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EU Risk Management Plan Delgocitinib cream

LEO Pharma A/S

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EU Risk Management Plan for delgocitinib cream

RMP version to be assessed as part of this application:

RMP Version number: 0.3

Data lock point for this RMP: 10-Oct-2023

The data lock-point is the final DBL for Trial 1403; newer data lock points for specific safety areas are applied (see the section Data lock points used in this RMP for details).

Date of final sign-off: Presented as an electronical signature on the last page of this document.

Rationale for submitting an updated RMP: The RMP is updated in alignment with the responses to CHMP Day 195 List of Outstanding Issues.

Summary of significant changes in this RMP (compared to version 0.2 submitted in connection with CHMP Day 180 List of Outstanding Issues) is included in Table 1.

Table 1 **Summary of significant changes in this RMP**

Part	Module	Significant changes made
III	1	Addition of case detail (treatment area) for relevant co-medication under enhanced safety surveillance
III	2	Updated milestones to Panel 5
III	3	Updated milestones to Table 17, Part III.1
VI	II	Addition of GVP Module V, rev 2 RMP template text to section

Other RMP versions under evaluation: Not applicable.



Risk management plan approval statement

The following person has reviewed and approved the RMP by using electronic signatures as presented on the last page of this document:

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Abbreviations

AD	atopic dermatitis
AE	adverse event
AUC	area under the concentration time-curve
BSA	body surface area
CHE	chronic hand eczema
CTR	clinical trial report
DBL	data base lock
DLP	data lock point
DMC	data monitoring committee
EMA	European medicines agency
EPAR	European public assessment report
IGA-CHE	Investigator's Global Assessment for chronic hand eczema
IL	interleukin
IMP	investigational medicinal product
JAK	janus kinase
JT	Japan Tobacco Inc.
MAA	marketing authorisation application
MedDRA	Medical Dictionary for Regulatory Activities
NMSC	non-melanoma skin cancer
PD	pharmacodynamic
PK	pharmacokinetics
PT	preferred term
PYE	patient years of exposure
PYO	patient years of observation
QTcF	QT interval corrected by Fridericia's
RMP	risk management plan
SmPC	summary of product characteristics
TCS	topical corticosteroids



Part I: Product overview

Table 2 **Product overview**

Active substance (INN or common name)	Delgocitinib
Pharmacotherapeutic group (ATC Code)	D11AH11: Other dermatological preparations, agents for dermatitis, excluding corticosteroids
Marketing Authorisation Applicant	LEO Pharma A/S Industriparken 55 DK-2750 Ballerup Denmark
Medicinal product to which this RMP refers	Delgocitinib cream
Invented name in the European Economic Area (EEA)	Anzupgo
Marketing authorisation procedure	Centralised
Brief description of the product	Delgocitinib is a pan-JAK inhibitor that effectively inhibits the activity of all 4 members of the JAK family in a concentration dependent manner. The cream includes the following excipients listed in the EMA excipient guideline: - Benzyl alcohol - Butylhydroxyanisole (E320) - Cetostearyl alcohol
Hyperlink to the Product Information (SmPC)	Link to Product Information
Indication(s) in the EEA	Proposed: Anzupgo is indicated for the treatment of moderate to severe chronic hand eczema (CHE) in adults for whom topical corticosteroids are inadequate or inappropriate.



Dosage in the EEA	Proposed: A thin layer of Anzupgo should be applied twice daily to the affected skin of the hands and wrists until the skin is clear or almost clear (see Section 5.1). It is recommended to apply the cream at regular intervals, approximately 12 hours apart. In the event of recurrence of the signs and symptoms of CHE (flares), twice-daily treatment of the affected areas should be re-initiated as needed. Treatment should be discontinued if no improvement is seen after 12 weeks of continuous treatment.
Pharmaceutical form(s) and strengths	Cream, 20 mg/g
Is/will the product be subject to additional monitoring in the EU?	Yes



Part II: Safety specification

Part II: Module SI – Epidemiology of the indication and target population

Indication: Chronic hand eczema

CHE is a heterogeneous chronic inflammatory skin disorder located anywhere on the hands and wrists. According to the guideline developed by the European Society of Contact Dermatitis, CHE refers to hand eczema which persists for more than 3 months or returns twice or more often within 12 months (1). Key symptoms include intense itch and pain, and patients may present signs such as erythema, scaling, lichenification, hyperkeratosis, vesicles, edema, and fissures (2-4). CHE has a significant impact on the quality of life and is associated with a high psychological and socioeconomic burden (1, 5-10).

Incidence and prevalence

Hand eczema is a highly prevalent disease in the general population and carries a significant risk of becoming chronic (11, 12). The reported prevalence and incidence rates of hand eczema vary considerably, depending on the methodology in the collection of data. In a review of data available from 1964 to 2019, the point prevalence of hand eczema in the general population was 4.0%, 1-year prevalence 9.1%, and lifetime prevalence was 14.5%. 2 studies showed that 9–16% of patients with hand eczema reported symptoms ‘nearly all the time’, implying a chronic state of the disease (13, 14).

Demographics of the population in the proposed indication – age, gender, and racial origin

Based on a meta-analysis, the pooled incidence rate of hand eczema was 7.3 cases/1000 person years in the general population, 7.5 cases/1000 person years in adults and with a 1.5-2 times higher occurrence in women than in men. More than one third of the patients suffered from moderate or severe hand eczema and around one third had a history of AD (12). Data on hand eczema prevalence among different races have not been described in available epidemiological studies.

Risk factors for the disease

CHE has a multifactorial and complex aetiology attributed to both endogenous and exogenous factors. Endogenous factors are often related to skin barrier function. An impaired skin barrier allows higher penetration of allergens and irritants, which activates local immune response leading to development of hand eczema. AD patients have an inherent impaired skin barrier function and thus, a personal history of childhood eczema or having persistent/severe AD is



considered a strong risk factor for developing hand eczema (11). Previous hand eczema, hand eczema with low age of onset, and current allergic contact dermatitis also constitute risk factors often associated with hand eczema (15).

Environmental factors account for as much as 59% of aetiology. Exposure to wet work or irritants, cold/dry weather conditions, and decreased indoor humidity have a positive association with hand eczema. Female gender is an identified risk factor for hand eczema although this difference is largely explained by more frequent exposure to wet work rather than anatomical or physiological differences between genders (11).

As per the European guideline for hand eczema, it remains unclear whether hand eczema is associated with asthma, rhino-conjunctivitis, and mental stress. Other potentially associated factors mentioned are elevated specific IgE, a parental history of atopy, body weight, alcohol consumption and educational level (15).

The main existing treatment options

Mild CHE may to some extent be conservatively managed by elimination of triggers and general skin care, whereas management of moderate to severe CHE is more cumbersome. Currently, there are no medicines with an indication for the treatment of moderate to severe CHE. The only treatment specifically approved for CHE is alitretinoin, which is indicated for severe CHE in adults who are unresponsive to treatment with potent TCS. It is a systemic treatment associated with various safety risks and has several safety limitations, such as contraindication in pregnancy (due to teratogenic effects), and a pregnancy prevention program requirement (1, 16).

Basic management strategies in CHE include education, avoidance of clinically relevant allergens, protection from irritants, and frequent use of emollients. First line medical treatment is TCS of at least moderate potency, which can be used as flare treatment or for maintenance on an intermittent basis. Although TCS have shown effect in treatment of acute flares of CHE, subjects with moderate to severe CHE may require use of TCS that exceeds the recommended treatment duration, where evidence for efficacy is limited. It is well known that prolonged treatment with TCS may result in a worsening of the prognosis of CHE as TCS inhibit repair of the stratum corneum, can cause skin atrophy, and may interfere with recovery of the skin in the long-term (1, 17). TCS are therefore not suitable for long-term use.

Additional treatment options for CHE are mostly limited to use of products and modalities indicated for other skin diseases with an inflammatory pathophysiology. These include short courses of oral corticosteroids and phototherapy or off-label treatments such as topical



calcineurin inhibitors and other systemic therapies (cyclosporine, azathioprine, or methotrexate). Of note, products such as topical calcineurin inhibitors and cyclosporin are licensed for use in AD but are used off-label for all other subtypes than atopic hand eczema.

Thus, the currently available treatment options are all associated with limitations for use, safety concerns, or both. There is therefore a high unmet medical need for an efficacious and well tolerated treatment option specifically developed for the long-term control of moderate to severe CHE.

Natural history of the indicated condition in the untreated population, including mortality and morbidity

CHE is a fluctuating disease that is often characterised by a course of recurrent flares and accordingly, a poor prognosis. In the acute phase, CHE is typically characterised clinically by erythema, edema, vesicles, and oozing. In the chronic phase, the morphology progresses to include scaling, lichenification, hyperkeratosis, and fissures. The condition may be exacerbated by bacterial infections (2-4). The delays in diagnosis and the lack of specific treatment in the early stages of the disease lead to the increasing severity and chronicity of the condition. While not life-threatening, CHE has a significant impact on quality of life and is associated with a high psychological burden (e.g., anxiety, low self-esteem, social phobia) and socioeconomic burden. In occupational settings, CHE may lead to reduced work capacity, job loss or job changes, and increased sick leave, resulting in significant costs to health care systems (1, 2, 5-10, 18).

Important comorbidities

Previous or current AD is a well-established individual risk factor for hand eczema (11). Asthma and/or hay fever and nickel allergy were also related to hand eczema, but to a lesser extent (15, 19). In primary dermatology clinic studies, comorbidities associated with hand eczema included allergies, AD, foot eczema, anxiety, depression, and suicidal ideation (20, 21).

Comorbidities in AD

Because there is a substantial overlap in the comorbidities seen in hand eczema and AD, it is relevant to have other comorbidities seen with AD in mind when evaluating safety data reported in CHE clinical trials. According to the AAD guidelines on comorbidities with AD in adults, these include allergic and atopic conditions (asthma, allergic rhinitis, food allergy), immune-mediated conditions (alopecia areata, urticaria), mental health conditions (depression and anxiety), bone health conditions, and skin infections. Evidence also suggests a small



association with various cardiovascular conditions including stroke, congestive heart failure, and cardiovascular death, with the risk increasing in more severe AD (22). A modestly increased risk of deep vein thrombosis (OR 1.22, 95% CI 1.17–1.27) and pulmonary embolism (OR 1.08, 95% CI 1.02–1.15) was found in a US cohort study (23).

Part II: Module SII – Non-clinical part of the safety specification

Key safety findings from non-clinical studies and their relevance to human use:

Key issues identified from acute or repeat-dose toxicity studies

Decreased lymphocyte counts, slight decreases in erythrocyte cell parameters, and decreased size of lymphoid organs (spleen and thymus) were observed in oral repeated dose non-clinical toxicity studies (rats: at 3 mg/kg and above; dogs: at 0.1 mg/kg and above) and were attributed to the pharmacological properties (JAK inhibition) of delgocitinib. No hematological or histopathological findings were seen when delgocitinib ointment at a concentration up to 5% (corresponding to 20 mg/kg) was applied topically to minipigs (10% BSA) for up to 9 months.

Other changes suggestive of immunosuppression due to exaggerated pharmacology of delgocitinib (i.e., JAK inhibition) included suppression of antibody production in rats after oral administration at ≥ 3 mg/kg and opportunistic infections related to demodicosis in dogs after oral administration at 3 mg/kg.

All findings noted after oral repeat dosing in rats and dogs are of limited clinical relevance as they were only observed at exposures exceeding the human exposure and not seen when delgocitinib was applied topically to minipigs for up to 9 months.

Genotoxicity

In the genotoxicity studies, the result of the bacterial reverse mutation test was negative. In the in vitro chromosomal aberration test, delgocitinib had the potential to induce polyploidy in human peripheral blood lymphocytes, but no chromosomal structural aberrations were seen. In addition, no genotoxic potential was demonstrated in the in vivo chromosomal aberration test in rat bone marrow cells or in a dermal skin micronucleus test in hairless mice. Based on the negative in vivo results, delgocitinib is judged to have no genotoxic potential.

Carcinogenicity

In a 2-year dermal carcinogenicity study in mice, topical doses of 1%, 3% and 5% delgocitinib ointment were administered once daily for 104 weeks. No drug-related neoplastic



findings were noted at topical doses up to 5% delgocitinib ointment (at exposures approximately 600 times the human exposure based on AUC).

In a 2-year oral carcinogenicity study in rats, pancreatic acinar cell adenomas and subcutaneous lipoma were noted at doses ≥ 3 mg/kg/day (males only), thymoma were noted at doses ≥ 10 mg/kg/day (females only) and Leydig cell tumor at 30 mg/kg/day (corresponding to exposures approximately 160, 580, and 1800 times the human exposure based on AUC, respectively).

Reproductive and developmental toxicity

Fertility and embryonic development

Orally administered delgocitinib did not result in effects on fertility at any dose level evaluated in male rats (at exposures approximately 1700 times the human exposure). In female rats decreases in body weight gain, food consumption, numbers of corpora lutea and implantations, and fertility index were observed at 100 mg/kg (corresponding to exposures approximately 5800 times the human exposure). In the early embryonic development study, embryonic death increased after implantation at 10 mg/kg and above (corresponding to exposures approximately 430 times the human exposure based on AUC).

Embryo-fetal development

In the embryo-fetal development studies in rats and rabbits, delgocitinib was not teratogenic at any of the oral doses administered. In rats, a decrease in fetal weights and skeletal variations were seen at 10 mg/kg and above (corresponding to exposures 512 times the human exposure), and a tendency towards an increase in the post-implantation loss index was seen at 30 mg/kg (corresponding to exposures approximately 1400 times the human exposure). In rabbits, an increased post-implantation loss index, a reduced number of live fetuses, and a tendency towards a decrease in fetal weights were observed at 10 mg/kg (corresponding to exposures approximately 990 times the human exposure based on AUC).

Lactation

Following oral administration to lactating rats, delgocitinib was secreted in milk at concentrations approximately 3-fold those in serum.

Juvenile toxicity in rats

Administration of oral delgocitinib to juvenile rats for 10 weeks (from 21 days of age) resulted in exposures and pharmacologic effects on the lymphoid system similar to those observed in adult rats. No new or unique toxicities were seen.



Cardiovascular system, including potential effect on the QT interval

Delgocitinib slightly inhibited the hERG channel at concentrations $\geq 10 \mu\text{mol/L}$ but had no effect on the electrocardiograms (ECG). Following oral administration in dogs, delgocitinib decreased blood pressure and increased heart rate, although these effects were transient. No cardiovascular effects were seen when delgocitinib was administered topically to minipigs.

Discussion and conclusions on non-clinical data

Adverse effects in non-clinical studies, including hematological changes, reduced weight of lymphoid organs, and reduced fertility and implantation loss were observed only after oral administration at exposures sufficiently in excess of the human exposure (>100 -fold) indicating little relevance to clinical use in humans. In both non-clinical studies and clinical trials with topically applied delgocitinib, the systemic exposure was minimal as compared to oral dosing and it is therefore considered unlikely, that topically administered delgocitinib will cause systemic toxicity.

All the neoplastic/pre-neoplastic changes observed in rats were considered to represent a low risk to humans following topical use, given the tumor types and benign status in a single species and single sex and adequate safety margins. Since delgocitinib is judged to have no genotoxic potential, neoplastic/pre-neoplastic changes were considered to have occurred through a non-genotoxic mechanism and hence, with the existence of a threshold. Furthermore, Leydig cell tumors and pancreatic acinar cell adenomas are considered rat specific with no or limited human relevance. In the 2-year dermal carcinogenicity study in mice, no local or systemic treatment related tumors were observed.

Cardiovascular effects were observed solely following oral administration, at C_{max} values exceeding clinical C_{max} by over 1000-fold, and these findings are deemed clinically irrelevant.

Based on safety findings from the non-clinical studies, no safety concerns are proposed.

Safety concerns from non-clinical data	
Important identified risks (confirmed by clinical data)	None
Important potential risks (not refuted by clinical data or which are of unknown significance)	None
Missing information	None



Part II: Module SIII – Clinical trial exposure

Introduction to delgocitinib clinical development program

Delgocitinib cream is currently being developed for the treatment of moderate to severe CHE in adult subjects.

Delgocitinib was originally discovered by JT and formulated as an ointment. In November 2014, JT and LEO Pharma entered into a license agreement for delgocitinib, giving LEO Pharma the rights to research, develop, and commercialise delgocitinib for topical treatment in dermatological skin diseases globally, excluding Japan. In Japan, delgocitinib was approved in 2020 under the brand name CORECTIM® and is currently approved for topical treatment of adult and pediatric patients (≥6 months) with AD.

The clinical proof-of-concept for treatment of CHE was obtained by LEO Pharma in a phase 2a trial (Trial 1180) with delgocitinib ointment, which included adults with at least mild CHE. To increase patient user-friendliness, a cream formulation was developed by LEO Pharma for further clinical development. The cream formulation was introduced with the phase 2b trial (Trial 1273) and has been used in several clinical trials in CHE, including phase 1 trial (Trial 2285) and all phase 3 trials.

The clinical phase 3 program for delgocitinib cream 20 mg/g in the proposed indication, consists of 2 pivotal trials (Trials 1401 and 1402) and a long-term extension trial (Trial 1403).

Phase 1 and phase 2 trials in healthy subjects and in subjects with AD are also included in this MAA submission as supporting information. While AD is a distinct indication, it still has specific relevance to CHE as an independent risk factor and as a disease subtype. Furthermore, blinded exposure data from 2 ongoing phase 3 trials in CHE (Trials 1426 and 1528 with cut-off date 30-Dec-2022) are included (Trial 1528 is final now but included with blinded data to align with M2.7.4).

An overview of the clinical trials with delgocitinib used to support the safety evaluation in the MAA submission is presented in Panel 1.



Panel 1 Overview of clinical trials with delgocitinib included in the overall safety evaluation

Chronic hand eczema		Atopic dermatitis	Healthy subjects
Completed trials	Ongoing trials	Completed trials	Completed trials
Phase 1 LP0133-2285 (PK)		Phase 1 LP0133-1181 (PK/MUsT)	Phase 1 LP0133-1408 (phototoxicity) LP0133-1409 (capsules, QTcF prolongation) LP0133-1411 (photoallergy)
Phase 2 LP0133-1273 (dose-ranging) LP0133-1180 (ointment, Proof of concept trial)		Phase 2 LP0133-1275 (dose-ranging)	
Phase 3 LP0133-1401/DELTA 1 (pivotal) LP0133-1402/DELTA 2 (pivotal) LP0133-1403/DELTA 3 (LTE - safety)	Phase 3^{a)} LP0133-1426 (adolescents) LP0133-1528 ^{a)} (H2H)		

Abbreviations: H2H = head to head; LTE = long term extension; MUsT = maximal usage trial;
PK = pharmacokinetics; QTcF = corrected QT interval by Fridericia.
Notes: a) LP0133-1528 has been completed after the initial submission; to align with M2.7.4, the trial is grouped with the ongoing trials for safety evaluation.

Clinical trials included in this RMP

To minimise clinical and safety variability in the patient population and keep the integrated safety analyses relevant to the proposed indication and to the to-be-marketed cream formulation, clinical trial exposure in this RMP presents data from 9 clinical trials with delgocitinib cream 20 mg/g across CHE and AD indications: 7 trials in CHE (Trials 1273, 1401, 1402, 1403, 2285, 1426, and 1528) and 2 in AD (Trials 1181 and 1275) (Panel 1).

An overview of the trial designs of the completed (in the initial MAA) and ongoing clinical trials with delgocitinib cream 20 mg/g in CHE are presented in Panel 2 and Panel 3, respectively. An overview of the trial designs of the completed clinical trials with delgocitinib cream 20 mg/g in AD is presented in Panel 4.

4 safety pools are used to present the clinical trial exposure of delgocitinib, which correspond to the same pools used in the safety evaluation. The safety pools and the trials included in each pool are described in the succeeding section.

Panel 2 **Trial designs of the completed clinical trials with delgocitinib cream 20 mg/g in CHE in the initial MAA – Trials 1401, 1402, 1403, 1273, and 2285^a**

Trial ID	Phase/type/ trial periods	Randomisation ratio/ Treatments/ Regimen	Subjects with delgocitinib/ Vehicle/ Population	Pool
CHE				
1401	Phase 3/confirmatory/ • Screening: 1-4 w • Treatment: 16 w • Follow-up ^a : 2 w	2:1/ delgocitinib cream 20 mg/g, or cream vehicle/twice-daily	325/162 Adults with moderate to severe CHE	• Primary pool • Long-term safety pool • Intermittent-use pool • Exposure pool
1402	Phase 3/confirmatory/ • Screening: 1-4 w • Treatment: 16 w • Follow-up ^b : 2 w	2:1/ delgocitinib cream 20 mg/g, or cream vehicle/twice-daily	313/159 Adults with moderate to severe CHE	• Primary pool • Long-term safety pool • Intermittent-use pool • Exposure pool
1403	Phase 3/long-term extension open-label/ • Screening: 1-4 w (overlaps with last 4 weeks of treatment period in Trials 1401 and 1402) • Treatment: 36 w • Follow-up: 2 w	Single-arm/ delgocitinib 20 mg/g twice-daily as needed for IGA-CHE ≥ 2 . Treatment is stopped whenever IGA-CHE is 0 or 1 (clear or almost clear) and initiated whenever IGA-CHE ≥ 2 (mild, moderate or severe)	801 subjects on delgocitinib cream 20 mg/g as needed Adults from Trials 1401 and 1402	• Long-term safety pool • Intermittent-use pool • Exposure pool
1273	Phase 2b/dose-ranging/ • Screening: 1-4 w • Treatment: 16 w • Follow-up: 2 w	1:1:1:1/ delgocitinib cream 1, 3, 8, 20 mg/g, or cream vehicle twice-daily	208 ^c /50 ^c Adults with mild to severe CHE	• Primary pool • Exposure pool
2285	Phase 1/PK/ • Screening: 1-4 w • Treatment: 1 w • Follow-up: 2 w	Single-arm/ delgocitinib cream 20 mg/g twice-daily	16/- Adults with moderate to severe CHE	• Exposure pool

Abbreviations: AD = atopic dermatitis; CHE = chronic hand eczema; MUSt= maximal usage trial;
PK = pharmacokinetics; IGA-CHE = Investigators global assessment of chronic hand eczema; w = week;
Notes: a) Trial 1528 has been completed after the initial submission; to align with M2.7.4, the trial is grouped with the ongoing trials for safety evaluation (see below panel). b) 2-week follow-up period in Trials 1401 and 1402 only applied to subjects who did not continue to Trial 1403. c) Only subjects on delgocitinib cream 20 mg/g (53 subjects) and cream vehicle (50 subjects) are used in the Primary pool.



Panel 3 Trial designs of the ongoing clinical trials with delgocitinib cream 20 mg/g in CHE as of 30-Dec-2022 – Trials 1426 and 1528

Trial ID	Phase/type/ trial periods	Randomisation ratio/ Treatments/Regimen	Planned subjects with delgocitinib/ comparator/ Population	Pool
CHE				
1426	Phase 3/Efficacy and safety in adolescents • Screening: 1-4 w • Treatment: 16 w • Follow-up: 2 w	3:1/ delgocitinib cream 20 mg/g, or cream vehicle/ twice-daily	Delgocitinib: 69/ Vehicle: 23 Adolescents with moderate to severe CHE	• None
1528 ^a	Phase 3/Efficacy and safety versus alitretinoin • Screening: 1-4 w • Treatment: 24 w • Follow-up: 2 w	1:1/ delgocitinib cream 20 mg/g/ twice-daily/ alitretinoin capsules 30 mg/ once daily (may be reduced to 10 mg)	Delgocitinib: 255/ Alitretinoin: 255 Adults with severe CHE	• None

Abbreviations: CHE = chronic hand eczema; w = week.

Notes: a) Trial 1528 has been completed after the initial submission; the trial is grouped with the ongoing trials for safety evaluation.

Panel 4 Trial designs of the completed clinical trials with delgocitinib cream 20 mg/g in AD – Trials 1275 and 1181

Trial ID	Phase/type/ trial periods	Randomisation ratio/ Treatments/ Regimen	Subjects with delgocitinib/ vehicle/ Population	Pool
AD				
1275	Phase 2b/dose-finding/ • Screening: 2-4 w • Treatment: 8 w • Follow-up: 2 w	1:1:1:1:1/ delgocitinib cream 1,3,8,20 mg/g, or cream vehicle/ twice-daily	200/50 Adults with mild to severe AD	• Exposure pool
1181	Phase 1/MUsT/ • Screening: 1-4 w • Treatment: 8 w • Follow-up: 2 w	Single-arm/ delgocitinib cream 20 mg/g twice-daily	46/- Adults, adolescents, and children with moderate to severe AD	• Exposure pool

Abbreviations: AD = atopic dermatitis; MUsT = maximal usage trial; w = week



Pooling strategy

The 4 pools used in the presentation of clinical exposure and for the safety evaluation of delgocitinib cream are:

- **Primary pool.** This includes all completed phase 2b and phase 3 trials (Trials 1273, 1401, and 1402) in CHE with 16-week duration. This pool is used for the primary evaluation of clinical safety because these trials provide 16-week controlled trial design for the comparison of delgocitinib cream 20 mg/g versus cream vehicle. All 3 trials were of similar indication, trial population, and trial duration. To support the to-be-marketed dose of 20 mg/g, only subjects allocated to delgocitinib 20 mg/g and cream vehicle in Trial 1273 are included in this pool.
- **Long-term safety pool.** The Long-term safety pool is the main source of the evaluation of long-term safety of delgocitinib cream 20 mg/g (up to 52 weeks). This comprises all subjects in the CHE phase 3 trials: subjects in Trials 1401 and 1402 (including early terminators) and the continuation of these subjects on as needed treatment in Trial 1403. Subjects from Trial 1273 are not included as subjects did not have the option to continue into the long-term extension trial. For the long-term safety evaluation, AEs reported during Trial 1403 are assigned to the current treatment (on- or off-delgocitinib treatment) and safety data in this pool are presented in 2 treatment groups:
 - *Delgocitinib 20 mg/g:* includes AEs that occurred during treatment with delgocitinib 20 mg/g in parent trials (Trials 1401 and 1402) and during on-treatment periods in Trial 1403.
 - *Vehicle or off-treatment:* includes AEs that occurred with cream vehicle in parent trials (Trials 1401 and 1402) and off-treatment periods in Trial 1403.

Since subjects in Trial 1403 can go on- or off-treatment at any time during the trial depending on their IGA-CHE score, subjects in this pool can belong to both treatment groups. In this RMP, only the exposure/duration of observation for the delgocitinib 20 mg/g group is presented.

Safety data from the Long-term safety pool has been evaluated using rates rather than percentages to account for subjects in single-arm Trial 1403 being on-treatment more than 3 times longer than they were off-treatment (408 vs. 128 patient years of observation).



- **Intermittent-use pool.** This is a pool of phase 3 trials (Trials 1401, 1402, and 1403) used for the evaluation of long-term safety data with the intermittent-use of delgocitinib cream 20 mg/g as needed after 16 weeks of continuous treatment, as allocation of AEs to subject's parent trial treatment may be relevant for AEs with long time to onset. Therefore, for the long-term intermittent-use safety evaluation, AEs reported during Trial 1403 are assigned according to parent trial treatment regardless of current treatment and safety data in this pool are presented in 2 treatment groups:
 - *Delgocitinib 20 mg/g to on/off delgocitinib cream:* subjects treated with delgocitinib cream 20 mg/g for 16 weeks in parent trial and as needed delgocitinib cream 20 mg/g in Trial 1403.
 - *Vehicle to on/off delgocitinib cream 20 mg/g:* subjects treated with cream vehicle for 16 weeks in parent trials and as needed delgocitinib cream 20 mg/g treatment in Trial 1403.

In this RMP, the combined exposure/duration of observation for the 2 treatment groups is presented.

- **Exposure pool.** All LEO Pharma sponsored clinical trials in subjects with CHE and AD with delgocitinib cream included in the initial MAA (Trials 1181, 1273, 1275, 1401, 1402, 1403, and 2285) are pooled to evaluate the risk of less frequent adverse events including rare events, cardiovascular events of interest, all-cause mortality, embolic and thrombotic events, and malignancies in a larger group of subjects. For the Exposure pool, safety data for all delgocitinib cream doses and cream vehicle are included to increase the likelihood of detecting infrequent events and evaluating any potential imbalances.
- **Exposure pool + Trial 1528.** As described above, but also including delgocitinib cream data from Trial 1528 (not including the comparator alitretinoin data in 1528). This pool is used for events related to the important potential risk, only.



Exposure calculation

Delgocitinib exposure numbers in this RMP are based on calculations applied in M2.7.4. The calculations for the pools evaluated include the data from the full trial periods.

- **Primary pool:** The total treatment duration (days) is calculated as the number of days from date of first application of IMP to the date of last application of IMP, both days included. PYE is calculated as total treatment duration divided by 365.25. PYO is calculated as number of days from first IMP application to the end of trial divided by 365.25.
- **Long-term safety pool:** Exposure in terms of observation time for this pool is calculated for delgocitinib cream 20 mg/g as the combination of the PYO (start of treatment to end of trial) from delgocitinib-treated subjects in parent trials with the on-treatment periods from all subjects in Trial 1403. The on-treatment period is calculated from the day treatment is initiated (when an IGA-CHE ≥ 2 is observed by the investigator) to the day the treatment is stopped (when an IGA-CHE of 0 or 1 is observed by the investigator), including both start and stop day.
- **Intermittent-use pool:** Delgocitinib as needed exposure is calculated differently depending on the treatment group (based on parent trial treatment). The sum of exposure from the 2 groups are presented for the delgocitinib as needed exposure in this RMP.
 - *Delgocitinib 20 mg to on/off delgocitinib 20 mg/g:* Patient years of as needed exposure is calculated from date of first IMP application in parent trial to end of treatment period in Trial 1403. For subjects not continuing in Trial 1403, PYE from parent trial is used.
 - *Vehicle to on/off delgocitinib 20 mg/g:* Patient years of delgocitinib as needed exposure is calculated from baseline visit in Trial 1403 to end of treatment period in Trial 1403.
- **Exposure pool:** Exposure in terms of observation time is calculated for delgocitinib cream as the combination of the PYO (start of treatment to end of trial) from delgocitinib-treated subjects in Trials 1181, 1273, 1275, 1401, 1402 and 2285 together with the on-treatment periods from all subjects in Trial 1403.



Exposure to delgocitinib cream (all doses) in the completed clinical trials in CHE and AD indications (Exposure pool)

A total of 1343 subjects have been treated with delgocitinib cream across the CHE and AD indications, of which 1097 (81.7%) had CHE. This number includes subjects who were initially randomised to cream vehicle in the parent trials (Trials 1401 and 1402) and subsequently received delgocitinib cream in the long-term extension Trial 1403. Observation time by indication in the completed clinical trials is presented in Table 3.

Table 3 Exposure (PYO) to delgocitinib cream (all doses) in the completed clinical trials in CHE and AD indications (Exposure pool)

Indication	Number of subjects	Patient years of observation
Atopic dermatitis	246	56.18
Chronic hand eczema	1097	672.96
Total	1343	729.13

Abbreviations: AD = atopic dermatitis; CHE = chronic hand eczema; PYO = patient years of observation.

Exposure to delgocitinib cream 20 mg/g in the completed clinical trials in CHE (Primary pool)

To focus on the intended strength, formulation, and indication, exposure by duration (Table 4), exposure by age and sex (Table 5), and exposure by race (Table 6) are based on the Primary pool.

The majority of subjects with CHE (92.9%) were exposed to delgocitinib cream 20 mg/g for at least 16 weeks, reflecting the 16-week treatment period of all 3 trials in the Primary pool.

Approximately 64% of the subjects exposed to delgocitinib cream 20 mg/g were female and most of the subjects were 18-64 years of age. 91% of the exposed subjects were White.



Table 4 Exposure (PYE) to delgocitinib cream 20 mg/g in the completed clinical trials in CHE (Primary pool)

Duration of exposure	Number of subjects
≥8 weeks	664
≥16 weeks	642
Total number of subjects	691
Patient years of exposure (PYE)	205.86

Abbreviations: CHE = chronic hand eczema; PYE = patient years of exposure.

Notes: Weeks rounded to next whole number of weeks.

Table 5 Exposure (PYO) to delgocitinib cream 20 mg/g in the completed clinical trials in CHE by age group and sex (Primary pool)

Age group	Number of subjects			Patient years of observation		
	M	F	Total	M	F	Total
18 to 64 years	221	411	632	68.35	128.07	196.41
≥65 years	31	28	59	9.75	8.55	18.30
Total	252	439	691	78.10	136.62	214.72

Abbreviations: CHE = chronic hand eczema; F = female; M = male; PYO = patient years of observation.

Table 6 Exposure (PYO) to delgocitinib cream 20 mg/g in the completed clinical trials in CHE by race (Primary pool)

Race	Number of subjects	Patient years of observation
White	629	196.45
Black or African American	5	1.28
Asian	23	7.10
Other	34	9.89
Total	691	214.72

Abbreviations: CHE = chronic hand eczema; PYO = patient years of observation.

Exposure to delgocitinib cream in the completed clinical trials by strength and indication (Exposure pool)

Exposure by strength of delgocitinib cream (1, 3, 8, and 20 mg/g) is presented in Table 7. Among the 4 strengths, the exposure is highest in the to-be-marketed strength of 20 mg/g for both indications, with CHE having a much higher exposure than that of AD. This is due to the longer trial periods in the CHE Trials 1273, 1401, and 1402, and the long-term extension Trial 1403, since the AD program did not continue into phase 3.



Table 7 Exposure (PYO) to delgocitinib cream in the completed clinical trials by strength and indication (Exposure pool)

Delgocitinib strength (AD)	Number of subjects	Patient years of observation
1 mg/g	49	10.80
3 mg/g	50	11.87
8 mg/g	50	12.77
20 mg/g	97	20.75
Total	246	56.18
Delgocitinib strength (CHE)	Number of subjects	Patient years of observation
1 mg/g	52	16.80
3 mg/g	51	16.44
8 mg/g	52	17.68
20 mg/g	942	622.04
Total	1097	672.96

Abbreviations: AD = atopic dermatitis; CHE = chronic hand eczema; PYO = patient years of observation.



Exposure to delgocitinib cream 20 mg/g in the ongoing clinical trials in CHE

Only blinded safety data as of the 30-Dec-2022 data cut-off are included from the ongoing trials, and thus observation time presented in Table 8 is blinded to delgocitinib 20 mg/g or cream vehicle for Trial 1426 and blinded to delgocitinib 20 mg/g or alitretinoin for Trial 1528.

Table 8 **Blinded exposure (PYO) in the ongoing clinical trials in CHE**

Trials	Number of subjects	Patient years of observation
1426	18	1.83
1528	103	15.721
Total	121	17.551

Abbreviations: CHE = chronic hand eczema; PYO = patient years of observation.

Notes: Trial 1528 has been completed after the initial submission; the trial is grouped with the ongoing trials for safety evaluation.

As needed exposure to delgocitinib cream 20 mg/g in Trials 1401, 1402, and 1403 in CHE

Delgocitinib as needed exposure of up to 52 weeks is presented in Table 9. This table, based on the Intermittent-use pool, shows the 16 weeks exposure time on delgocitinib cream 20 mg/g (parent Trials 1401 and 1402) and or the as-needed treatment phase of up to 36 weeks in Trial 1403.

736 subjects with CHE were exposed to delgocitinib cream 20 mg/g for at least 6 months either for:

- 16 weeks with twice-daily delgocitinib cream 20 mg/g treatment (Trials 1401 and 1402) and 10 weeks with as needed treatment (Trial 1403) or
- 26 weeks of as needed delgocitinib cream 20 mg/g treatment in Trial 1403 after 16 weeks of cream vehicle in parent trial 1401 or 1402.

466 subjects with CHE were exposed to delgocitinib cream 20 mg/g for at least 12 months: 16 weeks with twice-daily delgocitinib cream 20 mg/g treatment (Trials 1401 and 1402) and 36 weeks with as needed treatment (Trial 1403).



Table 9 Exposure (incl. as needed exposure) to delgocitinib cream 20 mg/g in Trials 1401, 1402, and 1403 in CHE (Intermittent-use pool)

Duration of exposure (incl. as needed exposure)	Number of subjects
≥8 weeks	849
≥16 weeks	815
≥26 weeks	736
≥36 weeks	696
≥46 weeks	484
≥52 weeks	466
Total number of subjects	959
Patient years of exposure (PYE incl. as needed exposure)	694

Abbreviations: CHE = chronic hand eczema; PYE = patient years of exposure.

Notes: Weeks rounded to next whole number of weeks. Delgocitinib including delgocitinib as needed exposure comprises exposure time on delgocitinib cream 20 mg/g (in parent Trials 1401 and 1402) and/or the as needed treatment period of Trial 1403 (up to 36 weeks). As needed exposure includes both on- and off-treatment periods in Trial 1403.

Long-term exposure to delgocitinib cream 20 mg/g in Trials 1401, 1402, and 1403 in CHE

Duration of observation time to delgocitinib cream 20 mg/g up to 52 weeks is presented in Table 10. This table, based on the Long-term safety pool, shows the combined observation time from Trials 1401 and 1402 in subjects treated with delgocitinib cream 20 mg/g, and the observation time from delgocitinib on-treatment periods for all subjects in Trial 1403.



Table 10 Long-term exposure (PYO) to delgocitinib cream 20 mg/g in Trials 1401, 1402, and 1403 in CHE (Long-term safety pool)

Duration of exposure	Number of subjects
≥8 weeks	850
≥16 weeks	812
≥26 weeks	659
≥36 weeks	502
≥46 weeks	302
≥52 weeks	206
Total number of subjects	873
Patient years of observation (PYO)	603

Abbreviations: CHE = chronic hand eczema; PYO = patient years of observation.

Notes: Weeks rounded to next whole number of weeks.

Part II: Module SIV – Populations not studied in the clinical trials

SIV.1 Exclusion criteria in pivotal clinical studies within the development program

The exclusion criteria listed below are those pertinent to the safety of the enrolled subjects.

Subjects with elevated levels of alanine aminotransferase or aspartate aminotransferase

Reason for exclusion: Subjects with elevated levels of alanine aminotransferase (≥2.0 times upper limit of normal) or aspartate aminotransferase (≥2.0 times upper limit of normal), both of which are indicative of moderate to severe hepatic impairment, were excluded from the clinical trials in CHE. The reason to exclude these subjects was to avoid exposing subjects with moderate to severe hepatic impairment to delgocitinib before the safety of delgocitinib had been established in CHE subjects with normal hepatic function.

Is it considered to be included as missing information?: No

Rationale: There was no overall difference in the safety profile of delgocitinib between subjects with normal hepatic function and mild hepatic impairment. The systemic exposure of topically applied delgocitinib cream has been shown to be minimal and any hepatic metabolism of delgocitinib is expected to be insignificant. There are no clinical data indicating that delgocitinib cream would cause harm to subjects with moderate to severe CHE and moderate to severe hepatic impairment.



Subjects who are pregnant

Reason for exclusion: Pregnant subjects were excluded from the clinical trials in CHE to avoid exposing unborn babies to delgocitinib before the safety of delgocitinib had been established in adult subjects with CHE.

Is it considered to be included as missing information?: No

Rationale: Reproductive and developmental effects in non-clinical studies were observed only after oral administration at exposures sufficiently above the human exposure (>100-fold) indicating little relevance to clinical use in humans (see [Part II:SII](#)). There are limited clinical data available to draw any final conclusions on the safety of using delgocitinib cream during pregnancy, however, the systemic exposure of topically applied delgocitinib cream has been shown to be minimal in adults with CHE. Therefore, it is considered unlikely that delgocitinib applied topically during pregnancy will cause reproductive and developmental toxicities.

Subjects who are breastfeeding

Reason for exclusion: Subjects who are breastfeeding were excluded from the clinical trials in CHE to avoid exposing new-born babies to delgocitinib before the safety of delgocitinib had been established in adult subjects with CHE.

Is it considered to be included as missing information?: No

Rationale: In non-clinical studies, orally administered delgocitinib decreased fetal viability and reduced pup weights during the early postnatal period at exposures >1800 times the human exposure indicating little to no relevance to clinical use of delgocitinib cream. The systemic exposure of topically applied delgocitinib cream has been shown to be minimal in adults with CHE. Based on the safety margin calculated from orally administered delgocitinib in rats and findings during pre- and postnatal development, it is considered unlikely, that delgocitinib administered topically by the breastfeeding mother will cause systemic toxicity in the breastfed infant .



Subjects with clinically significant skin infection on the hands

Reason for exclusion: Systemic JAK inhibition has the potential to suppress mediators of the immune response, possibly increasing the risk of infection (24). In this context, there is a theoretical concern of an increased risk of local skin infections with delgocitinib cream. Subjects with clinically significant skin infections on the hands were excluded from the clinical trials to avoid a potential risk of worsened or more serious skin infection upon exposure with delgocitinib and to avoid interference with local safety and efficacy assessments in the trials.

Is it considered to be included as missing information?: No

Rationale: Skin infection on the hands were not identified as a safety concern based on the low frequency of local skin infections in clinical trials with delgocitinib and the similar rates reported between delgocitinib cream 20 mg/g and cream vehicle treatment groups. None of the reported events were serious or severe and only one event with onset on the first day of delgocitinib cream 20 mg/g treatment led to permanent discontinuation of IMP.

Subjects with clinically significant systemic infections requiring parenteral antibiotics, antiviral, or antifungal medication within 28 days prior to randomisation

Reason for exclusion: Systemic JAK inhibition has the potential to suppress mediators of the immune response, possibly increasing the risk of infection (24). Subjects with clinically significant systemic infections were excluded from the clinical trials to avoid exposure to delgocitinib before safety has been established in subjects without latent infections and avoid interference with safety assessments of the individual subjects in the trials.

Is it considered to be included as missing information?: No

Rationale: Systemic infection was not identified as a safety concern based on the overall low rate and number of events of systemic infections and infections that are considered severe and/or serious in clinical trials with delgocitinib cream. Serious and/or severe infections were reported at similar frequency with delgocitinib cream 20 mg/g and cream vehicle and there was no clustering or pattern in the events reported, the timing of onset, and all but 1 resolved without treatment interruption.



Subjects with a history of malignancy

Reason for exclusion: Oral JAK inhibitors for different indications have been associated with or suspected to have an increased risk of malignancy presumably due to an effect on natural killer cells which could potentially diminish the host's immunosurveillance for cancer (25). Subjects with a history of malignancy, except those in full remission, were excluded from the clinical trials to avoid exposure to delgocitinib before safety is established in adult subjects with CHE and avoid interference with safety assessments of the individual subjects in the trials.

Is it considered to be included as missing information?: No

Rationale: The carcinogenic potential of delgocitinib has been studied in non-clinical oral and dermal studies. The neoplastic/pre-neoplastic changes observed in rats were only observed in the oral carcinogenicity study and due to limited human relevance and adequate safety margins (>100-fold above human exposure), the findings are considered to represent a low risk to humans following topical application of delgocitinib, where the systemic exposure has been shown to be minimal (see [Part II:SII](#)). In the clinical trials with delgocitinib, there has been no evidence of an increased risk of malignancy for delgocitinib cream compared to cream vehicle. Malignancies are therefore not considered a safety concern for delgocitinib, however as non-melanoma skin cancers (NMSCs) are a recognised risk for JAK-inhibitors and NMSCs develop over longer period of time, NMSC at long term use is included as an important potential risk for delgocitinib.

Subjects with positive HIV test at screening and primary immunodeficiency disorders

Reason for exclusion: Systemic JAK inhibition leads to downregulation of Interferon gamma (IFN γ) and granulocyte-macrophage colony-stimulating factor (GM-CSF), which are cytokines crucial for host defence against opportunistic pathogens (24). Subjects with immunodeficiency disorders or conditions at risk of opportunistic infections were excluded from the clinical trials to avoid exposure to delgocitinib before the safety has been established in immunocompetent subjects with CHE.

Is it considered to be included as missing information?: No

Rationale: In clinical trials with delgocitinib, no increased risks of opportunistic infections or viral reactivation were identified in subjects exposed to delgocitinib cream 20 mg/g compared to cream vehicle based on a review of AEs. Based on the clinical data, opportunistic infections or viral reactivation are not considered a safety concern.



Subjects with hypersensitivity to components of IMP

Reason for exclusion: Allergic contact dermatitis is a common subtype of CHE and avoidance of known triggers is paramount to the management of the condition. Therefore, subjects with known hypersensitivity to components of IMP are excluded from the clinical trials to avoid worsening of CHE upon topical application of delgocitinib cream or cream vehicle.

Is it considered to be included as missing information?: No

Rationale: Local and systemic hypersensitivity reactions are not considered a safety concern based on the clinical data where an overall low frequency of local or systemic hypersensitivity reactions to delgocitinib cream 20 mg/g or cream vehicle were observed in the clinical trials, with lower rates and proportion seen in delgocitinib cream 20 mg/g than cream vehicle.

SIV.2 Limitations to detect adverse reactions in clinical trial development programs

The clinical development program is unlikely to detect certain types of adverse reactions such as rare adverse reactions, adverse reactions with a long latency, or adverse reactions caused by prolonged or cumulative exposure.

SIV.3 Limitations in respect to populations typically under-represented in clinical trial development programs

Table 11 Exposure of special populations included or not in clinical trial development programs

Type of special population	Exposure
Pregnant women	No clinical trials with delgocitinib cream have been conducted in pregnant women, and pregnant women were excluded from participation in all clinical trials with delgocitinib cream. As of 08-Feb-2024, a total of 11 pregnancies in female subjects were reported across the delgocitinib cream clinical programme, all reported in CHE clinical trials and none in AD; 10 pregnancies were reported in the delgocitinib 20 mg/g group and 1 in the alitretinoin group (in Trial 1528). See Part II SVII.1.1 and Table 12 for details. There are limited clinical data available to draw any conclusions about the safety of using delgocitinib during pregnancy.



Type of special population	Exposure
Breastfeeding women	No clinical trials with delgocitinib cream have been conducted in breastfeeding women, and breastfeeding women were excluded from participation in all clinical trials with delgocitinib cream. Therefore, no clinical data are available to draw conclusions about the safety of using delgocitinib cream during breastfeeding. Based on safety margins (>100-fold above human exposure), data from non-clinical studies, and considering the minimal systemic exposure of topically administered delgocitinib in the breastfeeding mother, no effects on the breastfed newborns/infants are anticipated (see Part II SVII.1.1 for details).
Patients with relevant comorbidities: • Patients with hepatic impairment • Patients with renal impairment • Patients with cardiovascular impairment • Immunocompromised patients • Patients with a disease severity different from inclusion criteria in clinical trials	<u>Subjects with hepatic impairment:</u> Subjects with elevated levels of alanine aminotransferase (≥ 2.0 times upper limit of normal) or aspartate aminotransferase (≥ 2.0 times upper limit of normal), both of which are indicative of moderate to severe hepatic impairment, were excluded from the clinical trials in CHE. The reason to exclude these subjects was to avoid exposing subjects with moderate to severe hepatic impairment to delgocitinib before the safety of delgocitinib had been established in CHE subjects with normal hepatic function. There was no overall difference in the safety profile of delgocitinib between subjects with normal hepatic function and those with mild hepatic impairment. The systemic exposure of topically applied delgocitinib cream is minimal and thus any hepatic metabolism of delgocitinib is expected to be insignificant. There are no clinical data indicating that delgocitinib cream would cause harm to subjects with moderate to severe CHE and moderate or severe hepatic impairment. <u>Subjects with renal impairment:</u> No subjects with severe renal impairment have been randomised in delgocitinib cream trials. Oral delgocitinib was found to be primarily eliminated by renal excretion but the systemic exposure of delgocitinib cream is minimal and thereby not expected to undergo substantial renal metabolism or excretion. There was no difference in the overall safety profile of delgocitinib cream for subjects with normal renal function, mildly impaired renal function, and moderately impaired renal function. There are no clinical data indicating that delgocitinib cream would cause



	harm to subjects with moderate to severe CHE and renal impairment. <u>Subjects with cardiovascular impairment:</u> Subjects with unstable disorder, including but not limited to cardiovascular conditions, which in the investigator's assessment could affect subject's safety throughout the trial were excluded from delgocitinib trials. Clinical trials with delgocitinib, including the phase 1 QTcF Trial 1409 in healthy subjects administered with oral delgocitinib, did not demonstrate any significant electrocardiogram findings or QT prolonging effect and there is no indication of an increased risk of cardiovascular events in subjects treated with delgocitinib cream. <u>Immunocompromised patients:</u> Subjects with history of malignancy, primary immunodeficiency, or confirmed positive HIV at screening were excluded from the clinical trials. No increased risks of opportunistic infections or viral reactivation were identified in subjects treated with delgocitinib cream compared to cream vehicle based on review of AEs. There are no clinical data indicating that delgocitinib cream would cause harm to immunocompromised subjects with moderate to severe CHE. <u>Patients with disease severity different from inclusion criteria in clinical trials</u> Only subjects with baseline moderate to severe CHE were enrolled in Trials 1401 and 1402. However, 61 subjects with mild CHE were randomized in Trial 1273, 12 of which were exposed to delgocitinib cream 20 mg/g and included in Primary pool assessments. Additionally, 345 subjects from parent Trials 1401 and 1402 entered Trial 1403 with mild CHE and were exposed to delgocitinib cream 20 mg/g. These subjects were included in the Long-term safety pool. Overall, there are no safety concerns identified in both Primary and Long-term safety pools where subjects with mild CHE were included.
Population with relevant different racial origin	Among the 691 CHE subjects in the Primary pool exposed to delgocitinib cream 20 mg/g, 91.0% were White, 3.3% were Asian, and 0.7% Black or African American. Based on the available data, there was no indication of any



	difference in the overall safety profile of delgocitinib cream among racial subgroups. Delgocitinib cream has minimal systemic exposure and is not expected to undergo substantial hepatic or renal metabolism. Racial differences in drug metabolism are therefore not expected to alter the safety profile of delgocitinib cream among racial subgroups.
Subpopulations carrying relevant genetic polymorphisms	No screening for relevant genetic polymorphisms were performed in the clinical trials with delgocitinib cream.
Other	<u>Pediatric population:</u> As of the DLP for this RMP, the clinical trial investigating efficacy and safety of delgocitinib cream in adolescents (12-17 years) with moderate to severe CHE is still ongoing and therefore only blinded safety data as of 30-Dec-2022 cut-off is available. An external, independent DMC reviews the unblinded safety data from this clinical trial on a regular basis. No safety concerns have been identified by the DMC to date. A phase 1 trial (Trial 1181) with delgocitinib cream in AD has been completed, where 20 children (2-11 years) and 12 adolescents (12-17 years) have been exposed to 20 mg/g delgocitinib cream for 8 weeks. No safety concerns were identified by an independent DMC in either age group during the course of the trial nor from the evaluation of safety data upon trial completion. Overall, there was no clinically relevant difference in the safety profile of delgocitinib between pediatric and adult populations observed in this trial. <u>Elderly population:</u> 108 elderly subjects (≥ 65 years) have been exposed to delgocitinib cream in the Exposure pool of which 59 elderly subjects had CHE and received 20 mg/g. Based on the safety analysis of CHE subjects in the Primary pool, there was no clinically relevant differences in the overall safety profile of delgocitinib between elderly subjects and adult subjects aged 18-65 years.



Conclusions on the populations not studied and other limitations of the clinical trial development program

Safety concerns identified from populations not studied	
• Important Potential Risks	None
• Missing information	None

Part II: Module SV – Post-authorisation experience

Delgocitinib was originally developed by JT, who launched delgocitinib ointment on the Japanese market in June 2020 for the indication AD under the brand name CORECTIM[®]. Post-authorisation exposure and a cumulative analysis of the available post-authorisation safety data for CORECTIM[®] is available in M5.3.6.

SV.1 Post-authorisation exposure

Not applicable.

Part II: Module SVI – Additional EU requirements for the safety specification

Potential for misuse for illegal purposes

Based on the mechanism of action, delgocitinib is not expected to have any potential for abuse, dependence, or rewarding effects related to treatment.

No evidence of potential drug abuse or misuse has been observed in the clinical trials with delgocitinib.

Any potential risk for misuse for illegal purposes is considered negligible, hence no risk minimisation plan is deemed necessary.

Part II: Module SVII – Identified and potential risks

SVII.1 Identification of safety concerns in the initial RMP submission

SVII.1.1. Risks not considered important for inclusion in the list of safety concerns in the RMP

Potential harm from overdose

Potential harm from overdose has been evaluated via systemic exposure using oral delgocitinib. No potential harm from overdose was observed at single oral doses up to 100 mg



(fasted condition). Multiple oral dose administrations (fed condition) for 14 days at doses up to 50 mg once daily, and at doses up to 25 mg twice-daily were confirmed to be well tolerated.

Minimal systemic exposure of delgocitinib cream was shown in the PK Trial 2285 in adults with CHE (assessed on Day 1 and Day 8) and confirmed in the phase 3 Trial 1402 (assessed at week 1, 4 and 16) after twice-daily application of delgocitinib cream 20 mg/g.

In the clinical trials with delgocitinib, investigators were instructed to report events of overdose in case of a clinical consequence or a potential clinical consequence. Accidental overdose or underdose could be recorded as a medication error based on the investigator's judgement. Intentional overdose was to be recorded as abuse or misuse.

The highest multiple dose regimen with delgocitinib cream in CHE was 20 mg/g twice-daily. The delgocitinib cream 20 mg/g twice-daily dose regimen was well tolerated with no apparent dose response or clustering of events compared with cream vehicle or the lower delgocitinib dosing regimens (1, 3 and 8 mg/g twice-daily). No events of intentional misuse, abuse, or accidental overdose were reported in the CHE clinical trials.

No systemic signs of overdose are expected following topical application and the proposed label and patient information specify that any excess of delgocitinib cream can be wiped off.

No safety concern has been identified for overdose with application of delgocitinib cream.

Potential risks common to the pharmacological class

A recent evaluation by EMA has identified a potential, increased risk of serious adverse reactions with systemic JAK inhibitors used to treat several chronic inflammatory disorders. These serious adverse reactions include an increased risk of major cardiovascular conditions, embolic and thrombotic events, serious infections, malignancy, and all-cause mortality (24).

Cardiovascular safety including thromboembolic events

In non-clinical studies, no cardiovascular effects were seen when delgocitinib was administered topically to minipigs (see [Part II:SII](#)).

There have been no cardiovascular events of interest, no pulmonary embolisms and no deep vein thromboses reported in the clinical trials with delgocitinib cream. A total of 2 thromboembolic events were identified in the Exposure pool. Of these, 1 non-serious, not related event (reported as superficial thrombophlebitis right inner thigh) was reported in a delgocitinib-treated subject, who had pre-existing cardiovascular risk factors.



Considering the clinical data and the minimal systemic exposure of topically applied delgocitinib cream there is no evidence to support an increased risk of cardiovascular or thromboembolic events for delgocitinib cream 20 mg/g.

Routine pharmacovigilance activities will be used to monitor cardiovascular events, including thromboembolic events, reported post-authorisation and these events will be reported to regulatory authorities, as required.

Infections

Serious infections

In non-clinical studies with oral delgocitinib, effects including hematological changes and reduced weight of lymphoid organs were only observed at exposures sufficiently in excess of the human exposure (>100-fold) indicating little relevance to clinical use in humans (see [Part II:SII](#)).

Data from clinical trials with delgocitinib cream 20 mg/g in CHE showed that a small proportion of subjects had serious or severe infections. Similar rates of events were reported with delgocitinib cream 20 mg/g and cream vehicle. There was no apparent pattern or clustering of the events reported and in the timing of onset, and none of the serious or severe infections were lesional/perilesional. Most of the events were common conditions and expected in the general population, while 1 non-serious, severe unexpected event (PT pseudomembranous colitis) had confounding factors, including hospitalisation and antibiotics. All events were reported as not related to IMP, and none of the events raised any safety concerns. There was no increase in the rates over time based on data from the Long-term safety pool.

Based on the evaluation of non-clinical and clinical data for delgocitinib, and taking the minimal systemic exposure of delgocitinib cream into account, there is no scientific evidence to support an increased risk of serious infections with topical application of delgocitinib cream 20 mg/g.

Routine pharmacovigilance activities will be used to monitor serious infections reported post-authorisation and these events will be reported to regulatory authorities, as required.

Local skin infections

Systemic JAK inhibition has the potential to suppress mediators of the immune response and there is a theoretical concern of an increased risk of local skin infections with delgocitinib.



Non-clinical studies with delgocitinib ointment showed no hematological or histopathological findings when delgocitinib was applied topically for up to 9 months (see [Part II:SII](#)).

Data from clinical trials with delgocitinib cream in CHE showed that the reporting of ‘local skin infections’ was low and similar between delgocitinib cream 20 mg/g and cream vehicle. All the events were non-serious, of mild or moderate severity, and had resolved by the end of trial. There was no pattern in the type of local skin infections reported, and no increase in the rates over time based on data from the Long-term safety pool.

Based on the evaluation of non-clinical and clinical data with delgocitinib, there is no scientific evidence to support an increased risk of local skin infections with topical application of delgocitinib cream 20 mg/g.

Routine pharmacovigilance activities will be used to monitor adverse events of local skin infections and these events will be reported to regulatory authorities, as required.

Malignancy

Concerns for an increased risk of malignancy is currently reflected in the warnings and precautions seen in the EU SmPCs for other JAK inhibitors, based on their theoretical potential to influence cancer immunosurveillance (26).

The proposed mechanism for the potential risk of malignancy with systemic JAK inhibition has been described in relation to impaired T cell responses (27), and in particular for NK cells (28). Impaired function and low levels of NK cells in the peripheral blood have been associated with the development of NMSC (29), and skin cancers associated with the use of oral JAK inhibitors have been described, with inconclusive trends towards a small increased risk (30-32).

Delgocitinib is a topical product indicated for a disease (CHE) affecting a BSA of up to 5%. It has a low systemic bioavailability of 0.6%. Due to the low BSA and low systemic bioavailability, the systemic exposure is minimal in moderate to severe CHE patients treated with delgocitinib cream 20 mg/g. The minimal systemic exposure is further supported by the non-overlapping systemic exposure observed between delgocitinib cream 20 mg/g and the lowest tested oral dose of delgocitinib in Trial 1409. The exposure from topical administration of delgocitinib is also significantly lower than the in vitro functional cell-based IC₅₀ value (10-100 ng/mL range) where meaningful systemic JAK inhibition is expected, thereby eliminating the risk of meaningful systemic JAK inhibition, including potential immunosuppression of NK cells.



In a 2-year dermal carcinogenicity study with delgocitinib in mice, no local or systemic treatment related tumors were observed. In a 2-year oral carcinogenicity study with delgocitinib in rats, pancreatic acinar cell adenomas, subcutaneous lipoma, thymoma, and Leydig cell tumor were noted. Both Leydig cell tumors and pancreatic acinar cell adenomas are considered rat specific with no or limited human relevance. In conclusion, all the neoplastic/pre-neoplastic changes observed in rats after oral administration of delgocitinib were considered to represent a very low risk to humans following topical use, given the tumor types and benign status in a single species, and the safety margins >100-fold above the clinical (topical) exposure (see [Part II:SII](#)).

Data from clinical trials with delgocitinib in CHE showed that the overall rates of malignancies were low and comparable between treatment groups in the Intermittent-use pool, with no pattern in the types of malignancies reported. Overall, there was no pattern to suggest a causal relation between delgocitinib cream treatment and the development of malignancies, considering the location and type of malignancies, the subjects' risk factors, the time from first dose to onset of events and the lack of an accumulation of malignancies over time.

Based on the evaluation of non-clinical and clinical data with delgocitinib, there is no scientific evidence to support an increased risk of malignancies with topical application of delgocitinib cream 20 mg/g.

However, NMSC is considered a potential risk for oral JAK-inhibitors and included as an important potential risk for another topical JAK-inhibitor. There is no evidence pointing to an increased risk of NMSC in CHE patients treated with delgocitinib cream 20 mg/g for up to 52 weeks. Nevertheless, given the long latency of NMSCs and the uncertain mechanism of a potential local immunosuppressive effect on its pathogenesis, NMSC at long term use is included as an important potential risk for delgocitinib ([See SVII.1.2](#)).

Routine pharmacovigilance activities will be used to monitor malignancy events reported post-authorisation and these events will be reported to regulatory authorities, as required. Further, specifically for NMSC, enhanced safety surveillance will be initiated (details listed in Other forms of routine pharmacovigilance activities, Table 16) and a PASS is included (see [Part III.2 Additional pharmacovigilance activities](#) for details).

All-cause mortality



3 fatal cases have been reported in the delgocitinib cream clinical development programme. All fatal events occurred in or after Trial 1403 and in subjects who had received delgocitinib cream 20 mg/g at some point. The events did not raise any safety concerns.

The cases are described below.

- In the first case, a 60-70-year-old subject went to the hospital with abdominal pain on the first day of delgocitinib dosing in Trial 1403 (the subject received cream vehicle in the parent trial). The subject was diagnosed with progressing neuroendocrine carcinoma in the esophagus with metastases to the liver and passed away approximately 1 month later. The event was assessed as not related to delgocitinib by investigator and sponsor due to the lack of temporal relation and extensive progression of the tumor at time of diagnosis.
- In the second case a 70-80-year-old subject died during an off-treatment period 236 days after the first dose of delgocitinib in Trial 1403 (the subject received delgocitinib in the parent trial). The subject had a fall and was hospitalised. 7 days later the subject died in the hospital, with the cause of death reported as unknown. The subject had a mass on the neck that was suspected as metastasis from unknown primary and a previous SAE of peripheral facial nerve palsy. The subject had a medical history of hypertension, epilepsy, renal cell carcinoma, spinal stenosis, previous chronic alcohol abuse, hepatitis B, and liver cirrhosis, and the event was assessed as not related to delgocitinib by both investigator and sponsor.
- In the third case, a 70-80-year-old subject was hospitalised for a myocardial infarction 10 days after completing Trial 1403 off-treatment, which was 6½ months (204 days) after last dose of delgocitinib cream 20 mg/g (the subject received delgocitinib in the parent trial). The subject was being treated for hypertension (ACE inhibitor) prior to the myocardial infarction. The death occurred 13 days after the myocardial infarction. The event was assessed as not related to IMP by the investigator and sponsor.

No fatal cases have been received from the post-marketing experience available for delgocitinib ointment (CORECTIM®), licensed in Japan.

Considering the clinical data and the minimal systemic exposure of delgocitinib cream there is no evidence to support a risk of increased all-cause mortality with topical delgocitinib.

Routine pharmacovigilance activities will be used to monitor adverse events with a fatal outcome and these events will be reported to regulatory authorities, as required.



Risks in pregnant and lactating women

Use in pregnant women

Delgocitinib could potentially be used in pregnant women with moderate to severe CHE as there are limited treatment options for this population.

In non-clinical studies, reproductive and developmental adverse effects were only observed after oral administration at exposures sufficiently above the human exposure (>100-fold) indicating little relevance to clinical use in humans. When delgocitinib was applied topically in both non-clinical studies and clinical trials, the systemic exposure was minimal compared to oral administration and it is therefore considered unlikely that topically administered delgocitinib to the hands and/or wrists will cause reproductive and development toxicities (see [Part II:SII](#) for details).

No clinical trials with delgocitinib have been conducted in pregnant women, and pregnant women were excluded from participation in all clinical trials with delgocitinib.

As of the 08-Feb-2024 safety data cut-off date, a total of 11 pregnancies in female subjects were reported across the delgocitinib cream clinical programme, all reported in CHE clinical trials and none in AD; 10 pregnancies were reported in the delgocitinib 20 mg/g group and 1 in the alitretinoin group (in Trial 1528) (for details, see Table 12).

Table 12 Birth outcomes for maternal exposure pregnancies to delgocitinib in the clinical development program as of 08-Feb-2024

	Delgocitinib total	Vehicle total	Alitretinoin
CHE	10	0	1
Normal new born	2		
Elective abortion	3 ^a		1
Spontaneous abortion	2		
Ongoing	3		

a = 1 elective abortion was due to congenital malformation of Down's syndrome/Trisomy 21.

2 normal new born:

- Subject had LMP approximately 1 month prior to last dose of IMP. The subject wished to continue with the pregnancy. No risks were identified with the pregnancy. Planned induction at gestational week 40+1 due to advanced maternal age . An emergency caesarean section was performed due to the risk of loss of foetal wellbeing, non-



progression of labour, and suspicion of foetal head malposition. The subject gave birth to a live baby weighing 3.46 kgs and Apgar 10-10.

- Subject was in the off-treatment period and had stopped treatment with IMP 2 days prior to LMP. The subject planned to continue with the pregnancy. The subject had risk factors: smoking and obesity . The subject gave birth to a live baby by vaginal delivery at gestational week 39+5 after being admitted for planned induction of labour. The newborn weighed 2.79 kgs (reported as small for the gestational age) with Apgar 9 10-10.

The 3 **elective abortions** occurred at gestational week 7, 9 and 19, respectively. No complications to these procedures were reported. Of the 3 elective abortions, 1 abnormal outcome has been reported after maternal exposure to delgocitinib during pregnancy and concerned the elective abortion in gestational week 19 (week 18 + 6 days). This was due to a diagnosis of trisomy 21 in the fetus, in a woman 30-40 years treated with cream vehicle for approximately 4 months in Trial 1401 and delgocitinib for approximately 8 months in the long-term extension Trial 1403. The date of last menstrual period was 36 days prior to last application of delgocitinib. The event of trisomy 21 was assessed as not related to IMP by both the investigator and the sponsor; the obstetrician suspected the event to be related to the subject's age.

The principal cause of trisomy of chromosome 21 is advanced maternal age. Trisomy 21 is the major cause of Down syndrome, accounting for about 95% of the cases. Currently, Down syndrome is one of the most common birth defects, affecting around 1 in every 100 live births at a maternal age of 40 (33).

2 **spontaneous abortions** have been reported:

- 1 occurred prior to gestational week 4 of the pregnancy in a woman 20-30 years treated with delgocitinib for approximately 7 months in Trial 1401/Trial 1403. The date of last menstrual period was 3 days after last application of delgocitinib.
- 1 occurred at gestational week 10 in a woman 30-40 years treated with delgocitinib for approximately 4 months in Trial 1402. The date of last menstrual period was 19 days prior to last application of delgocitinib.

In both above cases, the spontaneous abortion occurred within the first 12 weeks of the pregnancy. Early pregnancy losses are common, and in a study from 1988 the incidence of early pregnancy loss was estimated to 31% (34).



There are insufficient clinical data available to draw any conclusions about the safety of using delgocitinib cream during pregnancy. Therefore, the proposed label and patient information state that there is limited data on the use of delgocitinib cream in pregnant women and as a precautionary measure, it is preferable to avoid the use of delgocitinib cream during pregnancy.

Routine pharmacovigilance activities will be used to monitor adverse events after delgocitinib cream use in pregnant women and these events will be reported to regulatory authorities, as required.

Use in lactating women

In non-clinical studies, delgocitinib was secreted in milk at concentrations approximately 3-fold above those in serum following oral administration to lactating rats. Orally administered delgocitinib in rats resulted in decreased fetal viability and reduced pup weights during the early postnatal period at exposures >1800 times the human exposure indicating little to no relevance to clinical use of delgocitinib cream. There was no effect on behavioral and learning assessments, sexual maturation, or reproductive performance of the offspring at any dose studied (see [Part II:SII](#) for details).

No cases concerning use in lactating women have been reported in any clinical trial with delgocitinib cream.

PBPK modelling of plasma exposure in a breastfed infant following delgocitinib exposure through breast milk is predicted to be only a fraction (<10%) of the corresponding systemic exposure in the breastfeeding mother having applied delgocitinib cream. In addition, based on animal data it is expected that long-term concentrations above approximately 40 ng/mL are needed before JAK inhibitor related effects start to manifest. Thus, even in the unlikely scenario that the plasma concentration of delgocitinib were similar in the breastfeeding mother and infant, there would still be no anticipated risk of JAK inhibitor related effects. Furthermore, the juvenile toxicity and PPND studies performed in rats clearly suggest that infants/juvenile animals do not exhibit increased sensitivity to JAK inhibition, as neither new findings nor more severe toxicities were observed in juvenile animals compared to adult rat toxicity studies. Based on the anticipated infant exposure through breast milk, the safety margins calculated from orally administered delgocitinib in rats and findings during pre- and postnatal development and considering the minimal systemic exposure of topically administered delgocitinib, it is considered unlikely that topically administered delgocitinib by the breastfeeding mother will cause systemic toxicity in the breastfed infant. Therefore, the proposed label and patient information state that based on the minimal systemic exposure



after topical application of delgocitinib cream, no effects on the breastfed newborns/infants are anticipated.

Routine pharmacovigilance activities will be used to monitor adverse events after delgocitinib cream use in lactating women and these events will be reported to regulatory authorities, as required.

Potential for off-label use

Delgocitinib cream is being developed for treatment of moderate to severe CHE in adults who have had an inadequate response to topical corticosteroids, or for whom topical corticosteroids are not advisable. Furthermore, delgocitinib cream is currently being investigated in adolescent patients, aged 12 to 17 years, with moderate to severe CHE.

Delgocitinib ointment (CORECTIM[®]) was initially approved in Japan in January 2020 for the treatment of AD in adults (aged ≥ 16 years). The indication was extended to include patients aged 2-15 years in March 2021, and patients aged 6 months to <2 years in January 2023.

Delgocitinib cream could potentially be used off-label in pediatric patients with more extensive inflammatory dermatoses such as AD.

Twice-daily, topical applications of 20 mg/g delgocitinib cream in children (aged 2-11 years) with AD for 8 weeks was investigated in Trial 1181. Overall, the systemic exposure following application of 20 mg/g delgocitinib cream in subjects with AD was low. A few pediatric subjects presented with systemic exposure levels ($C_{\max}$) significantly above the mean exposure levels on Day 1, however the systemic exposure levels for these subjects declined markedly on Day 8. No accumulation was seen following twice-daily application of delgocitinib from Day 1 to Day 8. The higher exposure in children reflects that Part 2 of the trial was conducted under maximum use conditions (only applicable for the children) and the higher baseline %BSA observed in children (46.0%) compared to adults (33.6%) and adolescents (31.8%). Delgocitinib cream was shown to be well tolerated with no identified safety concerns for the children with AD enrolled in this trial.

Post-marketing cases received for CORECTIM[®] concerning use in adolescents and children with AD has been evaluated. It was shown that the most frequently reported events in children with AD are consistent with the events reported in general for CORECTIM[®] from post-marketing sources, and no safety concerns in the pediatric population were identified.

In addition to off-label use in pediatric patients, delgocitinib cream could potentially be used in adult patients with more extensive inflammatory dermatoses such as AD, with a



significantly higher %BSA involvement. Delgocitinib cream will be available in a pack size of maximum 60 g, which is anticipated to be the maximum amount that would be needed to treat the entire hand and wrist of both hands within a month. Therefore, a patient would not be able to apply more than what is needed to cover the hands and wrists in a maximum use scenario over a month without needing several tubes.

The proposed label states that delgocitinib cream is only indicated for adults and treatment of CHE, and that efficacy and safety of delgocitinib cream in children below 18 years of age has not been established. Furthermore, the patient information states that delgocitinib cream should not be used in children and adolescents below the age of 18 years.

Based on the above, the risk associated with off-label use of delgocitinib cream is considered minimal.

Routine pharmacovigilance activities will be used to monitor off-label use and these events will be reported to regulatory authorities, as required.

Potential for medication error

Within the indication of CHE, the risk of potential medication error is considered negligible. Delgocitinib cream will be made available as a single strength formulation for as needed use and with a treatment area limited by the indication of CHE.

Potential for transmission of infectious agents

No excipients of human or animal origin are used in the manufacture of delgocitinib cream for topical use.

SVII.1.2. Risks considered important for inclusion in the list of safety concerns in the RMP

Table 13 Summary of safety concerns

Summary of safety concerns	
Important identified risks	None
Important potential risks	Non-melanoma skin cancer at long-term use
Missing information	None

SVII.2 New safety concerns and reclassification with a submission of an updated RMP

Not applicable.



SVII.3 Details of important identified risks, important potential risks, and missing information

SVII.3.1. Presentation of important identified risks and important potential risks

One important potential risk, non-melanoma skin cancer at long-term use, is included in this RMP for delgocitinib cream 20 mg/g.



Details of important potential risks

Table 14 Non-melanoma skin cancer at long-term use

Important potential risk: Non-melanoma skin cancer at long-term use	
Potential mechanisms	Delgocitinib is a pan-JAK inhibitor that effectively inhibits the activity of all 4 members of the JAK family in a concentration dependent manner. The proposed mechanism for the potential risk of NMSC with systemic JAK inhibition has been described in relation to impaired T cell responses (27), and in particular for NK cells (28). The ability of systemic JAK-inhibitors to impair NK cell function and reduce circulating cell levels are perceived to contribute to NMSC pathogenesis by potentially diminishing tumor immunosurveillance ultimately allowing cancer to progress (28, 35). A mechanism by which topically applied JAK inhibitors cause NMSC development at application sites, through local immunosuppression has yet to be elucidated. There are no current evidence showing strong association between NMSC and topical immunosuppressants, despite a risk associated with their systemic counterparts (36, 37). Topically applied delgocitinib cream 20 mg/g does penetrate the skin and could potentially have a local impact on cell immunosurveillance. Of note however, there are no application site NMSCs reported with delgocitinib cream 20 mg/g.
Evidence source(s) and strength of evidence	NMSC is considered a class-effect of systemic JAK inhibitors and included as an important potential risk of another topical JAK inhibitor due to their theoretical potential to influence cancer immunosurveillance. Topical application of delgocitinib cream has a minimal systemic exposure that does not overlap with the systemic exposure of an oral dose of delgocitinib regarded as sub-therapeutic. In the delgocitinib clinical programme, 2 NMSCs have been reported in patients treated with delgocitinib cream 20 mg/g, both occurring on location distant to application sites. The 2 NMSCs reported on delgocitinib cream were both basal cell carcinoma, one from Trial 1403, located on the ear of a 70-80-old male with 57 days of delgocitinib exposure, and the other from Trial 1528, located on leg of a 50-60-year-old male with 29 days of delgocitinib treatment. Both subjects had risk factors (age and sun exposure). No causal relationship to delgocitinib has been established given the clinical information and latency period of both events. No other events were reported in completed or ongoing clinical trials. Cumulative post-marketing safety data for delgocitinib ointment,



	CORECTIM[®], approved in Japan for the treatment of AD since 2020, include no confirmed reports of skin cancer. Based on current non-clinical and clinical data, there is no evidence pointing to an increased risk of NMSC in CHE patients treated with delgocitinib cream 20 mg/g for up to 52 weeks. However, since there is uncertainty in the effect of local immunosuppression in the pathogenesis of NMSCs and NMSCs develop over extended periods of time, further long-term data is needed.
Characterisation of the risk	To evaluate all NMSC events reported in the delgocitinib clinical programme as of 27-May 2024 cutoff, data from Exposure pool (comprising of 5 CHE and 2 AD trials) is combined with Trial 1528 (head-to-head trial with an active comparator, completed after MAA submission). In this Exposure pool + Trial 1528, a total of 2 NMSCs, both basal cell carcinoma, were reported in the delgocitinib (all doses) group and none in cream vehicle or off-treatment group. Another case of NMSC was reported in the active comparator group in Trial 1528. Both NMSC events reported in delgocitinib group were serious, assessed not related to IMP, resolved, and did not lead to IMP discontinuation or withdrawal from trial. Rate differences are provided as a replacement for rate ratios, as rate ratios are not defined when denominator rate is zero.



NMSC by SOC and PT – Exposure pool + Trial 1528 – SAF

System organ class/ preferred term	Delgocitinib (All doses) (N=1596, PYO=833.65)			Vehicle or off-treatment (N=1196, PYO=264.51)		
	n	(%)	E	R	n	(%)
All events	2	(0.1)	2	0.24		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	2	(0.1)	2	0.24		
Basal cell carcinoma	2	(0.1)	2	0.24		

Abbreviations: E = number of events. HLT = high-level term. MedDRA = Medical Dictionary for Regulatory Activities. N = number of subjects within a treatment group. n = number of subjects with events. PT = preferred term. PYO = patient years of observation. R = (E/PYO)*100. RMP = Risk management plan. SAF = safety analysis set. SOC = system organ class.

Notes: AEs with start date on or after the date of first IMP application or with a worsening in severity after first IMP application are included, whereas for Trial 1403 AEs with start date after Week 0 (in Trial 1403) or with a worsening in severity after Week 0 (in Trial 1403) are included. Classification according to MedDRA version 24.0. The search for non-melanoma skin cancer (NMSC) is based on the MedDRA HLT Skin neoplasms malignant and unspecified (excl melanoma). Delgocitinib (all doses) PYO = PYO from delgocitinib group(s) in Trials 1181,1273,1275,1401,1402,2285 + Trial 1403 and 1528 on-treatment periods. Vehicle or off-treatment PYO = PYO from vehicle group in Trials 1273,1275,1401,1402 + Trials 1403 and 1528 delgocitinib off-treatment periods and safety follow-up periods. AEs are allocated to the specific treatment when the AE occurs. Subjects may contribute with exposure to more than one treatment group for Trials 1403 and 1528. AEs are sorted by decreasing percentages in treatment column delgocitinib (All doses).

12JUN2024-/leo/clinical/lp0133/qna/ema_180d_2024may/safety/tfl/safety/programs/t_ae_by_soc_and_pt_nmsc.sas
-t_500020_rmp_nmsc_soc_pt.txt

Overview of NMSC (HLT) – all events – Exposure pool + Trial 1528 – SAF

	Delgocitinib (All doses) (N=1596, PYO=833.65)				Vehicle or off-treatment (N=1196, PYO=264.51)				Delgocitinib vs. vehicle Rate difference* (95% CI)
	n	E	R	(95% CI)	n	E	R	(95% CI)	
All events	2	2	0.24	(0.03, 0.87)	0	0	0.00	(0.00, 1.39)	0.24 (-0.35, 0.83)
Serious									
Yes	2	2	0.24	(0.03, 0.87)	0	0	0.00	(0.00, 1.39)	0.24 (-0.35, 0.83)
No									
Serious events									
Deaths									
Other	2	2	0.24	(0.03, 0.87)	0	0	0.00	(0.00, 1.39)	0.24 (-0.35, 0.83)
Severity									
Mild	1	1	0.12	(0.00, 0.67)	0	0	0.00	(0.00, 1.39)	0.12 (-0.30, 0.54)
Moderate	1	1	0.12	(0.00, 0.67)	0	0	0.00	(0.00, 1.39)	0.12 (-0.30, 0.54)
Severe									
Relation to IMP									
Probably									
Possibly									
Not related	2	2	0.24	(0.03, 0.87)	0	0	0.00	(0.00, 1.39)	0.24 (-0.35, 0.83)
AEs leading to withdrawal from trial or permanent discontinuation of IMP (disc.)									
Withdrawal from trial									
Disc. of IMP									
Outcome									
Fatal									
Not recovered/not resolved									
Recovering/resolving									
Recovered/resolved	2	2	0.24	(0.03, 0.87)	0	0	0.00	(0.00, 1.39)	0.24 (-0.35, 0.83)
Recovered/resolved with sequelae									
Unknown									
Action taken with IMP									
Dose not changed	2	2	0.24	(0.03, 0.87)	0	0	0.00	(0.00, 1.39)	0.24 (-0.35, 0.83)
Drug withdrawn									
Not applicable									
Unknown									

Abbreviations: CI = confidence interval. Disc. = discontinuation. E = number of events. HLT = high-level term. MedDRA = Medical Dictionary for Regulatory Activities. N = number of subjects within a treatment group. n = number of subjects with events. PYO = patient years of observation. R = (E/PYO)*100. RMP = Risk management plan. SAF = safety analysis set.

Notes: Delgocitinib (all doses) PYO = PYO from delgocitinib group(s) in Trials 1181,1273,1275,1401,1402,2285 + Trial 1403 and 1528 on-treatment periods. Vehicle or off-treatment PYO = PYO from vehicle group in Trials 1273,1275,1401,1402 + Trials 1403 and 1528 delgocitinib off-treatment periods and safety follow-up periods. AEs are allocated to the specific treatment when the AE occurs. A subject can contribute with AEs to multiple treatments groups. The search for non-melanoma skin cancer (NMSC) is based on the MedDRA HLT Skin neoplasms malignant and unspecified (excl melanoma). *Rate differences are provided as a replacement for rate ratios, as rate ratios are not defined when denominator rate is zero.

12JUN2024-/leo/clinical/lp0133/qna/ema_180d_2024may/safety/tfl/safety/programs/t_ae_rmp_rd.sas-t_500010_rmp_nmsc.txt



Risk factors and risk groups	Cumulative exposure to UV radiation, both from sun exposure and/or tanning beds, is considered a primary risk factor for NMSC pathogenesis. Immunosuppressed states, history of NMSC or pre-malignant skin conditions including HPV infections, exposure to ionizing radiation and carcinogenic chemicals, advanced age, fair skin, and genetic predisposition are also risk factors for NMSC (38). There are no available data on the risk of NMSC in patients with CHE but there are reports showing increased risk of NMSC, particularly of squamous cell carcinoma, in atopic dermatitis patients (39, 40). It is proposed that the filaggrin abnormalities in AD patients increases susceptibility of keratinocytes to UV-induced damage. Increased cell turnover due to the chronic inflammatory state may also explain the association of cancer and AD (41). CHE and AD are different disease entities, but an immunological process of CHE is shared with AD and about a third of CHE patients have a history of AD (11, 12, 42).
Preventability	Unknown.
Impact on the risk-benefit balance of the product	Based on current clinical data, there is no evidence pointing to an increased risk of NMSC in CHE patients treated with delgocitinib cream 20 mg/g for up to 52 weeks.
Public health impact	Based on current clinical data, there is no evidence pointing to an increased risk of NMSC in CHE patients treated with delgocitinib cream 20 mg/g for up to 52 weeks.

SVII.3.2. Presentation of the missing information

Not applicable.

Part II: Module SVIII – Summary of the safety concerns

Table 15 Table Part SVIII.1 – Summary of safety concerns

Summary of safety concerns	
Important identified risks	None
Important potential risks	Non-melanoma skin cancer at long-term use
Missing information	None



Part III: Pharmacovigilance Plan (including post-authorisation safety studies)

III.1 Routine pharmacovigilance activities

LEO Pharma has an appropriate pharmacovigilance system in place to monitor drug safety in accordance with the European legislation. Main routine pharmacovigilance activities consist of adverse reactions reporting, signal detection, Periodic Safety Update Report, and weekly literature review. Details regarding routine practices for conducting pharmacovigilance are described in the Pharmacovigilance System Master File.

Other forms of routine pharmacovigilance activities:

To further address the important potential risk ‘Non-melanoma skin cancer at long-term use’, the safety database will be used to perform enhanced safety surveillance of NMSC cases reported in the post-marketing setting.

The enhanced safety surveillance of NMSC cases will ensure that relevant information is gathered and that missing details are followed up; Table 16 is outlining the details.



Table 16 Enhanced safety surveillance of NMSC cases

Enhanced safety surveillance of NMSC cases ensures gathering of relevant information specifically related to NMSC, supporting further characterisation of NMSC occurrence. The following is to be included in addition to basic content, if not reported initially:

- Indication for delgocitinib, dosing, frequency
- Location of NMSC (within / outside delgocitinib treatment area)
- Type of NMSC
- Relevant co-medication used for skin conditions (product/compound, frequency, treatment area, etc.)
- Relevant medical history
- Results of investigations, including histopathology results
- Risk factors for cancer development

LEO Pharma standard operating procedure is to be updated to include the above information, including additional details for relevant risk factors.

The number and timing of follow-up attempt will also be specified.

The delgocitinib Safety Surveillance Plan* is to be updated to include the:

- Details of the enhanced safety surveillance, including details for relevant risk factors.
- MedDRA search strategy (will be reviewed every half year in connection with the MedDRA version update).
- Frequency of data analyses of NMSC cases in routine signal detection.

* The LEO Pharma Safety Surveillance Plan (SSP) is a comprehensive mandatory product-specific internal document, managed by standard operation procedures, describing and documenting the plan for safety surveillance. The SSP is continuously updated.



III.2 Additional pharmacovigilance activities

A post-authorisation safety study (PASS) with delgocitinib is included in this RMP:
Delgocitinib cream 20 mg/g in moderate to severe chronic hand eczema and risk of NMSC: a nationwide registry based long-term post-authorisation safety study.

The PASS is shortly described in Panel 5 and the PASS outline is provided in Annex 3.

Panel 5 Post-authorisation safety study of delgocitinib cream 20 mg/g in moderate to severe CHE and risk of NMSC

Short name / title of activity:
Delgocitinib cream 20 mg/g in moderate to severe CHE and risk of NMSC: a nationwide registry based long-term PASS
Rationale and objectives:
There is no indication of skin malignancy (including NMSC) developing in relation to use of delgocitinib cream 20 mg/g, but NMSC is considered a potential risk for JAK inhibitors. The study will investigate whether the use of delgocitinib cream 20 mg/g in patients with moderate to severe CHE is associated with a higher risk of developing NMSC compared to patients with moderate to severe CHE never exposed to delgocitinib cream 20 mg/g.
Design:
A nested case-controlled registry study within a cohort of Danish patients with CHE. NMSC cases are identified from the Danish Cancer Registry, with controls being a random subset of cohort patients with CHE at the time of case identification. Each case will be matched with up to 5 controls based on sex and year of birth. The endpoint of the study is the diagnosis of NMSC.
Population:
A population of adult patients with moderate to severe CHE identified in Danish patient registries using diagnostic codes related to hand eczema and prescriptions for medications commonly used to treat moderate to severe hand eczema.
Milestones:
Draft protocol submitted to the European Medicines Agency (EMA): Within 3 months after EC decision Q1 2025: Start date of data collection Q4 2029: Progress report including counts Q4 2033: End date of data collection Q1 2035: Data extraction Q4 2035: Final study report



III.3 Summary table of additional pharmacovigilance activities

Table 17 **Table Part III.1 – Ongoing and planned additional pharmacovigilance activities**

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
Category 3 – Required additional pharmacovigilance activities				
Post-marketing registry study – Delgocitinib cream 20 mg/g in moderate to severe CHE and risk of NMSC: a nationwide registry based long-term PASS Planned	To investigate whether the use of delgocitinib cream 20 mg/g in patients with moderate to severe CHE is associated with a higher risk of developing NMSC compared to patients with moderate to severe CHE never exposed to delgocitinib cream 20 mg/g.	Non-melanoma skin cancer at long-term use	Submission of the draft protocol for endorsement	Within 3 months after EC decision
			Expected start date of data collection	01-Jan-2025
			Progress report including counts	Q4 2029
			End date of data collection	31-Dec-2033
			Final report	Q4 2035



Part IV: Plans for post-authorisation efficacy studies

No post-authorisation efficacy studies are proposed.

Part V: Risk minimisation measures (including evaluation of the effectiveness of risk minimisation activities)

Risk Minimisation Plan

V.1. Routine risk minimisation measures

Table 18 **Table Part V.1 – Description of routine risk minimisation measures by safety concern**

Safety concern	Routine risk minimisation activities
Non-melanoma skin cancer at long-term use	Text related to a recommendation for periodic skin examination is included in the SmPC, Section 4.4 Special warnings and precautions for use.

V.2. Additional risk minimisation measures

Routine risk minimisation activities as described in Part V.1. are sufficient to manage the safety concerns of the medicinal product.



V.3. Summary of risk minimisation measures

Table 19 Table Part V.3 – Summary table of pharmacovigilance activities and risk minimisation activities by safety concern

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Non-melanoma skin cancer at long-term use	Routine risk minimisation measures: Text related to a recommendation for periodic skin examination is included in the SmPC, Section 4.4 Special warnings and precautions for use. Additional risk minimisation measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Enhanced safety surveillance of NMSC events reported in the post-marketing setting. Additional pharmacovigilance activities: Delgocitinib cream 20 mg/g in moderate to severe CHE and risk of NMSC: a nationwide registry based long-term PASS. Final study report due date: Q4 2035



Part VI: Summary of the risk management plan for delgocitinib

Summary of risk management plan for delgocitinib

This is a summary of the risk management plan (RMP) for delgocitinib cream 20 mg/g. The RMP details important risks of delgocitinib, how these risks can be minimised, and how more information will be obtained about delgocitinib cream's risks and uncertainties (missing information).

Delgocitinib cream's summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how delgocitinib cream should be used.

This summary of the RMP for delgocitinib cream should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all of which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of delgocitinib cream's RMP.

I. The medicine and what it is used for

Delgocitinib cream is authorised for the treatment of moderate to severe chronic hand eczema (see SmPC for the full indication). It contains delgocitinib cream as the active substance and it is given by topical application.

Further information about the evaluation of delgocitinib cream's benefits can be found in the delgocitinib cream's EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage:

II. Risks associated with the medicine and activities to minimise or further characterise the risks

Important risks of delgocitinib cream, together with measures to minimise such risks and the studies for learning more about delgocitinib cream's risks, are outlined below.



Measures to minimise the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals.
- Important advice on the medicine's packaging.
- The authorised pack size – the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly.
- The medicine's legal status – the way a medicine is supplied to the patient (e.g., with or without prescription) can help to minimise its risks.

Together, these measures constitute routine risk minimisation measures.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed, including PSUR assessment so that immediate action can be taken as necessary. These measures constitute routine pharmacovigilance activities.

II.A List of important risks and missing information

Important risks of delgocitinib cream are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely administered. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of delgocitinib cream. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g., on the long-term use of the medicine).

List of important risks and missing information	
Important identified risks	None
Important potential risks	Non-melanoma skin cancer at long term use
Missing information	None



II.B Summary of important risks

Important potential risk: Non-melanoma skin cancer at long term use	
Evidence for linking the risk to the medicine	NMSC is considered a class-effect of systemic JAK inhibitors and included as an important potential risk of another topical JAK inhibitor due to their theoretical potential to influence cancer immunosurveillance. Topical application of delgocitinib cream has a minimal systemic exposure that does not overlap with the systemic exposure of an oral dose of delgocitinib regarded as sub-therapeutic. In the delgocitinib cream clinical programme, 2 NMSCs have been reported in patients treated with delgocitinib cream 20 mg/g, both occurring on location distant to application sites. The 2 NMSCs reported on delgocitinib cream were both basal cell carcinoma, one from Trial 1403, located on the ear of a 70-80-year-old male with 57 days of delgocitinib cream exposure, and the other from Trial 1528, located on leg of a 50-60-year-old male with 29 days of delgocitinib treatment. Both subjects had risk factors (age and sun exposure). No causal relationship to delgocitinib cream has been established given the clinical information and latency period of both events. No other events were reported in completed or ongoing clinical trials. Cumulative post-marketing safety data for delgocitinib ointment, CORECTIM[®], approved in Japan for the treatment of AD since 2020, include no confirmed reports of skin cancer. Based on current non-clinical and clinical data, there is no evidence pointing to an increased risk of NMSC in CHE patients treated with delgocitinib cream 20 mg/g for up to 52 weeks. However, since there is uncertainty in the effect of local immunosuppression in the pathogenesis of NMSCs and NMSCs develop over extended periods of time, further long-term data is needed.



Risk factors and risk groups	Cumulative exposure to UV radiation, both from sun exposure and/or tanning beds, is considered a primary risk factor for NMSC pathogenesis. Immunosuppressed states, history of NMSC or pre-malignant skin conditions including HPV infections, exposure to ionizing radiation and carcinogenic chemicals, advanced age, fair skin, and genetic predisposition are also risk factors for NMSC. There are no available data on the risk of NMSC in patients with CHE but there are reports showing increased risk of NMSC, particularly of squamous cell carcinoma, in atopic dermatitis patients. It is proposed that the filaggrin abnormalities in AD patients increases susceptibility of keratinocytes to UV-induced damage. Increased cell turnover due to the chronic inflammatory state may also explain the association of cancer and AD. CHE and AD are different disease entities, but an immunological process of CHE is shared with AD and about a third of CHE patients have a history of AD.
Risk minimisation measures	Routine risk minimisation measures: Text related to a recommendation for periodic skin examination is included in the SmPC, Section 4.4 Special warnings and precautions for use. Additional risk minimisation measures: None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: Delgocitinib cream 20 mg/g in moderate to severe CHE and risk of NMSC: a nationwide registry based long-term PASS. See section II.C of this summary for an overview of the post-authorisation development plan.

II.C Post-authorisation development plan

II.C.1 Studies which are conditions of the marketing authorisation

There are no studies which are conditions of the marketing authorisation or specific obligation of delgocitinib cream.



II.C.2 Other studies in post-authorisation development plan

Study name: Delgocitinib cream 20 mg/g in moderate to severe CHE and risk of NMSC: a nationwide registry based long-term PASS.

Purpose of the study: There is no indication of skin malignancy (including NMSC) developing in relation to use of delgocitinib cream 20 mg/g, but NMSC is considered a potential risk for JAK inhibitors. The study will investigate whether the use of delgocitinib cream 20 mg/g in patients with moderate to severe CHE is associated with a higher risk of developing NMSC compared to patients with moderate to severe CHE never exposed to delgocitinib cream 20 mg/g.



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Part VII: Annexes

Appendix no.	Appendix title	Status
Annex 4	Specific adverse drug reaction follow-up forms	Not produced as no information to report.
Annex 6	Details of proposed additional risk minimisation activities (if applicable)	Not produced as no information to report.

