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ADISINSIGHT REPORT

Delgocitinib: First Approval

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Abstract
Delgocitinib, a janus kinase (JAK) inhibitor, is being developed by Japan Tobacco for the treatment of autoimmune disorders and hypersensitivity, including inflammatory skin conditions. The JAK family of tyrosine kinases plays an important role in mediating the biological effects of several inflammatory cytokines, e.g. IL-4, IL-13 and IL-31, which are elevated in patients with atopic dermatitis. Delgocitinib inhibits all members of the JAK family [JAK1, JAK2, JAK3 and tyrosine kinase 2]. Topical delgocitinib (Corectim®) is approved in Japan for the treatment of atopic dermatitis. This article summarizes the milestones in the development of delgocitinib leading to this first approval for the treatment of adults with atopic dermatitis. Clinical development of the topical formulation is also underway for alopecia areata, chronic hand eczema, discoid lupus erythematosus, inverse psoriasis and atopic dermatitis in several countries worldwide. Clinical development of an oral formulation of delgocitinib is also underway in Japan for the treatment of autoimmune disorders and hypersensitivity.

Delgocitinib: Key points

A JAK inhibitor being developed by Japan Tobacco for the treatment of autoimmune disorders and hypersensitivity, including inflammatory skin conditions

Received its first approval on 23 January in Japan

Approved for use in adults with atopic dermatitis

1 Introduction

Atopic dermatitis is a chronic inflammatory skin disease characterized by pruritis and symptoms that fluctuate with remissions and relapses [1, 2]. Skin barrier function is reduced in patients with atopic dermatitis, resulting in increased skin irritability to non-specific stimuli, frequently causing inflammation [2]. Reduced skin barrier function may be because of filaggrin gene mutations or reduced expression of filaggrin due to the presence of T-helper (Th)2 cytokines, such as interleukin (IL)-4, IL-13 and IL-31, in skin tissues. The Th2-type immune responses may develop in response to allergens, such as mites and pollen that that contain proteases [2].

The goal of treatment in patients with atopic dermatitis is to achieve and maintain a state in which symptoms are absent or mild and do not affect daily activities, and drug therapy is not required [2]. Topical treatment options include pharmacological options [e.g. topical corticosteroids, topical calcineurin inhibitors (e.g. topical tacrolimus and pimecrolimus ointment), topical antimicrobials and antiseptics, and topical antihistamines] and nonpharmacological options (e.g. moisturizers, wet-wrap therapy) [3]; however, currently there is no treatment option that completely cures the disease [2].

Topical agents (topical corticosteroids and topical tacrolimus) are the mainstay of treatment, recommended as first-line induction therapy to control pruritis and inflammation

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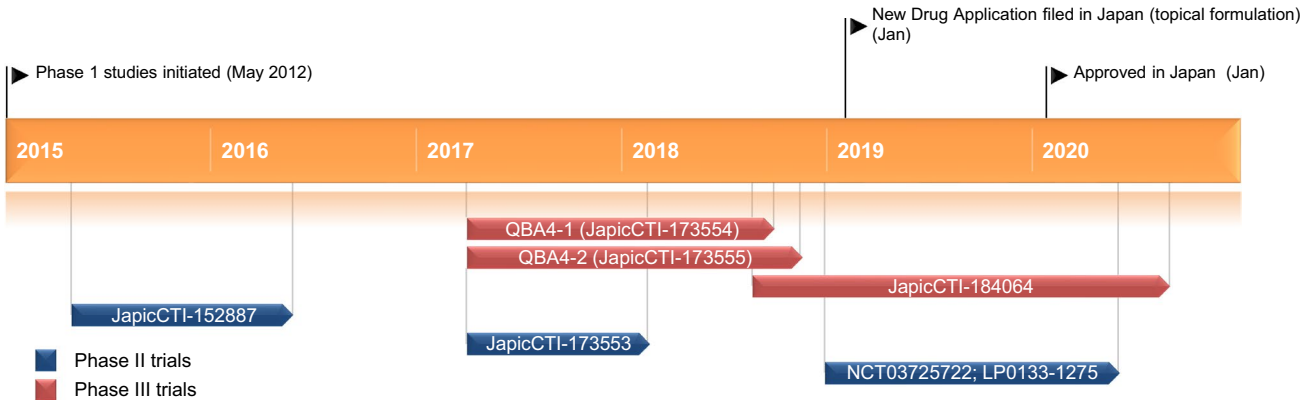


Key milestones in the development of delgocitinib for the treatment of atopic dermatitis

after diagnosis and during flares, as well as during maintenance therapy for disease persistence or frequent recurrences [3]. However, topical agents are associated with safety concerns. Chronic use of topical corticosteroids may be associated with skin atrophy and if absorbed to a sufficient degree may cause systemic side effects, such as hypothalamic-pituitary-adrenal axis suppression [2]. Topical calcineurin inhibitors are often associated with stinging and burning, and there have been rare cases of malignancy (e.g. skin cancer and lymphoma), although a causal relationship has not been established [3]. Thus, there is an unmet need for effective treatments with safer tolerability profiles.

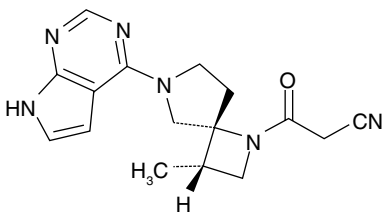
The JAK-signal transducer and activator of transcription (STAT) signalling pathway plays an important role in mediating the biological effects of several inflammatory cytokines, e.g. IL-4, IL-13 and IL-31, which are elevated in patients with atopic dermatitis. Delgocitinib is a novel agent that inhibits all members of the Janus Kinase (JAK) family. It is being developed by Japan Tobacco, for the treatment of autoimmune disorders and hypersensitivity, including inflammatory skin conditions. Topical delgocitinib 0.5% ointment (Corectim®) received its first approval in Japan for the treatment of adults with atopic dermatitis [4]. Delgocitinib (maximum dose 5 g per application) is to be applied to the affected area twice daily. This article summarizes the milestones in the development of delgocitinib leading to this first approval for the treatment of adults with atopic dermatitis. Clinical development of the topical formulation is also underway for alopecia areata, chronic hand eczema, discoid lupus erythematosus, inverse psoriasis and atopic dermatitis in several countries worldwide. Clinical development of an oral formulation of delgocitinib is also underway in Japan for the treatment of autoimmune disorders and hypersensitivity.

1.1 Company Agreements

LEO Pharma entered into an agreement with Japan Tobacco in November 2014, under which LEO Pharma gained the exclusive global license to develop, register and commercialize the topical formulation of delgocitinib for dermatological indications worldwide, excluding Japan where Japan Tobacco retained the rights. Japan Tobacco was eligible to an upfront payment, development and sales milestones and royalties on sales [5].

In October 2016, Japan Tobacco and Torii Pharmaceutical entered into an exclusive agreement for the co-development and commercialization of delgocitinib for topical use in dermatological disorders in Japan. The companies were to jointly develop delgocitinib in Japan; Torii agreed to commercialize it once the development and necessary approval procedures had been completed. Torii was to pay Japan Tobacco upfront licensing fees and payments upon the achievement of certain milestones [6].

In March 2018, Japan Tobacco signed an exclusive license agreement with Rohto Pharmaceutical for the development and commercialization of delgocitinib for the treatment of the specific diseases in ophthalmology in Japan. Rohto pharmaceutical agreed to initiate development of delgocitinib in these indications from a non-clinical stage [7].



Chemical structure of delgocitinib

Features and properties of delgocitinib	
Alternative names	Corectim®; JTE-052; JTE-052A; LEO 124249; LP-0133
Class	Antiallergics; antipsoriatics; nitriles; pyrimidines; pyrroles; skin disorder therapies; spiro compounds
Mechanism of Action	Janus kinase inhibitor
Route of Administration	Topical; oral
Pharmacodynamics	Inhibits the JAK family (JAK1, JAK2, JAK3 and Tyk 2) enzymes in an ATP-competitive manner
	Inhibits IL-2, IL-6, IL-23, GM-CSF and IFN α signalling
	Inhibits activation of inflammatory cells, such as T cells, B cells, monocytes and mast cells, and inhibits Th1-, Th2- and Th17-type cytokine production from both T cells and non-T cells
Pharmacokinetics	At weeks 4, 12, 28 and 52, plasma levels of delgocitinib were detected in 11.9%,15.8%, 14.2% and 11.5% of patients
	The protein binding of delgocitinib in human plasma was 21.8–29.1%
Adverse events	
Most common treatment emergent	Nasopharyngitis, contact dermatitis and acne
Most common treatment related	Application-site folliculitis, application site acne and application-site irritation
Serious treatment related	Kaposi's varicelliform eruption
ATC codes	
WHO ATC code	D11 and D11A (other dermatological preparations); D11A-H (agents for atopic dermatitis, excluding corticosteroids); L04 (immunosuppressants); V03 (all other therapeutic products)
EphMRA ATC code	D11 and D11A (other dermatological preparations); L4 (immunosuppressants); V3 (all other therapeutic products)
Chemical Name	3-[(3 *S*, 4 *R*) -3-Methyl-6- (7 *H* -pyrrolo [2,3- *d*] pyrimidin-4-yl) -1,6-diazaspiro [3.4] octan-1-yl] -3-oxopropanenitrile

ATP adenosine triphosphate, *GM-CSF* granulocyte/macrophage colony stimulating factor, *IL* interleukin, *IFN* interferon, *Th* T-helper, *Tyk* tyrosine kinase

2 Scientific Summary

2.1 Pharmacodynamics

In in vitro studies, delgocitinib inhibited the JAK family [JAK1, JAK2, JAK3 and tyrosine kinase (Tyk) 2] enzymes in an adenosine triphosphate (ATP)-competitive manner and inhibited IL-2, IL-6, IL-23, granulocyte-macrophage colony-stimulating factor and interferon α signalling [8]. Delgocitinib inhibited the activation of inflammatory cells, such as T cells, B cells, monocytes and mast cells [8] and inhibited Th1-, Th2- and Th17-type cytokine production from both T cells and non-T cells [9]. It inhibited cytokine-induced STAT3 phosphorylation, improved skin barrier function and enhanced keratinocyte terminal differentiation, as indicated by increased levels of proteins, such as profilaggrin, filaggrin monomer and loricrin [10].

In vivo, oral delgocitinib inhibited the inflammatory response in mice with more potency than tofacitinib (50% effective dose of 0.24 vs. 1.1mg/kg when administered 1 h prior to IL-2 injection) and ameliorated collagen-induced arthritis in rats [8]. Oral delgocitinib 3 and 30 mg/kg inhibited ear swelling in a dose-dependent manner ($p < 0.05$ vs. vehicle on day 11) and with greater efficacy than that of ciclosporin [which showed no clear inhibitory effect at the maximum tolerated dose (MTD) of 30 mg/kg] and appeared to be more effective than methotrexate (inhibited ear swelling at the MTD of 1 mg/kg) in murine models of atopic dermatitis and psoriasis-like dermatitis [9]. Oral delgocitinib also inhibited antigen-specific T cell activation and subsequent inflammation in acquired skin immunity, such as contact hypersensitivity [11]. Topical application of delgocitinib increased the levels of natural moisturising factors and ameliorated spontaneous atopic dermatitis-like skin inflammation and barrier disruption in murine models of atopic dermatitis and dry skin, and in a human skin graft model [10]. Topical application of delgocitinib 0.3% and 3% ointment reduced ear swelling in a rat model of chronic dermatitis ($p < 0.01$ vs. placebo for 3% ointment and $p < 0.01$ vs. non administration for 0.3% ointment); tacrolimus 0.1% ointment also reduced ear swelling ($p < 0.01$ vs. non administration).

A phase 1 study (QBX1-1) in 22 healthy volunteers showed that delgocitinib had no potential for skin irritation or photoallergy and had a low potential for phototoxicity [12].

2.2 Pharmacokinetics

The pharmacokinetics of multiple dose delgocitinib (maximum 5 g twice daily) was assessed in patients with atopic dermatitis. Following repeat application, plasma levels of delgocitinib were detected in 11.9% (59/494) of patients

at week 4, 15.8% (65/411) of patients at week 12, 14.2% (54/380) of patients at week 28 and 11.5% (30/262) of patients at week 52 [4]. The peak plasma concentration of delgocitinib was 10.8, 13.1, 13.3 and 7.3 ng/mL at weeks 4, 12, 28 and 52 of application, respectively. The protein binding of delgocitinib in human plasma was 21.8–29.1%. In vitro studies showed that delgocitinib is not metabolized in human skin microsomes and human hepatocytes; it is metabolized to a small extent in human liver microsomes, mainly by CYP3A4. Following intravenous administration of radiolabelled delgocitinib in rats, 45.6% of administered radioactivity is excreted in the urine and 57.1% is excreted in the faeces by 168 h; in dogs, after intravenous administration of radiolabelled delgocitinib, 68.6% of the radioactivity dose is excreted in the urine and 27.5% is excreted in the faeces by 168 h. Delgocitinib is a substrate of P glycoprotein, the organic anion transporter 3 and the organic cation transporter 2 in in vitro studies [4].

2.3 Therapeutic Trials

2.3.1 Phase 3 Trials

Delgocitinib 0.5% ointment twice daily improved clinical signs and symptoms of disease in Japanese patients with moderate to severe atopic dermatitis [investigators global assessment (IGA) score of 3 or 4] who were participating in the randomized, double-blind, multicentre, 2-part, phase 3 QBA4-1 (JapicCTI-173554) trial [13]. Patients (aged ≥ 16 years) with modified Eczema Area Severity Index (mEASI) score of ≥ 10 and inflammatory eczema affecting 10% to < 30% of the body surface area (BSA) received delgocitinib ($n = 106$) or vehicle ($n = 52$) for 4 weeks (part 1). Those who completed treatment could enter a 24-week extension (part 2), as could patients who did not complete therapy because of worsening of symptoms.

At the end of treatment (EOT, i.e. week 4 or treatment discontinuation), the mEASI score was significantly reduced with delgocitinib relative to vehicle [least-squares mean (LSM) percentage change from baseline −44.3% vs. +1.7%; $p < 0.001$; primary endpoint], with significant reductions seen from week 1 through week 4 (all $p < 0.001$ vs. vehicle). At least four times as many delgocitinib as vehicle recipients achieved ≥ 50% (mEASI-50; 51.9% vs. 11.5%) and ≥ 75% (mEASI-75; 26.4% vs. 5.8%) improvement from baseline in the mEASI score. The overall (10.4% vs. 3.8%) and face/neck (22.8% vs. 4.0%) IGA response rates were at least twofold higher with delgocitinib than vehicle, where response was defined as an IGA score of 0 (clear) or 1 (almost clear) with ≥ 2-point improvement from baseline. In addition, the daytime and nighttime pruritis score was significantly reduced with delgocitinib than with vehicle from week 1 through week 4 (all $p < 0.01$), with a significant reduction seen by nighttime on day 1 ($p < 0.001$) [13].

A 52-week, open-label, multicentre, phase 3 QBA4-2 (JapicCTI-173555) trial showed that treatment benefits with delgocitinib 0.5% ointment twice daily were maintained during longer-term treatment in 352 Japanese patients (aged ≥16 years) with mild to severe (IGA score of 2–4) atopic dermatitis affecting 5–30% of the body surface area [14]. At week 4, 31.5% and 10.9% of patients had achieved ≥ 50% and ≥ 75% improvement from baseline in the mEASI score, respectively, with the improvements maintained in 42.3% and 22.7% of patients at week 24, and 51.9% and 27.5% of patients at week 52.

Top-line results from a randomized, double-blind phase 3 study (JapicCTI-184064) in paediatric patients (aged 2 to < 16 years) with atopic dermatitis showed that 4 weeks' treatment with delgocitinib ointment was superior to vehicle in improving disease severity, as assessed by the percentage change from baseline in the mEASI score (primary endpoint) [15]. The 4-week double-blind period of the trial is followed by an ongoing 52-week open-label extension period.

2.3.2 Phase 2 Trials

In a 4-week, randomized, multicentre, phase 2 trial (JapicCTI-152887), delgocitinib ointment 0.25%, 0.5%, 1% or 3% ($n = 65$–69 per group) applied twice daily was significantly more effective in reducing disease severity than placebo ($n = 32$) in Japanese patients (aged 16–65 years) with moderate to severe atopic dermatitis [16]. At EOT (week 4 or treatment discontinuation), the LSM percentage change from baseline in the mEASI score with delgocitinib 0.25%, 0.5%, 1% and 3% was −41.7%, −57.1%, −54.9% and −72.9%, respectively compared with −12.2% with vehicle (all $p < 0.001$). In patients treated with reference tacrolimus 0.1% ointment ($n = 30$), the LSM percentage change from baseline was −62.0% (no statistical comparison with delgocitinib was performed) [16].

Another 4-week randomized, double-blind, multicentre phase 2 trial (JapicCTI-173553) showed that delgocitinib ointment improved clinical signs and symptoms of disease in paediatric patients (aged 2–15 years) with at least mild (IGA score of ≥ 2) atopic dermatitis [17]. Patients with an mEASI score of ≥ 5 and inflammatory eczema affecting 5–30% of the body surface area received delgocitinib 0.25% or 0.5% twice daily ($n = 34$ per group) or vehicle ($n = 35$) for 4 weeks. At EOT, the mEASI scores in the delgocitinib 0.25% and 0.5% groups were significantly lower than the score in the vehicle group (LSM percentage change from baseline −54.2% and −61.8% vs. 4.8%; both $p < 0.001$; primary endpoint). The mEASI-50 response rates were approximately twofold higher with delgocitinib 0.25% and 0.5% than with

Key clinical trials of delgocitinib

Drug(s)	Indication	Phase	Status	Location(s)	Identifier	Sponsor
Delgocitinib	Patients with skin diseases and healthy volunteers	1	Completed	Japan	JapicCTI-142494; QBX1-1 and QBX1-2	Japan Tobacco Inc.
Delgocitinib	Atopic dermatitis	1	Recruiting	Canada, USA	NCT03826901; LP0133-1181	LEO Pharma
Delgocitinib, placebo	Atopic dermatitis	2b	Completed	Japan	JapicCTI-152887	Japan Tobacco Inc.
Delgocitinib, placebo	Atopic dermatitis	2	Completed	Japan	JapicCTI-173553	Japan Tobacco Inc.
Delgocitinib, vehicle	Atopic dermatitis	2	Recruiting	Australia, Canada, USA	NCT03725722; LP0133-1275	LEO Pharma
Delgocitinib, vehicle	Alopecia Areata	2	Completed	USA	NCT02561585; EXP-1222	LEO Pharma
Delgocitinib, vehicle	Alopecia Areata	2	Terminated (futility)	Denmark	NCT03325296	LEO Pharma
Delgocitinib, vehicle	Chronic hand eczema	2b	Recruiting	Denmark, Germany, USA	NCT03683719; LP0133-1273	LEO Pharma
Delgocitinib, vehicle	Chronic hand eczema	2a	Completed	Germany	NCT02664805; LP0133-1180; 2015-002079-11	LEO Pharma
Delgocitinib, vehicle	Discoid lupus erythematosus	2	Recruiting	Multinational	NCT03958955; EXP-1373; 2018-003615-22	LEO Pharma
Delgocitinib, vehicle	Inverse Psoriasis	2	Completed	Germany	NCT02695940; LP0133-1182	LEO Pharma
Delgocitinib, placebo	Atopic dermatitis	3	Completed	Japan	JapicCTI-173554; QBA4-1	Japan Tobacco Inc.
Delgocitinib	Atopic dermatitis	3	Completed	Japan	JapicCTI-173555; QBA4-2	Japan Tobacco Inc.
Delgocitinib, placebo	Atopic dermatitis	3	Ongoing	Japan	JapicCTI-184064	Japan Tobacco Inc.

vehicle (67.6% and 58.8% vs. 31.4%) and the mEASI-75 response rates were at least fourfold higher with the two delgocitinib groups than with vehicle (38.2% and 50.0% vs. 8.6%). Likewise, overall IGA response rates (as defined in Sect. 2.3.1) were at least 10-fold higher with delgocitinib 0.25% and 0.5% than with vehicle (11.8% and 20.6% vs. 0%). Patient-reported daytime and nighttime pruritis scores at EOT were significantly lower with delgocitinib 0.25% and 0.5% than with vehicle (all $p \leq 0.002$) [17].

An 8-week randomized, double-blind, multicentre phase 2a proof-of-concept trial (NCT02664805) in Germany showed that delgocitinib ointment (30 mg/g) applied twice daily was effective in reducing disease severity in 91 patients (aged 18–65 years) with at least mild chronic hand eczema [assessed by the 5-point Physician's Global Assessment of disease severity (PGA)] [18]. At week 8, significantly more patients in the delgocitinib group than in the vehicle group achieved treatment success (primary endpoint; 46% vs. 15%; odds ratio 4.89; 95% CI 1.49–16.09; $p = 0.009$), where treatment success is defined as 'clear' or 'almost clear' skin with ≥ 2-point improvement in PGA scores. The adjusted mean Hand Eczema Severity Index (HECSI) score was significantly lower with delgocitinib than with vehicle (score of 13 vs. 26; mean treatment difference −12.88; 95% CI −21.5 to −4.3; $p = 0.003$) [18].

In addition to these trials, the efficacy of delgocitinib 30 mg/g ointment twice daily was evaluated in a randomized, double-blind, placebo-controlled phase 2 trial (NCT02561585) in 31 patients with alopecia areata in the US and a randomized, double-blind, phase 2a proof-of-concept trial (NCT02695940) in 69 patients with mild to moderate inverse psoriasis in Germany. A randomized, double-blind, phase 2 trial (NCT03325296) evaluating the efficacy of delgocitinib 30 mg/g ointment twice daily in 24 patients with alopecia areata in Denmark was terminated in October 2017. Results from these trials are not available.

2.3.3 Phase 1 trial

Delgocitinib 1% and 3% twice daily for 7 days reduced disease severity in Japanese patients (aged 18 to < 65 years) with moderate to very severe atopic dermatitis in part 3 of a phase 1 trial (JapicCTI-142494; QBX1-2) [12]. On days 4 and 8, the percentage change in EASI score was −31.0% and −53.1% in the delgocitinib 1% group and −17.3% and

−52.3% in the delgocitinib 3% group compared with −10.7% and −32.7% in the placebo group.

2.4 Adverse Events

Delgocitinib was generally well tolerated in Japanese patients with mild-to-severe atopic dermatitis in pooled data from the two phase 3 studies, QBA4-1 (JapicCTI-173554) and QBA4-2 (JapicCTI-173555) [14]. During 52 weeks' therapy, treatment-emergent adverse events (AEs) were reported in 69.0% (349/506) of patients, all of which were mild or moderate in severity, with the exception of one severe AE (rectal cancer), which was considered unrelated to treatment. The most common treatment-emergent AEs were nasopharyngitis (25.9%), contact dermatitis (4.5%) and acne (4.3%). Treatment-related AEs were reported in 78 (15.4%) patients, with the most common AEs being application-site folliculitis (2.4%), application-site acne (2.2%) and application-site irritation (1.8%). Serious AEs occurred in seven patients (1.4%), of which one serious AE of Kaposi's varicelliform eruption (developed on day 26) was considered related to delgocitinib. AEs led to treatment discontinuation in 17 (3.4%) patients, with contact dermatitis (1.0%) and application-site irritation (0.6%) being the most common AEs leading to study discontinuation [14].

2.5 Ongoing Clinical Trials

A 4-week, randomized, double-blind, placebo-controlled phase 3 trial (JapicCTI-184064) is currently underway in Japan to assess the efficacy and safety of delgocitinib in approximately 120 paediatric patients (aged 2–15 years) with mild to severe atopic dermatitis. The double-blind phase of the study will be followed by a 52-week open-label phase to assess the long-term efficacy and safety of delgocitinib. The primary endpoint is the percentage change in the mEASI score and the secondary endpoint is the change in the IGA score; the study has completed recruiting patients.

An 8-week, randomized, double-blind, multicentre, vehicle-controlled phase 2b study dose-ranging trial (NCT03725722) is currently recruiting adult patients with mild to severe atopic dermatitis in Australia, Canada and the USA. The study aims to enrol 250 patients to establish the optimal dose of delgocitinib and evaluate its safety and efficacy. In addition, an 8-week, open-label, multicentre, phase 1 trial (NCT03826901) is recruiting approximately 44 paediatric patients (aged 2–17 years) and adults (aged ≥ 18 years) with moderate to severe atopic dermatitis in Canada and the USA to assess the safety and pharmacokinetics of delgocitinib.

A 16-week, randomized, double-blind, vehicle-controlled phase 2b dose-ranging trial (NCT03683719) is underway in Denmark, Germany and the USA that will establish the optimal dose of delgocitinib and evaluate its efficacy and safety in approximately 250 adults with mild to severe chronic hand eczema. In addition, a 6-week, randomized, double-blind, multicentre, vehicle-controlled phase 2 trial (NCT03958955) is recruiting approximately 45 adults with discoid lupus erythematosus in several countries in Europe and the USA to evaluate the efficacy and safety of delgocitinib.

3 Current Status

Delgocitinib received its first approval in Japan on 23 January 2020 for the treatment of adults with atopic dermatitis.

Compliance with Ethical Standards

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Conflict of interest During the peer review process the manufacturer of the agent under review was offered an opportunity to comment on the article. Changes resulting from any comments received were made by the authors on the basis of scientific completeness and accuracy. S. Dhillon is a contracted employee of Adis International Ltd/Springer Nature, is responsible for the article content and declares no relevant conflicts of interest.

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