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TIME TO GET HANDS ON:
DELGOCITINIB'S PROMISE FOR
CHRONIC HAND ECZEMA

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VEHICLES MATTER



Leon Kircik MD

Chronic hand eczema (CHE), which affects up to 10% of the United States population annually, encompasses a diverse range of presentations. Designation of the condition as “chronic” owes to its persistence or its recurrence (at least two recurrences per year after the initial presentation).¹

Primary symptoms of CHE may include erythema, scaling, fissures, and itch. The potential impact on patients of these symptoms is easy to imagine. The chronic nature of the condition only serves to intensify this negative impact. One comprehensive review linked CHE with inability to work, absenteeism, and negative impacts on health-related quality of life.² Itch and pain attributed to CHE are associated with high rates of sleep disruption.³ Yet, data show that up to half of affected individuals have not sought medical care for the condition.²

Management of CHE can be complicated by numerous factors, including the possibility that contact irritants or allergens—including occupational exposures—contribute to the condition.² Additionally, there have been few effective directed treatment options available for the condition, and some of the most widely used treatments have potential limitations, including systemic exposure or tolerability concerns.

A promising new agent for treating CHE was approved by the FDA in the US in August 2025 and is now available. Delgocitinib (Anzupgo) is a pan-JAK inhibitor in a topical formulation that is intended for twice-daily application.

Among the promising data reviewed in the pages ahead, a pooled analysis of phase 3 trials for delgocitinib cream 20 mg/g in moderate to severe CHE shows benefit across all CHE subtypes. Within the initial 16-week treatment period, 42.0% of patients achieved an IGA-CHE treatment success (TS) at least once, increasing to 59.9% after 52 weeks of treatment. Additionally, 66.5% of patients reached a hand eczema severity index-75 (HECSI-75) at least once by week 16, increasing to 83.5% by week 52.⁴

Vehicles matter!

In the case of delgocitinib for CHE, the topical cream formulation appears to have two important features. First, this vehicle is associated with reduced systemic exposure to the active drug. While oral JAK inhibitors are used safely for dermatologic and other indications, there are theoretical concerns about systemic exposure from topical JAK inhibitors. Therefore, a formulation that limits systemic exposure is welcomed by patients and prescribers alike.

Additionally, the cream formulation, which has been shown to be well-tolerated, is convenient for patients. With its twice-daily application schedule, the moisturizing cream may provide soothing benefits for inflamed skin while avoiding greasiness or dryness.

Enhanced drug development focused on CHE has brought greater attention to this somewhat common disease and its burden on affected patients. The need for safe and directed treatment is clear. Evidence shows that topical delgocitinib cream is poised to fill a gap in patient care by offering an effective therapy in a moisturizing, convenient formulation base that is well-tolerated.

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The Utility of Delgocitinib in Chronic Hand Eczema

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ABSTRACT

Chronic hand eczema (CHE) affects up to 10% of the general population and is associated with significant physical discomfort, impaired hand function, and reduced quality of life, yet effective long-term treatment options remain limited. Delgocitinib cream, a nonsteroidal topical pan-JAK inhibitor, has demonstrated high efficacy and safety in adult Phase 3 pivotal trials, significantly improving clinical signs, symptoms, and quality of life for patients across diverse CHE subtypes. Comparative studies suggest delgocitinib offers superior or similar benefits to systemic therapies like the oral retinoid alitretinoin and the biologic dupilumab, with negligible systemic exposure. These findings support delgocitinib cream as an innovative and promising topical therapy addressing a critical unmet need in CHE patient management.

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INTRODUCTION

Chronic hand eczema (CHE) is a common, relapsing inflammatory skin condition characterized by redness, scaling, fissures, and intense itching or pain that can severely impair hand function and quality of life.^{1,2} It often persists for more than three months or recurs at least twice in a calendar year. High-risk individuals tend to be those with occupational exposure to irritants or allergens.³ Despite its prevalence and impact on patients' lives, treatment options are limited, with many patients showing inadequate response or intolerance to topical corticosteroids and systemic immunosuppressants. As a result, there is a significant unmet need for effective, well-tolerated, safe nonsteroidal therapies that provide long-term disease control with minimal systemic risk.⁴ This manuscript describes the underlying pathophysiology and clinical phenotypes of CHE, highlighting the complexity and heterogeneity of the disease both from a diagnostic and therapeutic perspective. It also discusses delgocitinib, a topical pan-JAK inhibitor, as the first treatment specifically indicated for CHE approved by the European Medicines Agency (EMA),⁵ and approved by the FDA in the US in August 2025, offering a multi-pronged anti-inflammatory mechanism and a favorable therapeutic option for this challenging and often debilitating condition.

Epidemiology and Burden of CHE

Hand eczema (HE) is a common inflammatory skin condition with a 1-year prevalence of approximately 9 to 10% in the general population and a lifetime prevalence of up to 14.5%.^{6,7} Prevalence is higher in women, likely due to differences in occupational and domestic exposures.^{6,8-10} Moderate to severe disease affects over one-third of patients, and around one-third have a history of atopic dermatitis.⁷ In children and adolescents, the 1-year prevalence ranges from 5.2% to 10%, with higher risk linked to female sex, childhood eczema, and family history of atopic disease.³ Among individuals aged 70 years and older, 2.7% reported a lifetime diagnosis of hand eczema.

The observational Chronic Hand Eczema epidemiology, Care, and Knowledge of real-life burden (CHECK) study estimated the annual prevalence of CHE across 6 European countries and Canada using a consistent definition and representative sampling.¹¹ Among over 60,000 adults surveyed, 4.7% reported physician-diagnosed CHE, with higher prevalence observed in females, urban residents, employed individuals, and those aged 30 to 39. These findings highlight CHE as a common and potentially underrecognized condition with important demographic patterns.

CHE is often a long-lasting disease, with a median duration of 11 to 16 years, characterized by recurrent flares with heightened inflammation, itching, and pain—especially due to fissures.⁴ Patients may also experience swelling. These symptoms significantly impair quality of life, with patients reporting physical discomfort, emotional and psychological distress, and functional limitations, often exacerbated by comorbid skin diseases like atopic dermatitis. The psychosocial impact includes anxiety, embarrassment, depression, suicidal ideation, and strained relationships, which can lead to social withdrawal and negatively influence broader life decisions.⁴ Given CHE's localization on the hands (including fingers and wrists) and frequent connection to occupational exposures, it also imposes a substantial economic burden on individuals and society. Studies show annual societal costs per patient in Europe ranging from €1,813 to €7,738, largely due to job loss, absenteeism, and presenteeism.¹² Up to 57% of patients report taking sick leave, and up to 25% change or leave their jobs because of CHE. Even among those who remain employed, reduced work performance is common, driven by fears of job insecurity and disease severity.

Itch is the most frequently reported symptom in chronic hand eczema (CHE), often leading to scratching and secondary symptoms such as bleeding, erythema, and flaking, or even infection.^{13,14} It is also a common cause of sleep disruption and affects up to 78.1% of patients, with a higher prevalence in females.¹⁵ Itch severity correlates closely with overall disease severity and is frequently associated with eczema flares. Pain is another significant and under-recognized burden in CHE, with a reported prevalence of 36 to 53% and a strong correlation with IGA-CHE and HECSI severity scores.¹⁵ In a study of 1,032 CHE patients and 11,166 controls from the Danish Skin Cohort, analgesic use was consistently higher in CHE patients, particularly those with more severe disease.¹⁶ Paracetamol and NSAIDs were the most commonly used analgesics, highlighting the need to address pain alongside inflammation and itch in CHE management.

Clinical Phenotypes and Histology of CHE

CHE is a heterogeneous condition with multiple clinical/morphological and etiological subtypes, each with distinct triggers and presentations.^{17,18} The most common subtype is irritant contact dermatitis (ICD), caused by repeated exposure to irritants such as water, soaps, and chemicals. ICD typically affects the backs of the hands, fingers, and interdigital spaces, presenting with erythema, scaling, fissures, and itch. Allergic contact dermatitis (ACD) results from exposure to allergens, which may be identified through patch testing and often affects the dorsum hands, palms, and fingertips with vesicles and localized pain. Atopic hand eczema, which can be associated with a personal or family

history of atopic dermatitis, may present in vesicular or lichenoid forms, often involving the hands, wrists, feet, and flexural areas. Contact urticaria/protein contact dermatitis is another subtype. Contact urticaria is an immediate (Type I) hypersensitivity reaction characterized by transient erythema, edema, and wheals at the site of allergen exposure. Protein contact dermatitis is considered the chronic form of contact urticaria involving both immediate (Type I) and delayed (Type IV) hypersensitivity responses to high-molecular-weight proteins. While it may initially present with urticarial symptoms akin to contact urticaria, it typically progresses to CHE after repeated exposures.¹⁹

Additional clinical forms include hyperkeratotic HE, acute recurrent vesicular HE, nummular HE, and pulpitis. These subtypes vary in appearance but commonly involve fissures, vesicles, scaling, or xerosis on the hands, palms, and fingertips. Notably, the morphology of lesions on the hands does not reliably indicate the underlying cause, and the clinical presentation may change over time despite a stable etiology.^{1,20} This means that clinical diagnosis of CHE is complicated, and a clinician may not be able to accurately identify a single subtype nor its exact cause just by physical exam. Moreover, data suggests that 50% or more of CHE patients have mixed subtypes, adding to the diagnostic and, ultimately, treatment challenges CHE patients and their clinicians experience.

Lifestyle and environmental exposures significantly influence disease course. Smoking is a major aggravating factor, especially for vesicular and hyperkeratotic HE, and is associated with increased severity and work-related impairment.²¹ Smokers have an increased propensity for combined allergic and irritant contact dermatitis, with the hyperkeratotic form being the most prevalent morphological subtype.²² A meta-analysis of 17 studies found low-quality evidence linking smoking to higher HE prevalence, while other lifestyle factors such as alcohol use, physical activity, and BMI showed no consistent associations.²³ Stress is also frequently reported by patients as a trigger, and although its role is not fully understood, it appears to contribute to disease persistence and flares.

Occupational hand eczema (OHE) is the most common occupational skin disease, with a prevalence as high as 40% in high-risk professions like healthcare, hairdressing, and cleaning.^{24,25} ICD is the predominant subtype in these settings, often due to repeated wet work and mechanical strain. Accurate diagnosis requires detailed clinical history, exposure assessment, and patch testing. Recent European consensus guidelines have emphasized improving prevention, recognition, and reporting of OHE.

Differentiating CHE from conditions like palmoplantar psoriasis or cutaneous T-cell lymphoma can be challenging.²⁶ Emerging molecular tools, including transcriptomic analysis and CE-marked classifiers, show promise in refining diagnosis.²⁷ Vesicular HE has demonstrated unique gene expression profiles, supporting the idea that it involves distinct immunologic pathways from other eczematous diseases.²⁸

Pathophysiology of CHE

CHE is driven by a complex interplay of skin barrier disruption, environmental triggers, and immune dysregulation, involving both innate and adaptive immune responses. Key pro-inflammatory cytokines such as interleukin (IL)-1 β , IL-6, and tumor necrosis factor-alpha (TNF- α) are upregulated in lesional skin, contributing to keratinocyte activation and inflammatory cell recruitment.²⁹ In CHE subtypes with atopic features, IL-4, IL-13, and IL-31—hallmarks of Th2/Th22-mediated inflammation—are frequently elevated, correlating with pruritus and barrier dysfunction.³⁰ Conversely, hyperkeratotic and irritant forms of CHE show stronger expression of Th1- and Th17-associated cytokines, including interferon-gamma (IFN- γ) and IL-17A, which promote epidermal hyperplasia and neutrophilic inflammation.³⁰ Recent transcriptomic analyses confirm that vesicular hand eczema exhibits a unique gene expression profile with overlap between Th2- and Th17-driven pathways. In allergic contact dermatitis-driven CHE, either the Th1/Th17 or the Th2/Th22 pathways can be activated depending on the specific allergen driving the inflammation, which scientifically explains why it may be difficult to determine subtype or cause from clinical exam alone. Protein contact dermatitis, a less common form of CHE, involves a Type I hypersensitivity reaction with IgE-mediated mast cell activation, leading to immediate urticarial symptoms followed by eczematous lesions.³¹

Despite the molecular and clinical heterogeneity described above, the cytokines central to CHE pathogenesis all signal through the Janus kinase/signal transducer and activator of transcription (JAK/STAT) pathway.³² Th2 cytokines like IL-4 and IL-13 activate JAK1/JAK3–STAT6. In contrast, Th1 (IFN- γ) and Th22 (IL-22) cytokines activate JAK1/JAK2–STAT1/STAT3. This overlap in JAK/STAT-mediated signaling across different CHE subtypes supports the clinical rationale for using JAK inhibitors as potential broad-spectrum therapies targeting both Th2 and non-Th2 pathogenic inflammatory pathways.³³

CHE Treatment Landscape Overview

The treatment landscape for CHE has evolved to include several topical, systemic, and targeted therapies. High-potency topical corticosteroids currently remain the mainstay of therapy. Clobetasol propionate 0.05% foam

achieved clinical improvement in 96.7% of subjects after 15 days in an open-label study.³⁴ Triamcinolone acetonide is also frequently used, though clinical efficacy varies across CHE subtypes.³⁵ Topical calcineurin inhibitors, including tacrolimus 0.1% ointment, have demonstrated benefit in steroid-resistant allergic contact dermatitis (ACD), with one study reporting complete clearance in only 44% of occupational CHE patients.^{36,37} Pimecrolimus 1% cream, evaluated in a randomized, double-blind study of 652 patients, narrowly missed significance for treatment success versus vehicle (29.8% vs 23.2%; $P = 0.057$), but symptom improvements were still observed.³⁸

Among nonsteroidal agents, calcipotriol 0.005% ointment twice daily was shown to be as effective as desoximetasone in a randomized controlled trial.³⁹ The PDE4 inhibitor crisaborole 2% has shown promise in a retrospective chart review of 251 patients with hand atopic dermatitis, where 72.2% experienced symptom improvement, and 61.1% achieved “clear” or “almost clear” status.^{40–42} Notably, ruxolitinib cream, a topical JAK1/2 inhibitor, was evaluated in a randomized, double-blind, vehicle-controlled phase 2 trial in 186 adults with moderate-to-severe CHE excluding AD of the hand. Treatment success (IGA score 0 or 1 with ≥ 2 -grade improvement) was achieved in 53.2% of treated patients vs 10.9% on vehicle ($P < 0.0001$); over 80% showed $\geq 75\%$ improvement in HECSI.⁴³

For more severe or refractory cases, systemic agents are often required. The oral retinoid alitretinoin remains the only drug specifically approved in Europe for severe CHE unresponsive to topical therapy. Clinical trials have shown that daily doses of 10–30 mg can lead to significant improvement or complete remission in up to 48% of patients, with efficacy linked to disease subtype and dose.^{44,45} Off-label use of systemic immunosuppressants such as cyclosporin, methotrexate, and mycophenolate mofetil is guided by clinical judgment and disease severity, but in atopic dermatitis-driven CHE, the safety risks should be considered.^{30,46} Recent biologic developments include the LIBERTY-AD-HAFT phase 3 trial, which evaluated dupilumab in patients with moderate-to-severe hand and foot eczema of the atopic subtype only. Dupilumab-treated patients showed significantly higher rates of clear or almost clear skin (40% vs 17%) and pruritus reduction (52% vs 14%) compared to placebo.⁴⁷

These findings highlight the increasing significance of cytokine-targeted therapies and JAK-STAT pathway modulation in managing CHE across various subtypes. Notably, a study of 724 patients revealed that adverse effects from topical corticosteroids—such as skin atrophy, hypopigmentation, pain, fissures, and symptom worsening—are common, with 76% of patients strongly

preferring nonsteroidal topical alternatives.⁴⁸ Despite these data, there remains a significant unmet need for an approved, nonsteroidal topical treatment specifically studied and indicated for CHE.

Delgocitinib: The First Topical Pan-JAK Inhibitor Designed for the Treatment of Chronic Hand Eczema

Delgocitinib was initially developed as an oral pan-Janus kinase (JAK) inhibitor, targeting all four JAK isoforms—JAK1, JAK2, JAK3, and TYK2—which are integral to cytokine signaling in immune-mediated diseases. While early oral formulations demonstrated systemic target engagement in phase 1 studies, concerns about broad systemic immunosuppression prompted a strategic shift toward a topical formulation to limit systemic exposure.⁴⁹ Topical delgocitinib was first evaluated in patients with atopic dermatitis, where clinical trials showed meaningful improvements in skin inflammation with minimal systemic absorption and a favorable safety profile.⁵⁰⁻⁵² Moreover, topical delgocitinib ointment (0.25% and 0.5% marketed under the brand name Corectim) has been in clinical use in Japan for over 4 years for atopic dermatitis, having successfully treated over 4 million patients with high efficacy and little to no adverse events. Building on this established success, the development program expanded to include CHE.

The safety, tolerability, and pharmacokinetics of delgocitinib were initially evaluated in two phase 1 studies involving adult Japanese males with healthy or atopic dermatitis (AD)-affected skin.⁴⁹ In the first study, delgocitinib (formerly JTE-052) demonstrated a low potential for phototoxicity and showed no evidence of skin irritation or photoallergic reactions. The second study confirmed low systemic exposure in both healthy and AD participants. In AD volunteers, repeated application of 3% delgocitinib ointment twice daily for seven days resulted in peak plasma concentrations (C_{max}) of 3.75 ng/mL on day 1 and 2.89 ng/mL on day 7, measured 4 hours after the morning application.

Delgocitinib bioavailability was specifically evaluated in the context of CHE. A Phase 1 study assessed systemic exposure following twice-daily application of delgocitinib 2% cream for one week in adults with moderate to severe CHE and compared it to systemic exposure data from two Phase 1 trials of oral delgocitinib in healthy adults (1.5–12 mg, NCT05050279; 1–100 mg, NBX1-1).⁵³ Topical delgocitinib resulted in minimal systemic exposure, with C_{max} values of 0.50 ng/mL on day 1 and 0.46 ng/mL on day 8. Relative bioavailability compared to oral administration was only 0.6%, indicating that twice-daily topical application is unlikely to result in clinically meaningful systemic pharmacologic effects in patients with moderate to severe CHE.

Delgocitinib 2% cream was studied as monotherapy for moderate-to-severe CHE in adults (age ≥ 18 years old) over 16 weeks in two phase 3, double-blind, randomized, parallel, vehicle-controlled trials (DELTA 1 and DELTA 2).⁵⁴ Disease severity was determined by the newly validated IGA-CHE scoring system with a score of 3 (moderate) or 4 (severe) required for trial inclusion and treatment success defined as a 2-point drop from baseline and achieving IGA-CHE of 0 (clear) or 1 (almost clear).⁵⁵ Participants were also required to have a HESD itch score of ≥ 4 and have demonstrated either an inadequate response to topical corticosteroids within the past 12 months prior to screening or had any contraindication to their use. Of note, some participants were noted to have a prior history of phototherapy and systemic medication use for CHE, including oral retinoids, corticosteroids, methotrexate, and cyclosporin. CHE subtypes included atopic hand eczema (the majority subtype), allergic contact dermatitis, hyperkeratotic eczema, irritant contact dermatitis, and vesicular hand eczema (pompholyx). Patients were randomized 2:1 to receive either delgocitinib cream 2% twice daily (DELTA 1: $n = 325$, DELTA 2: $n = 314$) or vehicle cream (DELTA 1: $n = 162$, DELTA 2: $n = 159$) for 16 weeks followed by a 2-week safety follow-up period or transfer to the long-term extension (LTE) trial (DELTA 3). Participants were instructed to maintain their usual skin routine, permitting the use of hand emollients. The primary endpoint at week 16 was IGA-CHE treatment success, defined as clear or almost clear (0/1) with ≥ 2 -point improvement and no/barely perceptible erythema and no other signs. In addition to IGA-CHE, HECSI-75 and HECSI-90 were included as clinician-assessed key secondary endpoints. Patient-reported efficacy outcomes included ≥ 4 -point improvement in HESD itch and pain reduction, and ≥ 4 -point improvement in DLQI. Systemic exposure of delgocitinib 20 mg/g cream in CHE specifically was assessed in the DELTA 2 trial.⁵⁶ Blood samples collected at weeks 1, 4, and 16 showed negligible systemic exposure, with a peak geometric mean plasma concentration of 0.21 ng/mL at week 1 (0.20 ng/mL at week 4, 0.12 ng/mL at week 16). In comparison, the lowest oral dose of delgocitinib (1.5 mg) in a Phase 1 study produced a much higher systemic exposure (C_{max} 7.2 ng/mL). All of these values are well below the IC_{50} value for delgocitinib in a human whole blood assay (24.2 ng/mL). The negligible systemic absorption of topical delgocitinib is not by random chance, but careful rational design and selection of the vehicle cream, which does not contain any penetration enhancers.

Pooled analysis showed that a greater proportion of participants treated with delgocitinib achieved IGA-CHE success at week 16 compared to those using vehicle cream (24.3% vs 8.4%).⁵⁷ Delgocitinib also led to higher rates of HECSI-75 (49.4% vs 20.9%), HECSI-90 (30.3% vs 10.6%), and ≥ 4 -point improvement in DLQI (73.3% vs 47.8%) at week 16.⁵⁷

Itch and pain were significantly reduced as early as week 1, with benefits sustained through week 16.⁵⁸ A clinically meaningful ≥ 4 -point reduction in itch was achieved by more participants in the delgocitinib group at both week 2 (14.2% vs 6.3%) and week 16 (47.2% vs 21.5%), with similar improvements observed for pain.⁵⁸ Significant least square (LS) mean reductions from baseline were detected for itch as early as day 1 (0.75 vs 0.32, $P < 0.001$) and for pain by day 3 (0.98 vs 0.58, $P < 0.001$), highlighting the rapid clinical relief patients may experience. A post hoc analysis further demonstrated a deep clinical response where 30.0% and 9.4% of patients achieved a HESD itch of 0 or 1, 35.2% and 16.0% achieved HESD pain 0 or 1, and 33.3% and 13.9% achieved a DLQI score of 0 or 1 at week 16 for delgocitinib and vehicle cream groups, respectively.⁵⁹ Impressively, 19.2% of patients in the delgocitinib group met all three deep response criteria simultaneously, and nearly 25% demonstrated consistent response defined as a 4-point or greater reduction in HESD itch or pain scores, or achieving Hand Eczema Severity Index-75 (HECSI-75) at weeks 4, 8, 12, and 16.

A pooled subanalysis of the Phase 3 DELTA 1 and DELTA 2 trials evaluated the effect of delgocitinib cream on individual clinical signs and specific regions of the hand and wrist affected by CHE.⁶⁰ Median improvements in HECSI sign subscores—erythema, infiltration/papulation, vesicles, fissures, scaling, and edema—were consistently greater in the delgocitinib group compared to vehicle, with statistically significant differences emerging as early as week 1. By week 16, median improvements from baseline in all sign subscores ranged from 50% to 100%. Similarly, HECSI subscores for anatomical regions (back of hand, fingers, fingertips, palm, and wrist) showed significantly greater improvements with delgocitinib from week 2 onward. At week 16, these regional subscores demonstrated a 75% to 100% median improvement from baseline. These findings support the broad and rapid efficacy of delgocitinib cream across both clinical signs and anatomical sites in CHE.

Delgocitinib was further evaluated in a long-term, open-label extension (LTE) study (DELTA 3) following the DELTA 1 and DELTA 2 trials, with the objective of assessing long-term safety and efficacy over 36 weeks using twice-daily, as-needed application.⁶¹ Adults who completed DELTA 1 or DELTA 2 were eligible. Those previously in the vehicle group switched over to delgocitinib. Participants initially receiving delgocitinib who achieved an IGA-CHE score of 0/1 (clear/almost clear) at DELTA 3 baseline discontinued treatment, while those with IGA-CHE ≥ 2 (mild to severe disease) continued receiving delgocitinib. Treatment was reinitiated upon disease flare (IGA-CHE ≥ 2), establishing a dynamic, response-driven treatment regimen. A total of 801 participants enrolled in DELTA 3. Among those previously

treated with delgocitinib who entered DELTA 3 with IGA-CHE 0/1, 40.6% and 28.3% maintained clear/almost clear status without treatment at weeks 4 and 8, respectively. These responders remained off treatment for a mean of 111.3 days, compared to 24.9 days in baseline nonresponders (IGA-CHE ≥ 2). Among responders who required reinitiation of therapy, the median time to regain IGA-CHE 0/1 status was approximately 8 weeks. Additionally, 48.1% of baseline nonresponders previously treated with delgocitinib and 54.4% of those previously on vehicle cream achieved IGA-CHE 0/1 at least once during the 36-week LTE.

Over the 36-week treatment period, the proportion of patients achieving IGA-CHE 0/1 among prior delgocitinib-treated participants was sustained (24.6% at baseline vs 30.0% at week 36) and increased substantially among those previously treated with vehicle (9.1% at baseline vs 29.5% at week 36). Similar trends were observed for HECSI-75 (51.8% to 58.6% for delgocitinib; 23.7% to 51.5% for vehicle) and HECSI-90 (31.8% to 36.6% for delgocitinib; 12.0% to 35.7% for vehicle), indicating consistent efficacy across multiple clinical endpoints. Furthermore, in a post-hoc analysis, 32.9% of patients who achieved complete clearance (IGA-CHE 0) maintained clear or almost clear skin (IGA-CHE 0/1) for 8 weeks after stopping treatment, suggesting potential remittive effect allowing for intermittent therapy or treatment holidays.⁵⁹

Treatment response to delgocitinib cream was evaluated across CHE subtypes—including atopic, hyperkeratotic, irritant contact dermatitis, allergic contact dermatitis, and vesicular—in a pooled analysis of the Phase 3 DELTA 1, DELTA 2, and DELTA 3 trials.⁶² Among participants, 27.7% had more than one CHE subtype. Within the initial 16-week treatment period, 42.0% of patients achieved an IGA-CHE treatment success (TS) at least once, increasing to 59.9% after 52 weeks of treatment. Similarly, 66.5% of patients reached HECSI-75 at least once by week 16, increasing to 83.5% by week 52. Clinical responses were consistently observed across all CHE subtypes, with improvements continuing over time. These findings underscore the sustained and broad efficacy of delgocitinib 2% cream in treating mild to moderate to severe CHE across diverse clinical subtypes.

Oral alitretinoin is currently the only approved systemic treatment for severe CHE in the European Union. The phase 3 DELTA FORCE trial was designed to directly compare the efficacy and safety of topical delgocitinib cream with 30 mg oral alitretinoin in patients with severe CHE in a head-to-head study.⁶³ Adults aged 18 years or older with severe CHE (defined as IGA-CHE score of 4) were randomized to receive delgocitinib 2% cream applied twice daily ($n=250$) or alitretinoin 30 mg taken once daily ($n=253$), for up to 24

weeks. The primary endpoint was the change from baseline to week 12 in HECSI score. At week 12, the least squares (LS) mean reduction in HECSI score was significantly greater in the delgocitinib group (−67.6) compared with the alitretinoin group (−51.5), yielding a treatment difference of −16.1 points (95% CI −23.3 to −8.9; $P < 0.0001$). Key secondary clinical endpoints further supported the superior efficacy of delgocitinib, with higher proportions of patients achieving HECSI-90 (38.6% vs 26.0%) and IGA-CHE 0/1 (27.2% vs 16.6%) compared to alitretinoin. Additionally, LS mean reductions in HESD-assessed itch and pain at week 12 were significantly greater with delgocitinib (−3.0 vs −2.4, $P = 0.005$ for itch; −2.9 vs −2.3, $P = 0.018$ for pain). Notably, improvements across all efficacy endpoints were observed as early as week 1 and remained consistently superior to alitretinoin throughout the treatment period. Safety analysis favored delgocitinib, with fewer patients reporting adverse events (49%) compared to those receiving alitretinoin (76%). The most frequently reported adverse events were headache (4% with delgocitinib vs 32% with alitretinoin), nasopharyngitis (12% vs 14%), and nausea (<1% vs 6%). In addition, more treatment discontinuations occurred with alitretinoin compared with delgocitinib. These results support delgocitinib 2% cream as an effective topical therapeutic option for patients with severe CHE, potentially offering a safer and more effective alternative to systemic therapy like oral alitretinoin.

A matching-adjusted indirect comparison (MAIC) was conducted to evaluate the efficacy of topical delgocitinib 2% cream versus systemic dupilumab in patients with atopic hand eczema (AHE), due to the absence of direct head-to-head trials.⁶⁴ Data from the DELTA 1 and 2 Phase 3 trials of delgocitinib were matched to the LIBERTY-AD-HAFT trial of dupilumab using individual patient data and aggregate published data, with adjustments for age, sex, race, and baseline HECSI score. Key endpoints included HECSI 75, HECSI 90, percent improvement from baseline, and investigator global assessments. While none of the differences reached statistical significance, all point estimates—including for HECSI responses and IGA scores—were numerically in favor of delgocitinib. The effective matched sample size included 201 patients, showing comparable efficacy between the topical and systemic treatments at week 16. These findings suggest that delgocitinib cream offers similar clinical benefits to dupilumab for AHE, while providing a non-systemic, topical alternative with comparable outcomes.

In addition to achieving key clinical endpoints, delgocitinib demonstrated molecular efficacy in a Phase 2a trial through gene expression profiling of treated skin biopsy samples.⁶⁵ Severe CHE was characterized by downregulation of skin barrier genes (eg, *FLG2*, *LORICRIN*) and upregulation of inflammatory pathway genes. Topical delgocitinib signifi-

cantly normalized the expression of Th1, Th2, Th17, and JAK pathway genes, while also restoring markers of skin barrier integrity. In contrast, vehicle-treated patients showed no meaningful changes in gene expression. These findings highlight delgocitinib's dual mechanism of action, targeting both immune dysregulation and barrier dysfunction, and support its role as a disease-modifying nonsteroidal topical therapy for CHE.

CONCLUSION

Despite the significant burden of CHE, effective and safe long-term treatment options remain limited. Delgocitinib 2% cream has emerged as a well-tolerated, highly effective topical nonsteroidal therapy for adults with mild-to-moderate-to-severe CHE, demonstrating rapid and sustained clinical improvements across diverse subtypes and patient populations. Its favorable safety profile, (no box warning), negligible systemic absorption, and comparable or superior efficacy to systemic agents such as dupilumab and alitretinoin position it as an encouraging alternative for long-term disease management. Two upcoming Phase 3 trials — DELTA Kids (NCT06319237) in children aged 2–11 years and DELTA Teens (NCT06319250) in adolescents aged 12–17 years — will evaluate the safety, pharmacokinetics, and efficacy of delgocitinib cream in younger populations, potentially expanding access of this topical JAK inhibitor to pediatric CHE population.

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