interactions. Epidermal barrier dysfunction, microbial dysbiosis, and immune dysregulation are considered key contributors to disease progression, perpetuating one another in a self-reinforcing cycle.[3-5]

Epidermal barrier impairment in AD is partly attributed to mutations in the filaggrin gene and alterations in the lipid composition of the stratum corneum, particularly ceramide deficiency.[19-21] These defects lead to increased transepidermal water loss and skin dryness, facilitating the penetration of allergens, irritants, and pathogens into the skin. The subsequent exposure to these antigens elicits an inappropriate activation of Th2 cell-mediated pathways, resulting in the excessive production of Th2 cytokines, including IL-4, IL-5, IL-13, and IL-31.[21]

IL-31 is a key neuroimmune cytokine involved in the pathogenesis of AD, contributing to pruritus induction and perpetuation of the itch-scratch cycle.[22,23] A member of the IL-6 family, IL-31 is predominantly secreted by activated Th2 cells, as well as mast cells, monocytes, macrophages, keratinocytes, fibroblasts, dendritic cells, eosinophils, basophils, and cutaneous peripheral nerves.[16,23,24] Its receptor is a heterodimeric complex composed of IL-31RA and the oncostatin Mβ receptor (OSMR), being expressed by a wide variety of cell types, such as keratinocytes, peripheral neurons, dorsal root ganglia (DRG), and immune cells.[16,24] IL-31 binds selectively to IL-31RA, with OSMR subsequently enhancing receptor affinity.[16] This interaction results in phosphorylation and consequently activation of multiple cellular signaling pathways, including JAK1/JAK2, along with their signal transducer and activator of transcription factors 1, 3 and 5 (STAT1, STAT3, and STAT5); phosphoinositide 3-kinase/protein kinase B (PI3K/AKT), and mitogen-activated protein kinase (MAPK).[16,23]

While multiple cytokines have been identified as contributors to pruritus, IL-31 is currently considered the primary driver of pruritus in AD, contributing to itch response through a histamine-independent sensory nerve stimulation.[16,23,24] In fact, elevated serum IL-31 levels have been observed in AD patients, correlating with disease severity and pruritic symptoms.[25,26] Furthermore, IL-31 signaling promotes elongation and ramification of the small DRG neuron, via STAT3 activation, enhancing sensitivity to minimal stimuli (like maintained itch) and contributing to neuronal hypersensitivity and persistent pruritus.[16,27]

IL-31 also plays a central role in barrier disruption and immune dysregulation in AD. IL-31 suppresses keratinocyte cell cycle and differentiation, as well as expression of barrier-associated proteins, such as filaggrin, involucrin, cytokeratin 10, and claudin-1. This dysfunction increases the expression of proinflammatory cytokines (IL-1α, IL-20, IL-24), further weakening the epidermal barrier and facilitating allergens and irritants penetration.[16,23] Physical damage from scratching and microbial dysbiosis, particularly *Staphylococcus aureus* overgrowth, further exacerbates skin disruption and inflammation.[3-5] Staphylococcal exotoxins have

been shown to rapidly induce IL-31RA expression in monocytes and macrophages, enhancing IL-31-mediated immune activation.[28]

IL-31 induces expression of chemokines in keratinocytes, attracting Th2 memory lymphocytes through C-C motif chemokine ligand (CCL) 17, CCL22, CCL19, CCL23, and CCL4, and promoting inflammation.[16] Furthermore, IL-31 amplifies type 2 immune responses by stimulating basophils to secrete large amounts of IL-4 and IL-13, which, in turn, promote Th2 differentiation and IL-31 secretion. In eosinophils and dendritic cells, IL-31 induces the release of proinflammatory mediators, including IL-1β, IL-6, C-X-C motif chemokine ligand (CXCL) 1, CXCL8, CCL2, CLL5, and CCL22, which attract neutrophils, dendritic cells, T helper 1 (Th1) and Th2 cells and promote angiogenesis, inflammation, and tissue remodeling.[16,23]

Beyond its role in inflammation, IL-31 contributes to skin remodeling and thickening during the chronic Th1-mediated phase of AD.[16,23] IL-31 has been shown to promote the induction of type I collagen and dermal fibroblast activation, suggesting a role in fibrotic processes.[16]

Although the IL-31/IL-31RA axis is well established as a primary driver of AD-associated pruritus, its broader implications in AD pathophysiology require further investigation.[23] Given its central role in the disease's pathogenesis, targeting IL-31 axis represents a valid strategy to expand the scope of AD treatment.

Clinical Efficacy in AD

Several clinical trials have evaluated the clinical efficacy of nemolizumab in patients with moderate-to-severe AD, the results of which are summarized below. Findings from phase II and III studies are presented in Tables I and II, respectively.

Phase II Trials

A two-part, phase II, randomized, placebo-controlled, double-blind trial (NCT01986933) was conducted to assess the efficacy and safety of nemolizumab. In the first part (part A), patients aged 18 to 65 years (n = 264) with moderate-to-severe AD (defined as Eczema Area and Severity Index (EASI) score ≥ 10, pruritus visual analogue scale (VAS) score ≥ 50 mm, and static Investigator's Global Assessment (sIGA) score ≥ 3) who were inadequately controlled with or intolerant to topical therapy were randomized in a 1:1:1:1:1 ratio into 5 arms to receive subcutaneous (1) nemolizumab 0.1 mg/kg every 4 weeks (Q4W), (2) nemolizumab 0.5 mg/kg Q4W, (3) nemolizumab 2.0 mg/kg Q4W, (4) placebo Q4W, and (5) nemolizumab 2.0 mg/kg every 8 weeks (Q8W) with placebo administered at week 4. The 12-week study assessed nemoluzimab as monotherapy, although rescue therapy with potent TCS was permitted from week 4 onward if patients showed no improvement on pruritus VAS and eczematous skin lesions. A significantly higher percentage of subjects receiving nemolizumab Q4W achieved the primary

endpoint, defined as percentage improvement from baseline in pruritus VAS at week 12 [-43.7% ($p = 0.002$) with 0,1 mg/kg; -59.8% ($p < 0.001$) with 0.5 mg/kg; -63.1% ($p < 0.001$) with 2.0 mg/kg Q4W], compared to placebo (-20.9%). Notably, a rapid decrease in pruritus VAS score was observed within week 1 of nemolizumab treatment. Furthermore, at week 12, most of the patients taking nemolizumab Q4W demonstrated superior response rates in secondary endpoints, including in EASI score (-23.0% in 0,1 mg/kg; -42.3% in 0.5 mg/kg; -40.9% in 2.0 mg/kg), versus placebo (-26.6%).[29]

A 52-week, double-blind extension (part B) of the previous trial (NCT01986933) evaluated the long-term efficacy and safety of continuous nemolizumab. Patients who received nemolizumab in part A continued the previously assigned dose for an additional 52 weeks (weeks 12-64), while previous placebo-treated participants were rerandomized in a 1:1:1 ratio to receive subcutaneous nemolizumab at a dose of 0.1, 0.5, or 2.0 mg/kg Q4W. Mild TCS was allowed as needed, and "potent" or "very potent" TCS were permitted as rescue therapy. In total, 191 patients enrolled in the extension phase. The two major secondary efficacy endpoints evaluated in part B were percentage changes from baseline in pruritus VAS and EASI scores. The improvement from baseline in pruritus VAS score seen in part A was sustained or further enhanced from week 12 to week 64, with the 0.5 mg/kg Q4W group demonstrating the greatest improvement throughout the study (percentage change from baseline at week 64: -73.0% with 0.1 mg/kg Q4W; -89.6% with 0.5 mg/kg Q4W; -74.7% with 2.0 mg/kg Q4W; -79.1% with 2.0 mg/kg Q8W). In placebo-treated patients who switched to nemolizumab at week 12, a response to therapy in pruritus VAS score was observed as early as week 16. Percentage reductions in EASI score were also maintained or increased from week 12 to week 64. The percentage changes from baseline in EASI score at week 64 were -68.5%, -75.8%, -78.9%, and -69.3% in the 0.1-, 0.5-, and 2.0-mg/kg Q4W and 2.0-mg/kg Q8W groups, respectively.[30]

A phase IIb randomized, placebo-controlled, double-blind, dose-ranging, multicenter, 24-week trial (NCT03100344) was conducted to further evaluate the efficacy and safety of several subcutaneous doses of nemolizumab in moderate-to-severe AD subjects, receiving TCS. The study population included patients ($n = 226$) aged ≥ 18 years with moderate-to-severe AD (required to have an Investigator's Global Assessment (IGA) score ≥ 3, an EASI score ≥ 12, and an affected body surface area (BSA) ≥ 10%) and with severe AD-associated pruritus uncontrolled by topical treatments (defined as a Pruritus Categorical Scale score of severe on at least 3 of the last 7 days before screening, and an average daily Peak Pruritus Numeric Rating Scale (PP-NRS) intensity ≥ 7 for 7 days before the baseline visit). Patients were randomly distributed 1:1:1:1 into 4 arms to receive (1) nemolizumab 10 mg Q4W, (2) nemolizumab 30 mg Q4W, (3) nemolizumab 90 mg Q4W, and (4) placebo Q4W, with all groups using concomitant medium- or low-potency TCS. In the primary endpoint, all nemolizumab doses demonstrated greater improvement in mean percentage change in EASI score at week 24 compared to placebo. The most pronounced difference from baseline at week 24 was observed with the 30-mg dose of nemolizumab (-68.8% versus -52.1% placebo, $p = 0.016$). Significant reductions in EASI score were observed by week 8 ($p \leq 0.01$). Concerning the secondary

endpoints, at week 24, an EASI improvement ≥ 75% (EASI-75) was achieved in 45.6% of patients in the 30-mg nemolizumab group, compared to 26.3% in the placebo group (p = 0.034), and an EASI improvement ≥ 90% (EASI-90) was achieved in 29.8% versus 10.5%, respectively (p = 0.011). Furthermore, all experimental groups demonstrated statistically significant improvements in PP-NRS scores as early as week 1 (p < 0.01), with maximal efficacious response seen in the 30-mg nemolizumab arm (-67.3% versus -35.8% placebo at week 24, p < 0.0001). Additionally, a greater proportion of patients in the nemolizumab 30 mg group achieved an IGA score of 0 (clear) or 1 (almost clear) (IGA 0/1), along with notable improvements in weekly average Sleep Disturbance Numerical Rating Scale (SD-NRS) and Dermatology Life Quality Index (DLQI) scores, compared with the placebo group.[31]

Sibury *et al.* carried out a phase II, single-group, open-label, multicenter, 16-week study (NCT03921411) in adolescent patients (*n* = 20) aged 12-17 years with moderate-to-severe forms of AD. Eligibility criteria included a baseline EASI ≥ 16, an IGA ≥ 3, an affected BSA ≥ 10%, and associated pruritus with baseline average daily PP-NRS intensity ≥ 4, alongside an inadequate response to topical therapy. Nemolizumab was administered subcutaneously as a 60 mg loading dose at baseline, followed by 30 mg Q4W until week 12, with background TCS or TCI therapy. Rescue therapy, including TCI and higher potency TCS, was permitted as needed at any time during the clinical trial, except for the first 2 weeks after baseline. Concerning the secondary endpoints, efficacy assessments included percentage change from baseline in EASI score and PP-NRS score, as well as the number of participants achieving an IGA score of 0/1 at week 16. The reduction from baseline observed at week 16 in EASI score and PP-NRS score was -66.5% and -43.2%, respectively. Additionally, 7 participants (35%) achieved IGA 0/1 response by week 16. These findings suggest that nemolizumab improved signs/symptoms of AD in adolescents to a degree comparable to adults.[32]

Currently, a recruiting phase II, open-label, single-group, multicenter, 52-week clinical trial (NCT04921345) is ongoing to evaluate the pharmacokinetics, safety and efficacy of nemolizumab in pediatric patients (aged between 2 and 11 years) with moderate-to-severe AD.[33] Ongoing clinical trials investigating nemolizumab for treatment of AD are available in Table III.

Phase III Trials

A phase III, randomized, double-blind, placebo-controlled, multicenter, Japanese trial (jRCT2080223684) was conducted to further elucidate the efficacy and safety of nemolizumab. Patients (*n* = 215) aged ≥ 13 years with moderate-to-severe AD (required to have a pruritus VAS score ≥ 50 and an EASI score ≥ 10), inadequately controlled with topical agents were randomized in a 2:1 ratio into 2 arms to receive subcutaneous (1) nemolizumab 60 mg Q4W, and (2) placebo Q4W until week 16. Participants were concomitantly treated with stable AD therapies, including medium-potency TCS, TCI, and oral antihistamines. Higher-potency TCS were

permitted as rescue therapy when worsening AD-associated eczema was reported. At week 16, the mean percentage change from baseline in the pruritus VAS score (primary endpoint) was -42.8% with nemolizumab and -21.4% with placebo (least-squares mean difference of -21.5 percentage points; $p < 0.001$). Concerning secondary efficacy endpoints, although the mean percentage change in EASI score at week 16 was -45.9% in the nemolizumab group and -33.2% in the placebo group and significant differences in daily VAS score were observed as early as day 2 (-10.3% in the nemolizumab group and -4.4% in the placebo group), no clinical inferences could be made because of the lack of adjustments for multiple comparisons.[34]

A 52-week, open-label extension (part B) of the previous study (jRCT2080223684) was conducted following the initial 16-week period (part A) to examine the long-term efficacy and safety of the drug. In total, 206 patients who completed part A were enrolled in the extension phase in which all of them received subcutaneous nemolizumab 60 mg Q4W up to week 64, concomitantly with TCS of any potency, resulting in two assessment groups: nemolizumab/nemolizumab and placebo/nemolizumab. Efficacy endpoints included percentage change through the duration of the study in pruritus VAS and EASI scores. In this extension trial, the mean pruritus VAS scores continued to demonstrate a maintained reduction over time. At week 68, the percentage change from baseline in pruritus VAS score was -65.9% in the nemolizumab/nemolizumab group. Only minimal increases were observed 12 weeks after the last administration, suggesting the durability of the drug's efficacy against pruritus. Similar results were reported concerning percentage change from baseline in EASI scores, with a decrease from baseline of 78.2% at week 68. Another phase III, open-label, multicenter, long-term clinical trial (jRCT2080223838) was conducted in Japan, in which 88 participants aged ≥ 13 years with AD and inadequately controlled pruritus received nemolizumab 60 mg Q4W up to week 48. Injections were administered by medical professionals at baseline, week 4, and week 8, whereas from week 12 onward half of the participants transitioned to self-injection. Concerning efficacy endpoints, no significant differences were observed between participants who self-injected and those who continued to receive injections from health care professionals. Overall, a consistent reduction in pruritus VAS score from baseline was observed at each study timepoint in all participants treated with nemolizumab. The changes in EASI score were also similar to those observed in the 52-week extension trial.[35]

A phase III, randomized, double-blind, placebo-controlled, multicenter, 16-week clinical trial (jRCT2080225289) was conducted in Japan to assess for the first time the efficacy and safety of nemolizumab, administered concomitantly with topical agents, in pediatric subjects (aged between 6 and 12 years) with AD and an inadequately controlled moderate to severe pruritus. The study population included patients ($n = 89$), required to have had on the day of randomization a 5-level itch score of ≥ 3 on at least two of the prior 3 days and a score of ≥ 2 on the remaining day, and an EASI score of ≥ 10. These participants were randomly assigned in a 1:1 ratio to receive either nemolizumab 30 mg or placebo Q4W. In the primary efficacy endpoint, defined as the change in 5-level itch score from baseline to week 16, a statistically significant difference was observed between the

nemolizumab treatment group (-1.3) and placebo (-0.5), with a least-squares mean difference of -0.8 ($p < 0.0001$). Notably, a greater improvement in the 5-level itch score with nemolizumab was observed from the second day after administration. Regarding secondary endpoints, the nemolizumab group demonstrated greater improvement in percentage change in EASI score at week 16 (-52.4%) compared to placebo (-41.5%), however, these differences were not statistically significant ($p = 0.2101$).[36]

The ARCADIA 1 (NCT03985943) and ARCADIA 2 (NCT03989349) trials were two identical 48-week randomized, double-blind, placebo-controlled phase III studies designed to assess nemolizumab in adolescents and adults patients (aged ≥ 12 years) with moderate-to-severe AD (required to have an IGA ≥ 3, EASI ≥ 16, and affected BSA ≥ 10%) and associated pruritus (PP-NRS score of ≥ 4). Participants (n = 941 in ARCADIA 1; n = 787 in ARCADIA 2) were randomized 2:1 to receive (1) 60 mg of nemolizumab as a loading dose at baseline followed by 30 mg Q4W, or (2) placebo Q4W. As a background therapy, both groups concomitantly used TCS with or without TCI. Rescue therapies were allowed at any time during the study, except during the first 2 weeks post-baseline to ensure minimum study drug exposure. Maintenance treatment period (weeks 16-48) is based on re-randomization 1:1:1 of responders at week 16 to receive (1) nemolizumab 30 mg Q4W, (2) nemolizumab 30 mg Q8W, or (3) placebo Q4W. All placebo-treated participants who demonstrated a clinical response to placebo during the first 16 weeks continued to receive placebo Q4W in the maintenance period. In both studies, a significantly higher percentage of patients receiving nemolizumab plus TCS-TCI achieved the coprimary endpoints at week 16, defined as an IGA score of 0/1, with a ≥ 2-point improvement from baseline and an EASI-75 response. In ARCADIA 1, 36% of participants in the nemolizumab plus TCS-TCI group achieved IGA success compared to 25% in the placebo plus TCS-TCI group (adjusted percentage difference 11.5%, $p = 0.0003$), and an EASI-75 response occurred in 44% of patients in the nemolizumab plus TCS-TCI group compared to 29% in the placebo plus TCS-TCI group (adjusted difference 14.9%, $p < 0.0001$). In ARCADIA 2, the corresponding data were 38% of subjects in the nemolizumab plus TCS-TCI group and 26% in the placebo plus TCS-TCI group for IGA success (adjusted difference 12.2%, $p = 0.0006$), and 42% and 30% for EASI-75 response (adjusted difference 12.5%, $p = 0.0006$), respectively. Subjects taking nemolizumab plus TCS-TCI also experienced statistically significant improvements in itch (as early as week 1) and sleep improvement by week 16, as measured by key secondary endpoints. By week 16, 43% of nemolizumab-treated subjects achieved a ≥ 4-point reduction in the PP-NRS versus 18% in the placebo plus TCS-TCI group (adjusted difference 24.9%, $p < 0.0001$) in ARCADIA 1 and 41% of nemolizumab-treated patients achieved this reduction, compared to 18% in the placebo plus TCS-TCI group (adjusted difference 23.2%, $p < 0.0001$) in ARCADIA 2. Moreover, a higher percentage of participants had an SD-NRS score reduction ≥ 4 points at week 16 in the nemolizumab plus TCS-TCI group (38% in ARCADIA 1; 34% in ARCADIA 2) than in the placebo plus TCS-TCI group (20% and 16%, respectively; $p < 0.0001$).[37]

An ARCADIA long-term extension trial (NCT03989206) (Table III) is already in progress to assess the safety and efficacy of nemolizumab in subjects with

moderate-to-severe AD. The study will include patients who did not meet protocol-defined response criteria at week 16 or who received rescue therapy during the induction period in ARCADIA 1 and ARCADIA 2.[38]

Safety

Safety results from phase II and III studies are summarized in Tables I and II, respectively.

In the first part of a phase II study (NCT01986933), adverse events (AEs) occurred at similar rates across placebo (68%) and each of the nemolizumab groups (67-77%), with most being nonserious. Treatment discontinuation due to AEs occurred more frequently in the nemolizumab groups (7.1%) than in the placebo group (2%), mainly due to AD exacerbations. The frequency and types of most of the AEs related to nemolizumab were largely identical to those observed in the placebo group, including nasopharyngitis, upper respiratory tract infection, and increased creatine kinase levels, reported in 12.8%, 6.6%, and 5.2% of nemolizumab-treated patients, respectively. However, AD exacerbations and peripheral edema were more commonly observed in the nemolizumab groups, compared to placebo, with an incidence of 19.4% versus 13.2%, and 5.7% versus 0.0%, respectively.[29]

In the 52-week extension phase of the previous trial, nemolizumab was well tolerated and maintained a safety profile consistent with that observed in part A, with no new AEs identified. Most AEs occurred within the first 12 weeks and were mild or moderate in intensity, nonserious and did not lead to withdrawal from treatment. The most common treatment-related AEs were exacerbation of AD (8%), upper respiratory tract infection (4%), nasopharyngitis (4%), peripheral edema (3%), increased blood creatine phosphokinase (3%), and injection-site reaction (2%).[30]

In the phase IIb trial (NCT03100344), nemolizumab treatment was associated with a slightly higher incidence of both treatment-emergent AEs (84%) and serious treatment-emergent AEs (4.1%) compared to placebo (76.8% and 1.8%, respectively). However, few AEs led to trial discontinuation (13 across nemolizumab-treated groups versus 4 in the placebo group). While no imbalance was observed in the incidence of skin infections between nemolizumab and placebo groups, nonskin infections, including nasopharyngitis (26.6% versus 21.4%), upper respiratory tract infections (8.3% versus 1.8%), and gastroenteritis (4.1% versus 0.0%), were more frequently reported in the nemolizumab groups. Additionally, a dose-dependent increase in asthma events was noted in patients with pre-existing asthma, though most cases were mild and reversible.[31]

The phase II adolescent study (NCT03921411) provided safety results comparable to those observed in adult trials, with AEs occurring in 33.3% of patients and being mostly mild or moderate in severity. Reported non-serious AEs included peripheral edema, upper respiratory tract infection, increased blood creatine phosphokinase, and AD exacerbations (each in 5.56% of patients). 3 serious AEs led to study discontinuation in 2 patients.[32]

In the phase III Japanese trial (jRCT2080223684), 71% of patients in both nemolizumab and placebo groups reported AEs that emerged during therapy, most of which were mild or moderate in severity and did not lead to drug discontinuation. Severe AEs were identified in 2% of nemolizumab-treated patients (including Meniere's disease, acute pancreatitis, and AD) versus 3% in the placebo group. The most reported AE of special interest was worsening AD (24% in the nemolizumab group versus 21% in the placebo group). Other AEs of special interest included injection-related reactions (8% in the nemolizumab group versus 3% in the placebo group), skin infection (7% versus 10%), and elevated creatine kinase (3% versus 1%).[34]

These data are consistent with the results of both phase III Japanese studies (jRCT2080223684 and jRCT2080223838) concerning the long-term safety profile of nemolizumab. In total, over 90% of patients who received nemolizumab across both studies experienced treatment-emergent AEs, while severe treatment-emergent AEs occurred in fewer than 5% of patients. Most treatment-emergent AEs were mild in severity and did not lead to trial discontinuation, with the most frequently reported being nasopharyngitis (33.9%), AD exacerbations (25.2%), and increased blood creatine phosphokinase (9.1%). The incidence of injection-related reactions declined over time, with no increased risk associated with long-term administration.[35]

In the phase III pediatric trial (jRCT2080225289), the overall safety profile in children aged 6-12 years was comparable to that reported in older patients. AEs were reported in 73.9% of nemolizumab-treated patients and 65.1% of placebo-treated patients, being mostly mild in severity. No AEs resulted in treatment discontinuation or death and no serious AEs were considered to be treatment-related. AD exacerbations, the most frequently reported AE, occurred at a similar incidence in both groups (10.9% with nemolizumab versus 11.6% with placebo) and only one event was considered to be related to the study drug. Erythema was the most common treatment-related AE (6.5% in the nemolizumab group versus 2.3% in the placebo group). Other frequently reported AEs included upper respiratory tract inflammation (8.7% in the nemolizumab group) and nasopharyngitis (6.5%).[36]

In ARCADIA 1 and ARCADIA 2, the safety profile of the study drug was identical between nemolizumab plus TCS-TCI and placebo plus TCS-TCI groups. At least one treatment-emergent AE occurred in 50% (ARCADIA 1) and 41% (ARCADIA 2) of nemolizumab-treated patients, compared to 45% and 44% in the placebo groups, respectively. Most treatment-emergent AEs were non-serious and mild to moderate in severity, and no deaths were reported across both trials. Serious treatment-emergent AEs occurred in 1% of participants in both groups in ARCADIA 1, and in 3% of nemolizumab-treated patients versus 1% of placebo-treated patients in ARCADIA 2. No notable differences in discontinuation rates due to treatment-emergent AEs were observed between the nemolizumab and placebo groups in ARCADIA 1 (1% in both groups), while in ARCADIA 2, 3% of nemolizumab-treated participants and 1% of placebo-treated patients discontinued treatment because of treatment-emergent AEs. Worsening of AD was the most frequently reported treatment-emergent AE, with a slightly higher incidence in the nemolizumab group

in both trials (12% versus 11% placebo in ARCADIA 1 and 7% versus 6% placebo in ARCADIA 2). Asthma events were more frequently reported in ARCADIA 1 (5% of nemolizumab-treated patients versus 4% of placebo-treated patients) than in ARCADIA 2 (2% versus 3%). Peripheral or facial edema occurred in 1-2% of nemolizumab-treated patients in both studies, with no meaningful differences between the groups.[37]

Currently, phase II and phase III clinical trials are being developed to further assess nemolizumab's safety in pediatric patients and its long-term safety in AD, as one of the primary endpoints (Table III).[33,38]

Discussion

AD is a prevalent, chronic inflammatory skin disease with a complex pathogenesis and a heterogeneous clinical presentation. Pruritus is considered to be the most burdensome symptom of AD,[8] significantly impacting overall quality of life for both patients and their caretakers.[3-5]

Currently, AD remains incurable and poses a therapeutic challenge. In recent years, several therapeutic strategies have emerged, focusing on specific immunologic pathways involved in the disease's pathophysiology, which led to a transformative shift in the therapeutic landscape of moderate to severe subforms of AD. Although currently approved therapies targeting IL-4 or IL-13 or inhibiting the activity of the JAK pathway marked a significant progress in the treatment of AD, a subset of patients remains inadequately controlled, underscoring the need for alternative therapeutic approaches.[15]

IL-31, a neuroimmune cytokine implicated in the pathophysiology of AD, plays a pivotal role in pruritus induction, skin barrier dysfunction, Th2-mediated inflammation, tissue remodeling, and fibrosis.[16,23] Given that itch relief is a primary treatment goal for most patients, IL-31 has emerged as a key target for novel biologic therapies. Such is the case with nemolizumab, a humanized monoclonal antibody that selectively inhibits IL-31 signaling via IL-31RA blockade.[16,23]

In the first part of the phase II clinical trial (NCT01986933), nemolizumab at all monthly doses led to significant improvement in pruritus at week 12 in adults with moderate-to-severe AD.[29] Results from the 52-week extension trial demonstrated that initial improvements in pruritus and dermatitis measures versus placebo were maintained or further increased with long-term treatment.[30] Findings from the 24-week phase IIb trial (NCT03100344) corroborated the rapid and sustained efficacy of the drug. Nemolizumab significantly improved EASI, IGA, and pruritus scores, with the 30 mg Q4W dose being most effective. Notably, significant reductions in pruritus scores were observed as early as week 1, alongside improvements in interference of itch on sleep and quality of life scores, with the greatest differences reported at week 16.[31] Similar benefits were observed in adolescents aged 12-17 years, further supporting nemolizumab's efficacy across various age groups.[32]

Findings from available phase III studies seem to support the efficacy of nemolizumab in the treatment of moderate-to-severe AD. In the initial phase of the phase III, Japanese study (jRCT2080223684), nemolizumab 60 mg Q4W in combination with topical therapies resulted in a greater reduction in pruritus over a period of 16 weeks, compared to placebo plus topical agents.[34] Data from two long-term (≥ 52 weeks) phase III studies evaluating nemolizumab in combination with TCS/TCI demonstrated sustained or further enhanced efficacy through the 68 weeks' duration of the studies. Post-treatment follow-up data suggested that the beneficial effects of nemolizumab on pruritus and rash persisted for 12 weeks after the last administration. The increasing efficacy of nemolizumab in alleviating pruritus over time, sustained even after treatment cessation, represents a clinically relevant attribute when considering the optimal long-term management of this chronic disease.[35] In children aged 6-12 years, nemolizumab 30 mg Q4W significantly improved pruritus scores, demonstrating reductions as early as day 2. Although the mean percentage reduction in the EASI score was higher in the nemolizumab group compared to the placebo group, the difference between groups was not statistically significant.[36] Data from ARCADIA 1 and ARCADIA 2 further corroborated effectiveness of nemolizumab plus TCS-TCI in the treatment of adults and adolescents with moderate-to-severe AD. Notably, nemolizumab showed a rapid onset of action, with significant improvements over placebo observed as early as week 1 in pruritus reduction and by week 16 in sleep disturbances. By week 16, more than 40% of patients receiving nemolizumab plus topical therapy achieved an EASI-75 response, with IGA success rates ranging from 36-38%.[37]

Thus, current data from phase II and phase III studies demonstrate that nemolizumab breaks the itch-scratch cycle, and that its fast effect on pruritus suppression translates immediately into improved sleep quality, dermatitis, and quality of life. However, a better understanding of the IL-31 antagonism in AD treatment is needed to elucidate whether its effects include exclusively symptomatic, antipruritic relief.[23]

The concomitant use of TCS/TCI protocoled in several clinical trials introduces additional complexity in study design and interpretation, affecting the assessment of the efficacy of nemolizumab as monotherapy. However, this approach closely reflects "real-world" treatment patterns, where systemic agents are frequently combined with topical therapies. Notably, nemolizumab treatment was associated with a reduction in the required amount of concomitant TCS/TCI use, potentially decreasing the application time required for topical treatments and minimizing adverse effects associated with prolonged steroid use.[35] Also, evidence suggests that concomitant use of TCS might enhance the antidermatitis effects of nemolizumab.[30]

Dupilumab is widely prescribed in real-world clinical practice, demonstrating high drug survival.[39,40] The EASI-75 response rate reported for dupilumab plus topical therapy at 16 weeks in clinical trials and real-world settings (64-69%) is somewhat higher than that achieved with nemolizumab plus TCS-TCI in ARCADIA 1 and ARCADIA 2. In contrast, the IGA success rate reported with a dupilumab regimen

(36-40%) was comparable to that achieved with nemolizumab plus topical therapy groups.[41-43] In a clinical trial evaluating lebrikizumab combined with background therapy, an EASI-75 response rate was observed in 70% of participants, while IGA success was achieved in 41%.[44] Furthermore, dupilumab and lebrikizumab showed apparent differences from placebo as early as week 2 and week 4, respectively, in reducing pruritus.[41,44] These findings suggest that blockage of IL-31 may not improve eczematous lesions as much as other biologics. However, it appears to be superior in improving pruritus more efficiently and rapidly, with sustained long-term efficacy. Direct comparison between nemolizumab and other targeted treatments is challenging due to the absence of head-to-head comparative studies, as well as the lack of consistency in study design, outcome measures, selection criteria of the participants, concomitant use of TCS/TCI therapy, and time points reported by several individual studies. Thus, future head-to-head studies are needed to further compare the efficacy and safety of nemolizumab with these drugs.

Concerning the safety profile, nemolizumab has demonstrated to be generally well tolerated in AD patients. Most of the AEs reported across phase II and phase III clinical trials were nonserious, mild to moderate in severity, and rarely led to treatment discontinuation. The most frequently described AEs were nasopharyngitis (4-34%), AD exacerbations (6-25%), upper respiratory tract inflammation (4-9%), and increased blood creatine phosphokinase (3-9%).[29-32,34-37] Of note, worsening of AD as a safety outcome was not associated with the efficacy outcome for reducing pruritus, and the underlying mechanisms are not fully understood.[34] Injection site reactions were also noted in a smaller incidence and tended to become less frequent with the continued use of the drug.[35] The dose-dependent increase in asthma events observed in patients with pre-existing asthma may be attributed to improved well-being and increased activity levels following nemolizumab treatment or to concomitant respiratory tract infections.[31]

With the ARCADIA extension trial, it is expected that further data on the long-term efficacy and safety of nemolizumab in moderate-to-severe AD will become available.[38] Additionally, a clinical trial is currently ongoing to further evaluate the durability and safety of nemolizumab in the pediatric population beyond 16 weeks.[33]

Conclusion

IL-31 plays a central role in the pathogenesis of AD. Findings from phase II and phase III trials support the efficacy of nemolizumab in the treatment of moderate-to-severe AD, demonstrating a rapid and sustained reduction of pruritus and severity scores, particularly when used in combination with topical therapies, alongside a suitable safety profile. A better understanding of the full interplay of the IL-31 axis in AD and further long-term, real-world, and head-to-head comparative studies are needed to clarify its place in AD treatment.

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Annexes

Table I Summary of phase II and IIb trial results assessing nemolizumab for the treatment of AD

Trial	Study design	Main endpoints	Main results	Main adverse events
Phase II (2017) - part A[29]	Randomized, placebo-controlled, double-blind *N* = 264 adults 1:1:1:1:1 0.1 mg/kg Q4W 0.5 mg/kg Q4W 2.0 mg/kg Q4W Placebo Q4W 2.0 mg/kg Q8W with placebo administered at week 4 12 weeks Rescue TCS use as needed	Primary: % change from baseline in pruritus VAS score at week 12 Secondary: % change from baseline in EASI score at week 12	Nemolizumab Q4W groups achieved significantly superior % changes in pruritus VAS score [-43.7% ($p = 0.002$) in 0,1 mg/kg; -59.8% ($p < 0.001$) in 0.5 mg/kg; -63.1% ($p < 0.001$) in 2.0 mg/kg] versus placebo (-20.9%) Most nemolizumab Q4W groups showed superior response rates in EASI score (-23.0% in 0,1 mg/kg; -42.3% in 0.5 mg/kg; -40.9% in 2.0 mg/kg) versus placebo (-26.6%)	Exacerbation of AD (19.4%), nasopharyngitis (12.8%), upper respiratory tract infection (6.6%), peripheral edema (5.7%), increased creatine kinase levels (5.2%)
Phase II (2018) - part B[30]	Randomized, double-blind *N* = 191 adults Patients randomized to nemolizumab in part A continued the previously assigned dose and previous placebo-treated participants were rerandomized in a 1:1:1 ratio 0.1 mg/kg Q4W 0.5 mg/kg Q4W 2.0 mg/kg Q4W	Secondary: % change from baseline in pruritus VAS and EASI scores at week 64	% changes in pruritus VAS score were maintained or further increased from week 12 to week 64 (-73.0% in 0.1 mg/kg Q4W; -89.6% in 0.5 mg/kg Q4W; -74.7% in 2.0 mg/kg Q4W; -79.1% in 2.0 mg/kg Q8W) % changes in EASI score were sustained or further enhanced from week 12 to week 64 (-68.5% in 0.1 mg/kg Q4W; -75.8% in 0.5 mg/kg Q4W; -78.9% in 2.0 mg/kg Q4W; -69.3% in 2.0-mg/kg Q8W)	Exacerbation of AD (8%), upper respiratory tract infection (4%), nasopharyngitis (4%), peripheral edema (3%), increased blood creatine phosphokinase (3%), and injection-site reaction (2%)

	2.0 mg/kg Q8W 52 weeks Rescue TCS use as needed			
Phase IIb (2020)[31]	Randomized, placebo-controlled, double-blind *N* = 226 adults 1:1:1:1 10 mg Q4W 30 mg Q4W 90 mg Q4W Placebo Q4W 24 weeks Concomitant use of continuous TCS	Primary: % change from baseline in EASI score at week 24 Secondary: % patients with EASI-75, EASI-90 at week 24, % change from baseline in PP-NRS score at week 24, % patients with IGA 0 or 1 at week 24, % change from baseline in weekly average SD-NRS at week 24	Nemolizumab 30 mg Q4W group achieved significantly greater % changes in EASI score versus placebo (-68.8% versus -52.1%; p = 0.016) Significantly more patients on 30 mg Q4W achieved EASI-75 versus placebo (45.6% versus 26.3%; p = 0.034) Significantly more patients on 30 mg Q4W achieved EASI-90 versus placebo (29.8% versus 10.5%; p = 0.011) Nemolizumab 30 mg Q4W group showed significantly superior improvements in PP-NRS scores versus placebo (-67.3% versus -35.8%; p < 0.0001) A higher percentage of patients on nemolizumab 30 mg Q4W group achieved an IGA 0/1 and better improvements in SD-NRS versus placebo	Nasopharyngitis (26.6%), upper respiratory tract infections (8.3%), gastroenteritis (4.1%)
Phase II (2022)[32]	Single-group, open-label *N* = 20 adolescents Loading dose of 60 mg at baseline followed by 30 mg Q4W 16 weeks Concomitant use of continuous topical therapy (TCS or TCI)	Primary: Number of Participants with treatment-emergent AEs and serious AEs Secondary: % change from baseline in EASI and PP-NRS scores at week 16, number of patients with IGA 0 or 1 at week 16	Improvement in EASI score (-66.5%) Improvement in PP-NRS score (-43.2%) IGA 0/1 achieved by 7 participants (35%)	Peripheral edema (5.56%), upper respiratory tract infection (5.56%), increased blood creatine phosphokinase (5.56%), AD exacerbations (5.56%)

AD, Atopic dermatitis; AE, Adverse event; EASI, Eczema Area and Severity Index; EASI-75, ≥ 75% improvement in Eczema Area and Severity Index; EASI-90, ≥ 90% improvement in Eczema Area and Severity Index; IGA 0/1, Investigator's Global Assessment score of 0 (clear) or 1 (almost clear); IGA, Investigator's Global Assessment; PP-NRS, Peak Pruritus Numeric Rating Scale; Q4W, Every 4 weeks; Q8W, Every 8 weeks; SD-NRS, Sleep Disturbance Numerical Rating Scale; TCI, Topical calcineurin inhibitors; TCS, Topical corticosteroids; VAS, Visual analogue scale.

Table II Summary of phase III trial results evaluating nemolizumab in the treatment of AD

Trial	Study design	Main endpoints	Main results	Main adverse events
Phase III (2020) - part A[34]	Randomized, double-blind, placebo-controlled *N* = 215 adolescents and adults 2:1 60 mg Q4W Placebo Q4W 16 weeks Concomitant use of continuous topical therapy (TCS or TCI)	Primary: % change from baseline in pruritus VAS score at week 16 Secondary: % change from baseline in EASI score at week 16	Nemolizumab group showed significantly superior improvements in pruritus VAS score versus placebo (-42.8% versus -21.4%; p < 0.001) Nemolizumab group showed greater improvements in EASI score versus placebo (-45.9% versus -33.2%)	Worsening of AD (24%), injection-related reactions (8%), skin infection (7%), elevated creatine kinase (3%)
Phase III (2022) - part B[35]	Open-label *N* = 206 adolescents and adults 60 mg Q4W 52 weeks Concomitant use of continuous topical therapy (TCS or TCI)	Secondary: % change from baseline in pruritus VAS and EASI scores at week 68	% changes in pruritus VAS score were maintained from week 16 to week 68 (-65.9%) % changes in EASI score were maintained from week 16 to week 68 (-78.2%)	Nasopharyngitis (33.9%), AD exacerbations (25.2%), increased blood creatine phosphokinase (9.1%)*
Phase III (2022)[35]	Open-label *N* = 88 adolescents and adults 60 mg Q4W self-injection from week 12 onward 60 mg Q4W administered by medical professionals through the duration of the study 52 weeks Concomitant use of continuous topical therapy (TCS or TCI)	Secondary: % change from baseline in pruritus VAS and EASI scores at week 52	Self-injection group provided similar clinical responses to those who continued to receive injections from health care professionals, with consistent reductions in pruritus VAS and EASI scores from baseline up to week 52	Nasopharyngitis (33.9%), AD exacerbations (25.2%), increased blood creatine phosphokinase (9.1%)*

Phase III (2023)[36]	Randomized, placebo-controlled, double-blind *N* = 89 pediatric patients 1:1 30 mg Q4W Placebo Q4W 16 weeks Concomitant use of continuous TCS	Primary: change from baseline in 5-level itch score at week 16 Secondary: % change from baseline in EASI score at week 16	Nemolizumab group achieved significantly greater change in 5-level itch score versus placebo (-1.3 versus -0.5; p < 0.0001) Nemolizumab group showed greater improvements in EASI score versus placebo (-52.4% versus -41.5%; p = 0.2101)	AD exacerbations (10.9%), upper respiratory tract inflammation (8.7%), erythema (6.5%), nasopharyngitis (6.5%)
ARCADIA 1 and 2[37]	Randomized, placebo-controlled, double-blind *N* = 941 (ARCADIA 1) and 787 (ARCADIA 2) adolescents and adults *16-week induction period* 2:1 60 mg loading dose at baseline, then 30 mg Q4W Placebo Q4W *32-week maintenance period* Re-randomization of responders 1:1:1 30 mg Q4W 30 mg Q8W Placebo Q4W Concomitant use of continuous topical therapy (TCS-TCI)	Primary: % patients with IGA 0/1 with reduction of ≥ 2 points and EASI-75 at week 16 Secondary: % patients with ≥ 4-point reduction in PP-NRS at week 16, % patients with ≥ 4-point reduction in SD-NRS at week 16	Significantly higher % of patients receiving nemolizumab plus TCS-TCI achieved IGA success versus placebo plus TCS-TCI [36% (p = 0.0003) versus 25% in ARCADIA 1; 38% (p = 0.0006) versus 26% in ARCADIA 2], as well as EASI-75 [44% (p < 0.0001) versus 29% in ARCADIA 1; 42% (p = 0.0006) versus 30% in ARCADIA 2] at week 16 Significantly higher % of patients receiving nemolizumab plus TCS-TCI achieved a ≥ 4-point reduction in PP-NRS versus placebo plus TCS-TCI [43% (p < 0.0001) versus 18% in ARCADIA 1; 41% (p < 0.0001) versus 18% in ARCADIA 2] at week 16 Significantly more patients on nemolizumab plus TCS-TCI achieved a ≥ 4-point reduction in SD-NRS versus placeblo plus TCS-TCI [38% (p < 0.0001) versus 20% in ARCADIA 1; 34% (p < 0.0001) versus 16% in ARCADIA 2] at week 16	Worsening of AD (7 to 12%), worsening of asthma (2 to 5%), peripheral or facial edema (1 to 2%)

*The reported percentages of the main adverse events are identical, as the analysis included participants from both clinical trials combined.

AD, Atopic dermatitis; EASI, Eczema Area and Severity Index; EASI-75, ≥ 75% improvement in Eczema Area and Severity Index; IGA 0/1, Investigator's Global Assessment score of 0 (clear) or 1 (almost clear); IGA, Investigator's Global Assessment; PP-NRS, Peak Pruritus Numeric Rating Scale; Q4W, Every

4 weeks; Q8W, Every 8 weeks; SD-NRS, Sleep Disturbance Numerical Rating Scale; TCI, Topical calcineurin inhibitors; TCS, Topical corticosteroids; VAS, Visual analogue scale.

Table III Ongoing clinical trials investigating nemolizumab for the treatment of AD

ClinicalTrials.gov	Title	Phase	Estimated enrollment (*n*)	Status	Estimated study completion date
NCT04921345[33]	A Multicenter, Open-Label, Single-Group Clinical Trial to Assess the Pharmacokinetics, Safety and Efficacy of Nemolizumab (CD14152) in Pediatric Subjects (Aged 2 to 11 Years) With Moderate-to-Severe Atopic Dermatitis	Phase II	105	Recruiting	July 2025
NCT03989206[38]	A Prospective, Multicenter, Long-Term Study to Assess the Safety and Efficacy of Nemolizumab (CD14152) in Subjects With Moderate-to-Severe Atopic Dermatitis	Phase III	1700	Active, not recruiting	31st August 2026

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