25 July 2024
EMA/372390/2024
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Anzupgo

International non-proprietary name: delgocitinib

Procedure No. EMEA/H/C/006109/0000

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us
Send us a question Go to www.ema.europa.eu/contact **Telephone** +31 (0)88 781 6000 An agency of the European Union

Table of contents

List of abbreviations

AD	atopic dermatitis
ADME	absorption, distribution, metabolism, and excretion
ADR	adverse drug reaction
AE	adverse event
AESI	adverse event of special interest
ALT	alanine aminotransferase
ANOVA	analysis of variance
anti-HCV	hepatitis C virus antibody
AST	aspartate aminotransferase
AUC	area under the concentration-time curve
AUC_{0-12}	area under the concentration-time curve 0-12 hours post-dose
AUC_{inf}	area under the concentration-time curve from time zero extrapolated to infinity
BMI	body mass index
BSA	body surface area
CD3	cluster of differentiation 3
cDNA	complementary deoxyribonucleic acid
CHE	chronic hand eczema
CHMP	Committee for Medicinal Products for Human use
CI	confidence interval
CK16	cytokeratin 16
CLDN	claudin
ClinRO	clinician-reported outcome
C_{max}	maximum plasma concentration
COA	Clinical Outcome Assessment
CPP	Critical process parameter
CQA	Critical Quality Attribute
CTD	common technical document
CTR	clinical trial report
CYP	cytochrome P450
DLQI	Dermatology Life Quality Index
DoE	Design of experiments
DSp	Design Space
EASI	Eczema Area and Severity Index
EASI75	at least a 75% improvement in EASI score from baseline
EMA	European medicines agency
ES	effect size
EQ-5D-5L	EuroQoL 5-dimension 5-level questionnaire
EU	European Union
FAS	full analysis set
FDA	United States Food and Drug Administration
FLG	filaggrin
FMEA	Failure mode effects analysis
F_{rel}	relative bioavailability

GC	Gas Chromatography
HBsAg	hepatitis B surface antigen
HBsAb	hepatitis B surface antibody
HE	hand eczema
HECSI	Hand Eczema Severity Index
HECSI-75/90	at least a 75%/90% improvement in HECSI score from baseline
HEIS	Hand Eczema Impact Scal
HEIS PDAL	Hand Eczema Impact Scale – Proximal Daily Activities Limitation
HESD	Hand Eczema Symptom Diary
HIV	human immunodeficiency virus
HPLC	High performance liquid chromatography
IC50	half maximal inhibitory concentration
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
IGA-CHE	Investigator's Global Assessment for chronic hand eczema
IGA-CHE TS	IGA-CHE treatment success
IL	interleukin
IMP	investigational medicinal product
JAK	Janus kinase
JT	Japan Tobacco Inc.
k	kappa coefficient
K16	keratin 16
KLK6	kallikrein related peptidase 6
LCE2b	late cornified envelope 2B
LDPE	Low density polyethylene
LSMean	least squares mean
LOR	loricin
LoQ	limit of quantification
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	mixed models for repeated measures
mRNA	messenger ribonucleic acid
MUsT	maximal usage trial
NOAEL	no observed adverse effect level
NOR	Normal Operating Range
OAT1	organic anion transporter 1
OAT3	organic anion transporter 3
OCT2	organic cation transporter 2
OFAT	One factor at a time
PaGA	Patient's Global Assessment
PaGA TS	PaGA treatment success
PAR	protease activated receptors
PAR	Proven Acceptable Range
PD	pharmacodynamic
PDE	Permitted daily exposure
PDE-4	phosphodiesterase-4
PGA	Physician Global Assessment for chronic hand eczema

PGA TS	PGA treatment success
PGI-C	Patient Global Impression of Change
PGI-S	Patient Global Impression of Severity
Ph. Eur.	European Pharmacopoeia
PI3	elafin
PK	pharmacokinetic
PP	Polypropylene
PRO	patient-reported outcome
PT	preferred term
PUVA	psoralen ultraviolet A
QOLHEQ	Quality of Life in Hand Eczema Questionnaire
qPCR	quantitative polymerase chain reaction
QTc	corrected QT interval
RH	Relative Humidity
RT	Retention time
S100	S100 calcium-binding protein
SAE	serious adverse event
SAF	safety analysis set
SAP	statistical analysis plan
SCE	Summary of clinical efficacy
SCEL	sciellin
SCP	summary of clinical pharmacology
SCS	Summary of clinical safety
SD	standard deviation
SE	standard error
SERPINB3	serpin family B member 3
SM	starting material
SmPC	Summary of Product Characteristics
SOC	System organ class
STAT	signal transducer and activator of transcription
TAMC	Total Aerobic Microbial Count
TYMC	Total Combined Yeasts/Moulds Count
TCS	topical corticosteroid
TYK2	tyrosine kinase 2
t½	half-life
tmax	time to maximum plasma concentration
TNF	tumor necrosis factor
TYMC	Total Combined Yeasts/Moulds Count
UV	Ultraviolet
UVB	ULTRAVIOLET b
vIGA-AD	validated Investigator's Global Assessment for atopic dermatitisTM (trademark of Eli Lilly and Company)
vIGA-AD TS	vIGA-AD treatment success, i.e. a vIGA-AD score of 0 (clear) or 1 (almost clear) with at least a 2-step improvement
WLQ	Work Limitation Questionnaire
WPAI:CHE	Work Productivity and Activity Impairment:Chronic Hand Eczema

1. Background information on the procedure

1.1. Submission of the dossier

The applicant LEO Pharma A/S submitted on 17 July 2023 an application for marketing authorisation to the European Medicines Agency (EMA) for Anzupgo, through the centralised procedure under Article 3 (2) (a) of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 22 April 2022. The invented name Anzupgo was agreed during the procedure.

The applicant applied for the following indication:

Anzupgo is indicated for the treatment of moderate to severe chronic hand eczema (CHE) in adults who have had an inadequate response to, or for whom topical corticosteroids are not advisable.

1.2. Legal basis, dossier content

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC - complete and independent application

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain test(s) or study(ies).

1.3. Information on paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision(s) P/0533/2023 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0533/2023 was not yet completed as some measures were deferred.

1.4. Information relating to orphan market exclusivity

1.4.1. Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

1.5. Applicant's request(s) for consideration

1.5.1. New active substance status

The applicant requested the active substance delgocitinib contained in the above medicinal product to be considered as a new active substance, as the applicant claims that it is not a constituent of a medicinal product previously authorised within the European Union.

1.6. Scientific advice

The applicant received the following scientific advice (SA) on the development relevant for the indication subject to the present application:

On 28 June 2018, EMEA/H/SA/3854/1/2018/II, the SA pertained to the following clinical aspects:

- The overall design of the phase 2b study, including study population and endpoints

On 9 July 2020, EMEA/H/SA/3854/1/2018/II, the clarification on SA pertained to the following clinical aspects:

- Validation of the CHE IGA scale

On 17 September 2020, EMEA/H/SA/3854/2/2020/II, the SA pertained to the following quality and non-clinical aspects:

- Acceptability of the proposed formulation from quality perspective, including specifications, in relation to its intended clinical use
- Acceptability of the formulation, manufacturing and control strategy in relation to its intended clinical use
- Adequacy of the non-clinical data package to support marketing authorisation application (MAA).

On 3 November 2020, EMEA/H/SA/3854/2/2020/II, the clarification on SA pertained to the following quality aspects:

- Clarification regarding advice on the drug product specification

On 11 December 2020, EMEA/H/SA/3854/3/2020/II, the SA pertained to the following clinical aspects:

- Adequacy of the clinical pharmacology programme, including drug interaction, ADME
- The overall design of the phase 3 studies in particular, study population, dosing regimen, endpoints, PROs, safety database

1.7. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Outi Mäki-Ikola Co-Rapporteur: Margareta Bego

The application was received by the EMA on	17 July 2023
The procedure started on	17 August 2023
The CHMP Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	6 November 2023
The CHMP Co-Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	20 November 2023
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC and CHMP members on	20 November 2023
The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	14 December 2023
The applicant submitted the responses to the CHMP consolidated List of Questions on	21 March 2024
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Questions to all CHMP and PRAC members on	6 May 2024
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	16 May 2024
The CHMP agreed on a list of outstanding issues in writing to be sent to the applicant on	30 May 2024
The applicant submitted the responses to the CHMP List of Outstanding Issues on	21 June 2024
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP and PRAC members on	10 July 2024
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to Anzupgo on	25 July 2024
Furthermore, the CHMP adopted a report on New Active Substance (NAS) status of the active substance contained in the medicinal product (see Appendix on NAS)	25 July 2024

2. Scientific discussion

2.1. Problem statement

2.1.1. Disease or condition

Hand eczema (HE) is a heterogeneous chronic inflammatory skin disorder located anywhere on the hands and wrists. It is a disabling condition which impacts quality of life and occupational performance. According to the European Society of Contact Dermatitis guideline, CHE refers to hand eczema which persists for more than 3 months or returns twice or more often within 12 months. In the context of the current MAA, 'moderate to severe' CHE is defined by signs and intensity of CHE (score of 3 or 4) in the Investigator's Global Assessment for chronic hand eczema (IGA-CHE) scale, which is a clinician-reported outcome (ClinRO) measure developed and validated by the applicant (Table 1).

Table 1 - Investigator's Global Assessment for chronic hand eczema (IGA-CHE)

IGA-CHE severity	IGA-CHE score	Sign and intensity
Clear	0	No signs of erythema, scaling, hyperkeratosis/lichenification, vesiculation, oedema or fissures
Almost clear	1	Barely perceptible erythema No signs of scaling, hyperkeratosis/ lichenification, vesiculation, oedema or fissures
Mild	2	At least one: • Slight but definite erythema (pink) • Slight but definite scaling (mostly fine scales) • Slight but definite hyperkeratosis/lichenification and at least one: • Scattered vesicles, without erosion • Barely palpable oedema • Superficial fissures
Moderate	3	At least one: • Clearly perceptible erythema (dull red) • Clearly perceptible scaling (coarse scales) • Clearly perceptible hyperkeratosis/lichenification and at least one: • Clustered vesicles, without visible erosion • Definite oedema • Definite fissures
Severe	4	At least one: • Marked erythema (deep or bright red) • Marked and thick scaling • Marked hyperkeratosis/lichenification and at least one: • High density of vesicles with erosions • Marked oedema • One or more deep fissures

Abbreviation: IGA-CHE = Investigator's Global Assessment for chronic hand eczema.

2.1.2. Epidemiology and risk factors

HE is a common skin disease with a 1-year prevalence of at least 9.1% in the general population (6.4% in men and 10.5% in women). An incidence of 5.5 cases per 1000 person-years has been found in adults, with a higher median incidence rate among women (9.6, range 4.6–11.4) than among men (4.0, range 1.4–7.4). Self-reported HE in women peaks at between age 19 and 29 years, and decreases with age, while in men the incidence increases gradually with age.

Risk factors often associated with HE include atopic dermatitis (AD) in childhood, persistent/severe AD, previous HE, and low age at onset of HE, being contact allergic, being exposed to wet work, cold/dry weather conditions, and decreased indoor humidity, as well as being exposed to certain occupations. It is the most common occupational skin disease with a prevalence up to 40% in high-risk occupations, particularly wet-work occupations. Lifestyle factors, including tobacco smoking, have been reported to influence the prognosis of occupational HE.

2.1.3. Aetiology and pathogenesis

CHE is characterised by skin barrier dysfunction, immune cell infiltration of the skin compartment and alteration of the skin microbiome. The pathophysiology of CHE is complex comprising different clinical patterns with multiple, potentially overlapping aetiologies and risk factors. The multifactorial pathogenesis and the immune inflammatory mechanisms behind the clinical manifestations of CHE rely on a complex interplay between skin, and immune cells. This interplay is orchestrated by the release of soluble mediators, including cytokines, and promotes multiple and distinct inflammatory cascades leading to a self-perpetuating pro-inflammatory loop promoting the chronic skin inflammation and the dysfunction of skin barrier function and immune homeostasis.

2.1.4. Clinical presentation, diagnosis

CHE is a heterogeneous disease and shows variable morphology, typically with more erythema, oedema, vesicles, and oozing in the acute phase, as well as erythema, xerosis, scales, lichenification, hyperkeratosis, and fissures in the chronic phase. CHE patients may report that certain triggers including skin irritants, proteins, and contact allergens elicit or worsen their disease. They typically experience itch, pain, and burning sensation, which can impede the performance of activities of routine daily living, work, and recreation.

Several different classifications of CHE subtypes have been proposed. The 2015 European Society of Contact Dermatitis guideline included 6 subtypes broken down by exogenous (irritant HE, allergic HE and protein contact dermatitis) or endogenous (atopic HE, pompholyx and hyperkeratotic HE) cause, whereas the updated 2022 guideline differentiate 4 aetiological subtypes (irritant contact dermatitis, allergic contact dermatitis, atopic hand eczema and protein contact dermatitis/contact urticaria) and 4 clinical subtypes (hyperkeratotic HE, acute recurrent vesicular HE, nummular HE and pulpitis). More than one aetiological and clinical subtypes are often present. For example, irritant contact dermatitis is often found together with allergic contact dermatitis and atopic HE, which complicates the classification of HE.

The diagnosis of HE is based on medical history, which includes careful assessment of occupational and domestic exposures, clinical examination and skin tests, e.g. epicutaneous patch test to diagnose contact allergy, skin prick tests to evaluate immediate skin reactions such as contact urticaria and sometimes microbiological tests if secondary infection is suspected.

2.1.5. Management

Basic management strategies in CHE include education, avoidance of clinically relevant allergens, protection from irritants, and frequent use of emollients. Along with emollients, the first line medical treatment is topical corticosteroids (TCS) of at least moderate potency to control acute flares of HE. Long-term intermittent use of TCS may be also considered. Although TCS are very effective in the short term, they inhibit repair of the stratum corneum and may cause skin atrophy and interfere with recovery in the long-term.

Currently, there are no approved products 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. Alitretinoin is teratogenic, and therefore pregnancy prevention measures are required for women of child-bearing potential.

2.2. About the product

Delgocitinib is a pan-Janus kinase (JAK) inhibitor that targets the activity of all 4 members of the JAK family of enzymes consisting of JAK1, JAK2, JAK3, and tyrosine kinase 2 (TYK2) in a concentration dependent manner. JAKs are intracellular enzymes specifically associated to the different cytokine receptors in either a heterodimeric or homodimeric complex and are essential for cytokine signalling. JAKs are activated upon cytokine-receptor interaction and thereafter phosphorylate and activate signal transducers and activators of transcription (STATs). Activated STATs, in turn, activate the expression of cytokine-responsive genes to induce specific biological responses in target cells. Thus, the JAK/STAT signalling pathway provides direct translation of extracellular signals, cytokines, into specific transcriptional responses and plays a key role in driving a broad range of physiological and pathological processes involving the innate and adaptive immune system. Delgocitinib is the first JAK inhibitor developed for the treatment of CHE.

2.3. Quality aspects

2.3.1. Introduction

The finished product is presented as a white to slightly brown cream containing 20 mg/g of delgocitinib as active substance.

Other ingredients are benzyl alcohol (E 1519), butylhydroxyanisole (E320), cetostearyl alcohol, citric acid monohydrate (E 330), disodium edetate, hydrochloric acid (E 507) (for pH-adjustment), liquid paraffin, macrogol cetostearyl ether and purified water.

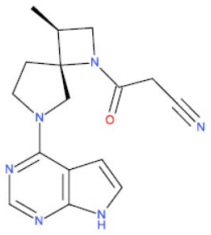
The product is available in a laminate tube with an aluminium barrier layer and an inner layer of low-density polyethylene fitted with a polypropylene flip-top cap as described in section 6.5 of the SmPC.

2.3.2. Active substance

2.3.2.1. General information

The chemical name of delgocitinib is 3-[(3*S*,4*R*)-3-methyl-6-(7*H*-pyrrolo[2,3-d]pyrimidin-4-yl)-1,6-diazaspiro[3.4]octan-1-yl]-3-oxopropanenitrile corresponding to the molecular formula $C_{16}H_{18}N_6O$. It has a relative molecular mass of 310.35 g/mol and the following structure:

Figure 1 - Active substance structure



The chemical structure of delgocitinib was elucidated by a combination of UV, ^{1}H-NMR, ^{15}N-HSQC, ^{15}N -HMBC spectroscopy, and mass spectrometry. The absolute stereochemical configuration of delgocitinib has been confirmed by single crystal X-ray structure determination.

Delgocitinib is slightly soluble in acetone, ethanol and methanol, sparingly soluble in pH 5.0 aqueous solution and slightly soluble in pH 7.5 aqueous solution.

Delgocitinib contains 2 stereocenters and in total 4 stereoisomers exist. Delgocitinib is the isomer with the absolute configuration 3S, 4R.The chiral centres originate from one of the proposed active substance starting materials (SMs)The chiral impurities are controlled in the specification for the starting material and the active substance specification.

Polymorphism of the active substance has been investigated. Delgocitinib was found to exhibit a complex solid form landscape consisting of 30 different solid forms, covering several anhydrates, hydrates and a range of solvates. Amongst these, seven anhydrous forms (6, 10, 12, 15, 17, 18 and 27) and two hydrates (5 and 16) were identified. The relevant forms seen from the manufacturing process point of view have been defined. Several forms may be produced by the manufacturing process. All these forms are similar in terms of solubility, hygroscopicity and stability. The manufacturing process is not able to control which of these polymorphic form is produced. However, since the active substance is used as a solution in the finished product, the polymorphic form has no impact on the finished product safety and efficacy and therefore, no control of polymorphic form is included in the active substance specification.

2.3.2.2. Manufacture, characterisation and process controls

Delgocitinib is manufactured in a convergent process consisting of three chemical transformation steps and a purification step in the main process branch and two steps in the side chain branch. The name and address of the suppliers of the SMs has been provided as well as the synthetic scheme of their preparation in which all used materials are indicated. Acceptable specifications and a brief description of analytical methods for the SMs testing as well as analytical method validation summaries are also presented. Several intermediates are isolated for which specifications and a brief description of the testing methods are presented as well as summary of the validation data of analytical procedures. Critical process parameters with their acceptance

criteria have been listed. Process operations were subjected to a risk assessment using Failure Mode and Effect Analysis (FMEA) approach. Based on the outcome of the risk assessment, a series of univariate experiments (OFAT) was performed to document the criticality of selected parameters towards the active substance critical quality attributes (CQAs) and to establish normal operating ranges (NORs) and proven acceptable ranges (PARs). The active substance CQAs comprise: identification, appearance, assay, organic impurities, inorganic impurities, residual solvents, water content and microbial quality. Additionally, each reaction step was studied through Design of Experiments (DoE) at in order to establish a design space (DSp) for each transformation step. Design spaces for several reaction steps are proposed. A scale-up dependency assessment for each step has been presented as requested by CHMP (Major Objection). The scalability of the design spaces to the desired batch size rangehas been verified and batch data provided to justify the proposed batch size A design space verification protocol is included in module 3.2.R.

The established design spaces ensure that the levels of impurities are not exceeded since the results from spike and fate/purge studies have been considered in the model calculations for impurities.

The available development data, the proposed control strategy and batch analysis data from commercial scale batches fully support the proposed PARs and design spaces.

Adequate in-process controls are applied during the synthesis. The specifications and control methods for intermediate products, starting materials and reagents have been presented.

The characterisation of the active substance and its impurities are in accordance with the EU guideline on the chemistry of new active substances.

Potential and actual impurities were well discussed with regards to their origin and characterised. A comprehensive impurity discussion has been provided, including spike and purge studies to study the fate of impurities both in starting materials and also process related impurities in the downstream synthesis. The control strategy for impurities, including mutagenic impurities, is considered acceptable.

The commercial manufacturing process for the active substance was developed in parallel with the clinical development program. Several important changes have been introduced during the development of the manufacturing process. It has been demonstrated that the changes did not have a significant impact on the quality of the product.

The quality of the active substance used in the various phases of the development is considered to be comparable with that produced by the proposed commercial process.

The active substance is packaged in low-density polyethylene (LDPE) bag placed in a drum made of plastic or fibre (carton). It is confirmed that the material of LDPE bags is in compliance with Commission Regulation (EU) 10/2011, as amended.

2.3.2.3. Specification

The active substance specification includes tests for appearance (visual), identification (HPLC, UV), assay (HPLC), organic impurities (HPLC), chiral impurities (chiral HPLC), residual solvents (GC) and sulphated ash (Ph. Eur.).

As requested by CHMP the three chiral impurities are included in the specification Organic solvents are adequately controlled Limits for benzene have not been included in the respective solvent specifications. It has been demonstrated that benzene is not detected in the active substance above 30 % of the ICH option 1 limit. However, omission of a test for benzene in the active substance is not acceptable and a non-routine

test for benzene should be included in the active substance specification in line with EMA guideline for residual solvents (CPMP/QWP/450/03 -Rev.1) (recommendation 1). The applicant has committed to do so by Q4 2024. Batch results have been provided demonstrating that the class 2 solvents used are not present above 10 % of the limit as per ICH Q3C in order to justify omission of limits in the active substance specification.

Acceptable justifications for the omission of tests for water content and microbiological quality in the active substance have been presented.

The analytical methods used have been adequately described and non-compendial methods appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for assay and impurities testing has been presented.

Batch analysis data have been provided from several pilot and commercial scale batches of the active substance Overall, the results are within the specifications and consistent from batch to batch.

2.3.2.4. Stability

Stability data from pilot and commercial scale batches of active substance manufactured as per the proposed commercial route and stored for up to 36 months under long term conditions (25 ºC / 60% RH) and for up to 6 months under accelerated conditions (40 ºC / 75% RH) according to the ICH guidelines were provided. Batches were packed in the intended commercial primary packaging.

The following parameters were tested: appearance, assay, and organic impurities. The analytical methods used were the same as for release and are stability indicating.

All results were within the specification limits and no significant trends were observed.

Photostability testing following ICH guideline Q1B was performed on one pilot scale batch. When delgocitinib stored in the primary packaging was exposed to the light, a change in colour was observed. Therefore, the active substance in LDPE bags should be stored in the secondary container to protect the active substance from light.

Stress testing of delgocitinib in solution under various conditions pH, oxidation and light was conducted. A sensitivity towards all conditions was observed.

The stability results indicate that the active substance manufactured by the proposed supplier is sufficiently stable. The stability results justify the proposed retest period and storage conditions.

2.3.3. Finished Medicinal Product

2.3.3.1. Description of the product and pharmaceutical development

The finished product is presented as a white to slightly brown cream containing 20 mg/g of delgocitinib as active substance. The site of action is the skin and in particular, the epidermis and dermis compartments where living cells express the target intracellularly.

The finished product is filled into laminate tubes with an inner layer of low-density polyethylene fitted with a polypropylene flip-top cap.

The pharmaceutical form and excipients were selected in order to obtain a patient-friendly and stable topical formulation.

The physicochemical properties of the active substance have been presented and discussed. Adequate information regarding justification of analytical methods and their validation has been provided.

All excipients are well-known pharmaceutical ingredients commonly used in topical pharmaceutical formulations and comply with their respective monographs in the Ph. Eur. There are no novel excipients used in the finished product formulation. The list of excipients is included in section 6.1 of the SmPC.

The selected concentrations of the excipients are within the commonly used ranges. An adequate justification for the selected amount of the antimicrobial preservative benzyl alcohol has been provided. It is proved that the concentration used is at the lowest feasible level and the required level of efficacy covers the intended shelf-life of the product, including the in-use period.

Initially an ointment was developed. The cream was introduced later in the development. Different strengths of delgocitinib cream were tested in clinical trials For the phase 3 trials, a 20 mg/g strength cream was used, which is the strength of the proposed commercial product.

The formulation development including the steps taken from the initial clinical trial formulations to the final to-be-market formulation have been described. The QTPP of the finished product was to develop a cream product for topical administration with a targeted dose per day, packaged in a laminate tube with a cap, designed for multiple uses, with stability of 3 years and in-use shelf life of 12 months, with no special storage conditions and complying with the finished product quality attributes.

The CQAs of the finished product are appearance of finished product, uniformity of active ingredient / homogeneity, assay delgocitinib, Impurities, (organic and inorganic), assay butyl-hydroxyanisole, assay disodium edetate, assay benzyl alcohol, microbiological quality, residual solvents, rheology / viscosity, pH, droplet size, tightness and fill weight.

The CQAs appearance, assay, organic impurities, preservative/antioxidant/chelating agent content, microbial purity, viscosity, pH and droplet size are routinely controlled in the finished product specification. For the CQAs homogeneity, inorganic impurities, residual solvents, tightness and fill weight, justification for omission from the finished product specification has been provided. The homogeneity of the bulk product has been demonstrated during development. The rheological properties of the finished product have been discussed. The spreadability is discussed in relation to the formulation development confirming that the selected formulation of cream is easy to apply. The density of the formulation is ensured by a relevant in-process control. The drug release and delivery to the site of action has been discussed. No skin permeation enhancers have been added to the finished product.

Risk assessments were conducted to identify the impact of relevant material attributes on the finished product CQAs. The risk assessment identified attributes to investigate during development studies. Follow up risk assessments were conducted following optimization of the product and manufacturing process and demonstrated low risk for all relevant CQAs.

The critical process parameters were identified, and a risk assessment was performed to inform mitigation of the potential risks.

The primary packaging is a laminate tube with an aluminum barrier layer and an inner layer of LDPE fitted with a polypropylene (PP) flip-top cap. The tubes are placed in a secondary cardboard box. The materials of the laminate tube in direct contact with the finished product (LDPE) comply with the Commission Regulation

(EU) No 10/2011 as amended on plastic materials and articles intended to come into contact with food. The proposed laminate tube with cap pack is common and acceptable packaging for semi-solid dosage forms. Representative certificates of analysis and IR spectra were provided for the primary packaging materials. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product.

2.3.3.2. Manufacture of the product and process controls

The manufacturing process is a conventional process for semi-solid preparations using standard equipment. It consists of the following main process steps: preparation of aqueous phase, preparation of fat phase, emulsification, cooling and discharge, and filling. The critical process parameters (CPPs) for each step have been identified and a risk evaluation of the critical process parameters based on the FMECA methodology was performed during the manufacturing process development. In-process controls during the manufacture were established based on the risk assessment. The in-process controls are adequate for this type of manufacturing process.

The flow diagram and description of the manufacturing process is considered sufficiently detailed. The parameters have been established based on the evaluations during the manufacturing process development. Several hold times have been included in the description of the manufacturing process. The equipment and containers for storage of intermediates and bulk product are considered suitable for the intended use.

Confirmation that the shelf life of the product is calculated according to the Note for Guidance on Start of Shelf-Life of the Finished Dosage Form (CPMP/QWP/072/96) has been provided.

Process validation has been performed on three full-scale batches. The validation demonstrated that the manufacturing process consistently and reproducibly yields a finished product of the desired quality. A statement is given that validation will be performed on the upper proposed commercial batch scale before commercial release of the finished product manufactured at this scale. This was not initially considered acceptable as the manufacturing process is considered non-standard due to the low active substance content, resulting in a Major Objection. In response, the applicant was able to demonstrate sufficient experience with this type of formulation and this manufacturing process can be considered to be a standard process for this manufacturer in line with the CHMP Guideline on process validation for finished products - information and data to be provided in regulatory submissions (EMA/CHMP/CVMP/QWP/BWP/70278/2012-Rev1,Corr.1).

2.3.3.3. Product specification

The finished product release specifications include appropriate tests for this kind of dosage form including appearance (visual), identification (HPLC, UV), assay (HPLC), organic impurities (HPLC), identification and assay of benzyl alcohol (HPLC, UV), identification and assay of butylhydroxyanisole (HPLC, UV), identification and assay of disodium edetate (HPLC, UV), pH (Ph. Eur.), viscosity (Ph. Eur.), droplet size (Ph. Eur.), microbiological quality (TAMC, TYMC, *Staphylococcus aureus*, *Pseudomonas aeruginosa* (Ph. Eur.)). At release, the cream must be white to almost white. During stability a slight change in colour is observed. The slightly brown colour that develops is uniform throughout the finished product and related to oxidation. The description (and shelf-life limit) accommodates the slight colour change observed during stability and is therefore justified.

The droplet size has been demonstrated not to change during manufacture and storage of the finished product; however, a test for droplet size in combination with the viscosity test has been included in the

finished product specification to ensure a consistent quality of the finished product as requested by CHMP (Major Objection). Based on the information it is concluded, that the assay test included in the specification can be regarded as the primary controlling parameter for the drug release rate from delgocitinib cream. The omission of an in vitro release test from the finished product specification is therefore justified.

Limits for related substances above the qualification threshold are proposed at shelf-life and have been qualified in non-clinical studies. The limits for impurities are acceptable based on the levels seen in the batch analysis and stability studies. The shelf-life limit for assay of delgocitinib was tightened following the request from CHMP, levels proposed are considered acceptable at the time of opinion since some degradation is seen during storage. However, the applicant is recommended to evaluate the results from the next 30 batches and submit a post approval variation to tighten the limit if the additional data demonstrate that the assay is consistently well above 95% (recommendation 2).The chiral impurities(described in the active substance section) are controlled by the manufacturing process of the active substance and the active substance specification. The chiral centres are stable to epimerization and therefore, no limits are needed in the finished product specification.

An elemental impurities risk assessment has been performed in accordance with the ICH Q3D (R2) guideline. The maximum possible daily intake of elemental impurities does not exceed 30% of the PDE. It was concluded that the risk of presence of elemental impurities is low. Based on the risk assessment and the presented batch data it can be concluded that it is not necessary to include any elemental impurity controls in the finished product specification. The information on the control of elemental impurities is satisfactory.

A risk assessment concerning the potential presence of nitrosamine impurities in the finished product has been performed considering all suspected and actual root causes in line with the "Questions and answers for marketing authorisation holders/applicants on the CHMP Opinion for the Article 5(3) of Regulation (EC) No 726/2004 referral on nitrosamine impurities in human medicinal products" (EMA/409815/2020) and the "Assessment report- Procedure under Article 5(3) of Regulation EC (No) 726/2004- Nitrosamine impurities in human medicinal products" (EMA/369136/2020) has been provided. A secondary aminea potential impurity in the active substance and also a degradation product in the cream, could react with traces of nitrite, originating from the excipients to form a nitrosamine impurity . As requested by CHMP (Major Objection), the Carcinogenic Potency Categorization Approach (CPCA) has been applied to that impurity following the flowchart in *EMA/451665/2023 (Appendix 2).* Confirmatory testing has been performed as requested in the Major Objection. Six finished product batches were tested. The batches tested were towards the end of shelf-life, since the potential nitrosamine impurity is formed from a degradation product of delgocitinib. The results were consistently below the LoQ which is less than 10% of the AI of 1500 ng/day. Hence, it is considered justified that a requirement for that nitrosamine impurity is not included in the finished product specification. Based on the information provided, it can be concluded that there is no risk of nitrosamine impurities in the active substance or the related finished product.

Descriptions of the analytical methods used to control the finished product are presented and found acceptable. The non-compendial methods have been adequately validated in accordance with ICH Q2. Robustness of the methods have been demonstrated during development and the stability indicating nature of the assay and purity methods has been adequately demonstrated by forced degradation studies. Suitability of the methods for microbial purity according to Ph. Eur. 2.6.12 and 2.6.13 has been demonstrated.

Adequate information on the delgocitinib reference standard as well as the relevant impurity reference standards are provided or appropriate reference to the active substance documentation is given.

Batch analysis results are presented for three production scale batches packed in 15 g and 60 g tubes, respectively. The results showed that the finished product meets the specifications proposed and confirmed batch-to-batch consistency.

2.3.3.4. Stability of the product

Stability data from 6 primary production batches of the finished product manufactured at the proposed manufacturing site and packaged in the proposed market packaging (three batches in each proposed tube size) stored for up to 36 months under long term conditions (25 ºC / 60% RH) and for 6 months under accelerated conditions (40 ºC / 75% RH) according to the ICH guidelines were provided. The batches of Anzupgo were identical to those proposed for marketing and were packed in the primary packaging representative of that proposed for marketing.

Additional stability data from 6 supportive stability batches (2 lab scale, 1 pilot scale and 3 production scale) batches stored for 24-36 months at 25 °C / 60% RH and 6 months at 40 °C / 75% RH have also been presented.

Samples were tested for aappearance, delgocitinib assay, organic impurities, butylhydroxyanisole content and microbiology. The analytical procedures used are stability indicating.

The appearance of the product changed to "white to slightly brown cream" during storage. In addition, there was a slight tendency for a decrease in assay of delgocitinib and butylhydroxyanisole and an increase in the specified degradation products, more pronounced under accelerated conditions. Nonetheless, all results from the primary and supportive stability batches were well within the proposed specifications at all times and under all conditions.

A photostability study in accordance with ICH Q1B has been carried out on 1 commercial scale batch from each tube size and demonstrated that the finished product is sensitive to light, since a significant degradation in assay of butylhydroxyanisole and an increase of one specified impurity and total impurities was observed. However, it was shown that the proposed packaging provides an adequate protection against light. There was no difference in the results obtained when the tubes were stored inside or outside of the secondary packaging.

The sensitivity of the cream on exposure to direct sunlight has been discussed. Based on the results of the photostability study and the phototoxicity study provided, no warning regarding exposure to direct sunlight after application of the cream is required.

An in-use stability study has been performed on 1 commercial scale batch from each tube size in the packaging intended for commercial use. The batches used were relatively close to the start of shelf-life. All parameters (appearance, delgocitinib assay, organic impurities, benzyl alcohol, BHA, EDTA, pH, viscosity and microbiological quality) were tested at each timepoint. An increase on one impurity and a corresponding increase in total impurities and decrease in assay were seen. A tendency for a decrease in BHA was seen. No changes in any other parameters were observed. All results remained within the specification limits. The efficacy of antimicrobial preservation was also demonstrated. A commitment has been made to confirm the in-use period on batches towards the end of shelf life in accordance with EMA guidance Note for guidance on in-use stability testing of human medicinal products (CPMP/QWP/2934/99). The proposed in-use period of 12 months is acceptable.

Storage at low temperature was studied on six batches stored at 5°C. No out of specification result on the parameters tested was observed.

A freeze/thaw cycle study was performed during development. which showed that the emulsion separates after freezing and then thawing. A storage restriction "do not freeze" is therefore imposed.

A temperature cycling study involving three cycles between 5 °C and 40 °C / 75% RH followed by storage of the tubes at 25 °C / 60% RH was also conducted on one batch from each tube size. No significant changes were observed in any of the parameters tested.

Based on available stability data, the proposed shelf-life of 36 months with the storage restriction "do not freeze" as stated in the SmPC (section 6.3) is acceptable for both packaging sizes.

2.3.3.5. Adventitious agents

No excipients derived from animal or human origin have been used.

2.3.4. Discussion on chemical, pharmaceutical and biological aspects

The finished product is a cream containing 20 mg/g of the active substance delgocitinib. Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner.

The applicant has applied QbD principles in the development of the active substance Several design spaces were claimed for the manufacturing process of the active substance. The scalability of the design spaces to the desired commercial batch size range has been verified. The active substance specification has been updated as requested by CHMP during the review.

Process validation of the manufacture of the finished product has been carried out at the lowest proposed commercial batch size and will also be performed at the largest proposed commercial batch size before batches manufactured at that scale can be released. The process validation demonstrated that the manufacturing process is reproducible and consistently yields a finished product of the desired quality.

Questions raised on the proposed finished product specifications, including the omission of testing for a potential nitrosamine impurity have also been satisfactorily resolved.

The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

At the time of CHMP opinion, there were a number of minor unresolved quality issues having no impact on the benefit/risk ratio of the product, which pertain to i) the addition of a non-routine test for benzene in the active substance specification, ii) the evaluation of whether the limit for assay of delgocitinib in the finished product specification can be tightened when data from 30 batches becomes available and iii) the need to confirm the in-use period on batches towards the end of shelf life. These points are put forward and agreed as recommendations for future quality development.

2.3.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.

2.3.6. Recommendations for future quality development

In the context of the obligation of the MAHs to take due account of technical and scientific progress, the CHMP recommends the following points for investigation:

1. The applicant should include a non-routine test for benzene in the active substance specification in line with EMA guideline for residual solvents (CPMP/QWP/450/03 -Rev.1) by Q4 2024.
2. The applicant should evaluate whether the limit of delgocitinib assay in the finished product shelf-life specification can be tightened when data from 30 batches becomes available
3. The applicant should confirm the in-use period on batches towards the end of shelf life in accordance with EMA guidance Note for guidance on in-use stability testing of human medicinal products (CPMP/QWP/2934/99).

2.4. Non-clinical aspects

2.4.1. Introduction

The non-clinical development programme of delgocitinib has been designed in accordance with current ICH guidelines to support long-term dermal administration of delgocitinib cream. The non-clinical *in vivo* studies have been performed in mice, rats, dog and minipig either orally as solution or topically on skin. The non-clinical findings should be put in context of the systemic vs. skin exposure following different routes of application as well as the different formulations assessed. The non-clinical ointment to cream bridging strategy was used as a basis to support clinical trials with the delgocitinib cream and included studies to assess the local tolerance in minipigs and potentially altered skin permeation. The ointment and cream formulations have different amount of delgocitinib and different composition of excipients, was considered in assessment of non-clinical findings including skin sensitisation and eye irritation potential of the products. See *Toxicology*-section.

2.4.2. Pharmacology

2.4.2.1. Primary pharmacodynamic studies

In vitro pharmacodynamics

The inhibitory effects on human JAK enzymes were investigated by kinase assay. The method of analysis was considered to be fit for the purpose. Delgocitinib demonstrated ATP-competitive inhibition of human JAK1, JAK2, JAK3 and TYK2. The inhibition of TYK2 was lower than of other studied enzymes by both Ki and IC_{50} values, with relatively higher standard error of the mean.

The inhibitory effect of delgocitinib on cytokine signalling was studied by the level of STAT phosphorylation by flow cytometry in human PBMC. Recorded IC_{50} values suggested the inhibition of the phosphorylation of STATs induced by IL-2, IL-6, IL-23, IFN-α and GM-CSF, the inhibition of GM-CSF signalling being greatly weaker than for other measured cytokines.

Comparison of human, mouse and rat T cells demonstrated a comparable inhibitory effect across all species, supporting the *in vivo* species selection. However, a functional assessment of potency in minipigs (the most

important species examining the clinical formulation and the route of administration) is missing. Nevertheless, a detailed homology analysis and blast of the kinase domain (JH1) across species in UniProt data base revealed that there is i) high sequence homology in the JH1 kinase domain of JAK proteins between human and minipig; ii) the identical JAK JH1 domain sequence homology to either human or mouse, rat, and dog sequence, the species in which the inhibitory activity of delgocitinib is confirmed; and iii) conserved sequence across species of the docking sites for ATP and predictively for delgocitinib, supporting the choice of minipig as a relevant species in delgocitinib non-clinical safety assessment.

The functional *in vitro* studies with delgocitinib in human cells suggested inhibition of IL-21 mediated proliferation of human B cells (IC_{50} 49.2 ± 5.6 nmol/L), IL-13 secretion by mast cells (IC_{50} 135 ± 24 nmol/L), and TNF-α production by monocytes ((IC_{50} 277 ± 146 nmol/L). The high standard error of mean (SEM) presented in TNF-α studies (n = 3) has not been discussed by the applicant. No effect on the proliferation of fibroblasts without the addition of cytokines was recorded (IC_{50} > 10 000 nmol/L). No reference materials were included in these studies.

Delgocitinib treatment of human primary keratinocytes demonstrated reversion of mRNA expression of filaggrin, loricrin, involucrin and β-defensin 3, reduced by stimulation with IL-4 and IL-13. Reference materials cyclosporine and prednisolone had no effect on the mRNA expression of filaggrin and loricrin. The selection of reference materials is acknowledged.

It is agreed that the proof of concept for delgocitinib in the intended indication is demonstrated *in vitro* with representative cell types and assays.

In vivo pharmacodynamics

The *in vivo* pharmacodynamics was studied after oral and topical administration of delgocitinib in mice and rats. The topical data better reflects the intended use of the medicinal product and was therefore considered as primary data. The formulation of topical delgocitinib used in the *in vivo* PD studies (ointment) differs from the suggested commercial formulation (cream). However, this is not considered to impact the assessment of *in vivo* PD of delgocitinib and the studies were considered acceptable.

The 29-day oral study with delgocitinib in mouse skin inflammation model (DNFB-induced dermatitis) showed suppression in skin inflammation in the selected animal model (female mice). Dose-responsive suppression of ear swelling and immunoglobulin E (IgE) were recorded, the decrease being statistically significant with 30 mg/kg (ear swelling) or ≥ 3 mg/kg (IgE). Histopathological changes in the skin (acanthosis, spongiosis and infiltration of inflammatory cells in dermis) were also suppressed dose-dependently. A high inter-individual variation was observed between epidermal acanthosis, spongiosis and infiltration of inflammatory cells in dermis in mice treated with delgocitinib. A material control ciclosporin showed capability to suppress ear swelling but no clear suppression in histological changes induced by DNFB treatment, and increased IgE levels were recorded. Based on the recorded results, a suppression of skin inflammation was demonstrated for the orally administered delgocitinib.

The topical administration of delgocitinib ointment for three weeks in the ears of rat skin inflammation model (DNCB-induced dermatitis) showed dose-dependent suppression of ear swelling (male rats). The decrease was statistically significant when comparing to control at concentrations 0.3% and higher. Dose-dependent decrease in histopathological changes of inflamed skin (acanthosis, spongiosis, infiltration of inflammatory cells) was also demonstrated. Tacrolimus ointment 0.1% was used as a reference treatment and showed significant suppression of histological changes in the rat skin inflammation model, however, not as effectively as 3% delgocitinib. The reference treatment selection is acknowledged.

The effect on the ear thickness in normal rats was investigated following topical administration of delgocitinib. No effect was reported for delgocitinib or reference treatments tacrolimus and betamethasone valerate ointment but one of the reference treatments, difluprednate ointment, reduced the ear thickness. The selection of reference treatments is acknowledged.

The effect of topical delgocitinib administration on the skin barrier-related molecules was investigated in dry skin mouse model (gender not specified). The mRNA expression of filaggrin was significantly increased as well as the presence of natural moisturising factor, suggesting improvement of skin barrier function in the selected disease model.

The effect of delgocitinib on IL-31 induced scratching behavior was investigated in mouse after repeat-dose administration (oral) or single-dose administration (topical). Cyclosporine was used as a reference treatment for the oral delgocitinib. Oral treatment study was performed in female Balb/c mice whereas topical treatment study in male C57BL/6J mice, and the vehicle group showed more sensitivity on female Balb/c mice (number of scratching/2h 295 ± 158.6) than on male C57BL/6J mice (103 ± 49). In addition, a large number of mice (n=120) was used in the topical study. Delgocitinib was mixed in acetone/DMSO solution and applied to the mice in 15 minutes prior IL-31 injection. The composition was not representative of the clinical formulation. Despite the listed deficiencies, mice responded on delgocitinib treatment in dose-dependent manner in both studies by decrease of scratching, suggesting that both oral and topical treatment with delgocitinib have an inhibitory effect in the IL-31 induced scratching behavior.

The mode of action (JAK inhibition) of delgocitinib is a well-known strategy in the treatment of inflammatory diseases and the studies demonstrated the proof of concept of the use of topical delgocitinib in CHE. The selected animal models were fit for purpose in the PD assessment of topical delgocitinib.

2.4.2.2. Secondary pharmacodynamic studies

The effect of delgocitinib on the activity of set of kinases was evaluated with validated assays, and 1 from 50 investigated kinases showed inhibition by delgocitinib (ROCK-II; IC50: 141 nmol/L).

Less than 50% binding affinity to studied receptors (total 23; including ion channels) or inhibitory effects on enzyme reactions (total 5) were recorded at a concentration 10 µmol/L. The positive controls indicated that there were no issues with the functionality of the assays.

None or weak off-target effects are expected for topical delgocitinib.

2.4.2.3. Safety pharmacology programme

The *in vivo* safety pharmacology programme was conducted in male rats and dogs using oral administration which can be considered as the worst-case scenario from the safety perspective in comparison to dermal administration.

No effects on CNS or behaviour of rats were reported. Dose-responsive reddening of skin was reported assumably due to the vasorelaxation caused by delgocitinib. This was also observed in toxicity studies.

The hERG inhibition assay showed some dose-dependent inhibition of hERG current. However, the difference in the relative inhibition was not significant as compared to the vehicle whereas the positive control E-4031 showed significant inhibition of hERG current.

The oral combined cardiovascular and respiratory system safety *in vivo* study in dogs did not show any significant effects in the ECG parameters or in the respiratory rate or blood gas parameters at any time point up to highest dose administered. Decreasing tendency of systolic, diastolic and mean blood pressure as well as increased heart rate (assumably compensation to the blood pressure decrease) was observed in dogs of the 3 mg/kg group up to 2h after administering delgocitinib but not in the later time points (up to 24h after administering delgocitinib). The same phenomenon was recorded in the oral *in vivo* study in male rats of the high dose (30 mg/kg) group. The recorded cardiovascular effects were attributable to off-target ROCK-II inhibition mediated vasorelaxant effects of delgocitinib.

Delgocitinib demonstrated highly reversible vasorelaxant effects on Phe or KCl induced contractions in ring preparations of the thoracic aorta. The respective IC_{50} values were 3.6 and 3.5 µmol/L. This may partly explain the observed decrease of blood pressure after oral administration, via vascular smooth muscle relaxation.

The coronary flow (CF) was investigated using the isolated rat heart as the vasodilation may cause increase in CF. The CF was increased at 30 µmol/L but no clear effects in the cardiac contractility were recorded.

The inhibition of gastrointestinal transport was observed with oral administration of 30 mg/kg of delgocitinib in male rats. This inhibition was comparable to positive control atropine sulphate monohydrate, while 3 and 10 mg/kg delgocitinib had no inhibitory effect on gastrointestinal transport.

Delgocitinib dose-dependently increased urinary potassium excretion in male rats, increase being statistically significant in the 30 mg/kg administration group. Slight increase in urine volume as well as Na+ and Cl- excretion were recorded in comparison to vehicle.

The relevance of reported effects after high dose oral administration of delgocitinib was discussed in relation to the expected clinical exposure. As the TK analysis was not included in the safety pharmacology studies, the safety margins have been calculated based on the exposure measured in the repeat-dose toxicity studies. An uncertainty is associated with this approach, however, as the dosing was identical in these rat and dog studies and the resulting safety margins for expected human clinical exposure are > 1000, this approach is acceptable to the CHMP. The observed safety pharmacology effects *in vivo* are not considered relevant in the clinical settings for the topical delgocitinib.

2.4.2.4. Pharmacodynamic drug interactions

Pharmacodynamic drug interactions were not investigated. This is acceptable to the CHMP.

2.4.3. Pharmacokinetics

Methods of analysis

The delgocitinib concentrations in mouse, rat, rabbit, dog and minipig plasma samples were determined by LC/MS or LC/MS/MS.

In validation studies of the bioanalytical methods, all results met the acceptance criteria.

The bioanalysis of plasma samples from the GLP toxicity studies was conducted in compliance with GLP.

Absorption

Several comparative single- and repeated dose (TK) intravenous (IV), dermal, and oral absorption studies with delgocitinib were conducted in mice, rats, dogs and minipigs. Systemic exposure increased dose-dependently and gender differences were not detected. The bioavailability (BA) and absorbed fraction after dermal application of ^{14}C-delgocitinib ointment to intact and damaged rat skin were low, but the amount of absorption from the skin was increased by removing the stratum corneum. The systemic exposure reached a steady state by Month 1 after repeated dermal application of ointment in minipigs. In the nine-month repeated dermal dose toxicity study in minipigs, the plasma delgocitinib concentrations were higher in some animals at the same dose level. These animals with higher concentrations had skin findings on the application site at sampling time points for delgocitinib concentrations, likely to be related to the increased plasma delgocitinib concentrations (see *Toxicology*-section). After oral administration to mice, rats, and dogs, delgocitinib was well and rapidly absorbed, with T_{max} of within one hour. After IV administration of delgocitinib to mice, rats, dogs, and minipigs, the plasma concentrations of delgocitinib decreased rapidly with a half-life of about two hours.

The systemic exposure (C_{max} and AUC_{0-24}) to delgocitinib was broadly similar in male minipigs following administration of ointment (30 mg/g) and cream (20 mg/g) as a single dose or once daily for seven days. The BA after dermal application of delgocitinib cream and ointment to minipig skin were ≤0.88% and ≤1.57%, respectively. Improved skin penetration of cream formulation compared to ointment was demonstrated using two *in vitro* skin models. In a study in pigs, results showed a higher delivery of delgocitinib from the cream compared with the ointment in both intact and damaged skin

As all dermal toxicity studies were performed with the ointment formulation, an uncertainty on the systemic effects of the topical delgocitinib cream was initially identified based on the skin penetration/permeation comparison in pigs and in human skin explants. The applicant acknowledges that the systemic exposure and bioavailability of the cream and ointment formulations are not necessarily fully comparable. There was a large standard deviation of systemic exposure in terms of AUC and calculated bioavailability in pigs after dermal application of 30 mg/g ointment under non-occluded conditions on Day 1. Further, very large deviation of systemic exposure and bioavailability was observed also on Day 7 for both cream and ointment. Nevertheless, these data are in line with human data showing large standard deviation of systemic exposure of delgocitinib cream and ointment in human subjects with CHE, presumably depending on severity of skin lesions. As a large number of subjects with CHE representing the variability in different factors affecting exposure have been included in the pivotal phase 3 studies, the systemic exposure in subjects with CHE is well described and is therefore judged to adequately reflect the target CHE patient population with different absorption profiles (e.g., skin barrier function). Therefore, the applicant finds it highly unlikely that results from the skin penetration and permeation studies should change or affect the conclusion of the exposure or safety data obtained in the target population in the clinical trials. This is endorsed.

Distribution

All dermal distributions studies have been conducted with delgocitinib ointment, though the commercial formulation is the cream. It was demonstrated in male minipigs that the systemic exposure to delgocitinib was broadly similar following a single or repeated application of ointment (30 mg/g) and cream (20 mg/g).

After a single dermal administration of ^{14}C-delgocitinib ointment on the damaged skin tissue (stratum corneum removed) concentrations of radioactivity in rats were measurable in almost all organs still at 24 hours compared to intact skin. Distribution study in dogs with ^{14}C-delgocitinib indicated binding of radioactivity to melanin-containing tissues including skin and eyeballs.

The protein binding of delgocitinib was low in all animal species tested without significant species differences.

Metabolism

In vitro

Delgocitinib was hardly metabolised in liver microsomes from various species except for the minipig. Metabolites M1, M2, and M3 were produced in mice, rats, rabbits, minipigs and humans, and M2 and M3 were produced in dogs, all in small amounts. The highest metabolic degradation rate of ^{14}C-delgocitinib was in minipigs. No metabolism occurred in human skin microsomes.

Delgocitinib in human liver microsomes is mainly metabolised by CYP3A4, whereas CYP2C9, CYP2C19, and CYP2D6 have only a minor role.

Delgocitinib did not inhibit the enzyme activity of any evaluated isoforms (CYP1A2, 2A6, 2B6, 2C8, 2C9, 2C19, 2D6, and 3A4/5), the IC_{50} values being >30 µmol/L. No time-dependent inhibitory effect was observed on any of the CYP isoforms. Based on enzyme activity and mRNA assays Delgocitinib does not pose induction potential for CYP1A2, 2B6 or 3A4.

Metabolite profiling of plasma

After oral administration, the main component in the rat plasma was delgocitinib and the proportion was 92.3% at 0.5 hours after administration. M3 was detected as a metabolite, and the proportion was 7.7%. In the plasma samples of the rat three-month toxicity study, M1, M3, M4, and M5 were detected. In the plasma samples of juvenile rats at 0.5 hours after administration, only delgocitinib was found. No metabolites were detected.

The main component in the dog plasma sample was delgocitinib, and the proportion was 80.9% at two hours after administration. M2 and M3 were detected as metabolites, and the proportions were 2.3% and 16.8%, respectively. In the plasma samples of the dog three-month toxicity study, M1, M3, and M4 were detected.

The main component in human plasma was delgocitinib. M1, M3, M4, and M5 were detected <2%.

Metabolite profiling of urine, feces and bile

By 24 hours after oral administration, M3 was the only metabolite identified in urine, feces or bile of the rat/juvenile rat and dog, and in addition M2 was the minor component in dog urine.

Excretion

After dermal application of ^{14}C-delgocitinib ointment 30 mg/g (2.4 mg/animal as delgocitinib, approximately 10 mg/kg) in rats, most of the radioactivity was recovered in the remaining ointment from the application site. After dermal application to intact and damaged rat skin, urine was the main route of excretion. After oral and IV administration in rats the absorbed ^{14}C-delgocitinib is excreted mainly in the urine, and in the feces through biliary excretion and intestinal secretion. After oral or IV administration of ^{14}C-delgocitinib (1 mg/kg) in dogs, the urine was the main route of excretion of radioactivity. After oral administration of ^{14}C-delgocitinib (1 mg/kg) in lactating rats on day 12 postpartum, radioactivity concentration at all time points was shown to be higher in the milk than into plasma indicating an effective excretion in the milk.

Pharmacokinetic drug interactions

Delgocitinib is a substrate of P-gp and weak substrate of OAT3 and OCT2. Delgocitinib is not a substrate of OAT1, BCRP, MATE1 nor MATE2-K.

Delgocitinib does not inhibit P-gp- or BCRP-mediated transport. OATP1B1 or OATP1B3 or OCT2-mediated uptake is not inhibited by the drug substance. Delgocitinib does not inhibit MATE1 or MATE2-K-mediated transport. On the other hand, it inhibits OAT1- and OAT3-mediated uptake.

Overall, *in vitro* studies suggest that relevant pharmacokinetic drug interactions are not expected at clinical concentrations of delgocitinib.

2.4.4. Toxicology

2.4.4.1. Single dose toxicity

Single-dose toxicity of delgocitinib by oral route was studied in mice, rats and dogs. In mice and dogs, systemic exposure after a single dose was studied while in rats a single-dose toxicity was assessed as a part of *in vivo* chromosomal aberration test in rat bone marrow cells. In mice the approximate lethal dose level was 1000 mg/kg. In rats the approximate lethal dose level was 300 mg/kg. Reddening of skin in mice and rats and reddening of auricles and/or visible mucous membranes (conjunctiva and sclera) in dogs attributable to the vasorelaxing action of delgocitinib at plasma concentrations more than 0.5 to 1 µg/mL were the main findings. At high dose in rats decreased locomotor activity, eyelid closure and irregular respiration was observed.

2.4.4.2. Repeat dose toxicity

Oral repeat-dose toxicity

Rats

In three-month oral dose toxicity study with a one-month recovery period systemic exposure to delgocitinib increased dose-dependently at up to the highest dose level of 30 mg/kg with no gender differences. Systemic exposure was generally similar in days 1, 27 and 89 indicating no drug accumulation in plasma. No changes suggestive of systemic toxicity or target organ toxicity (including the testes, epididymides, seminal vesicles and prostates) were observed at up to the highest dose level, 30 mg/kg. All of the treatment-related changes observed during and at the end of the dosing period were reversible.

In six-month oral dose toxicity study systemic exposure to delgocitinib increased dose-dependently at up to the highest dose level of 30 mg/kg with no gender differences. Systemic exposure was generally similar in days 1, 91 and 177 indicating no drug accumulation in plasma.

There were no changes suggestive of hepatotoxicity or inflammation in the clinical pathology or in the histopathology of the liver.

In the 10-week oral dose toxicity study in juvenile rats (21 days of age at initiation, dose levels: 3, 10, and 30 mg/kg), decreases in body weight gain and food consumption and an associated decrease in ulnar length were seen. Changes considered to be related to the pharmacological action of delgocitinib (i.e., a decrease in white blood cell counts and associated atrophic changes in lymphoid organs and slight decreases in erythrocyte-related parameters) and changes considered to be related to the vasorelaxant action of

delgocitinib (i.e., transient reddening of the skin and secondary hypertrophy of the adrenal zona glomerulosa) were also seen. A decrease in T cell-dependent antibody production and decreases in all lymphocyte subsets (mainly CD8+ T cells and NK cells) were observed and considered to be related to the pharmacological action of delgocitinib.

Dogs

In two-week oral dose toxicity study the systemic exposure to delgocitinib increased dose-dependently at up to the highest dose level of 3 mg/kg in both sexes with no gender differences. There were no differences in plasma levels of delgocitinib between days 1 and 14 of the dosing period in either sex at each dose level. A slight decrease in germinal center development in the lymph nodes, a slight decrease in the erythropoietic cell counts (basophilic or polychromatic erythroblast) in the bone marrow, a slight increase in myelocytic cells / erythrocytic cells ratios, slight decreases in plasma total protein, albumin and calcium levels, and a slight decrease in albumin/globulin ratio was observed. These changes were considered to be of little toxicological significance because there were no treatment-related histopathological findings in the thyroid, bone, kidney or liver at any dose level.

In three-month oral dose toxicity study with one-month recovery period the systemic exposure to delgocitinib increased dose-dependently at up to the highest dose level, 3 mg/kg, in both sexes, with no gender differences. There were no differences in exposure between days 1, 28 and 91 in either sex at each dose level. Changes related to the pharmacological action of delgocitinib were observed at the mid dose level (1 mg/kg) and above, however, all of the changes disappeared after a 4-week recovery period.

In nine-month oral dose toxicity study with a three-month recovery period the highest dose level of 3.0 mg/kg was reduced to 1.5 mg/kg from week 24 of the dosing period due to serious skin lesions and dosing was withdrawn from week 26 (week 1 of the recovery period) to investigate the reversibility of any toxicity during a 13-week recovery period.

The systemic exposure to delgocitinib increased dose-dependently in both sexes up to the highest dose level, 3 mg/kg, on day 1 of the dosing period and up to 0.6 mg/kg (no data for the 3 mg/kg group are available due to the interim sacrifice of this group) in week 39 of the dosing period, with no gender differences. There were no differences in exposure between day 1 and week 39 of the dosing period in either sex at each dose level.

Dermal repeat-dose toxicity

Minipigs

In the preliminary one-month dermal dose toxicity study in juvenile minipigs the plasma delgocitinib concentration on day 1 of the dosing period was below the lower limit of quantification (0.5 ng/mL) in all the animals at all dose levels except for one female at the high dose level. On day 28 of the dosing period, the plasma delgocitinib concentration tended to increase dose-dependently, however, it remained low at all time points. No gender differences were observed. Since most of the plasma concentrations following dermal application of delgocitinib to juvenile animals were below the lower limit of qualification, no formal PK calculation could be performed in study 77052. Consequently, the dermal bioavailability in juvenile minipigs could not be estimated due to the few animals /sample points with measurable delgocitinib concentrations. Instead, comparing the sparse C_{max} measurements obtained in juvenile animals (Day 3) with C_{max} measurements obtained in the repeat dose toxicology studies in minipigs treated with a 3% ointment for 1-month (study 61282) (Day 28) and 9-month (study 77057) (Week 13), they are roughly in the same 1-3 ng/ml range. Since plasma concentrations do not differ significantly across minipig studies and animal age,

the applicant assumed that the systemic bioavailability after dermal application in juvenile animals is similar to that determined in older minipigs i.e., approximately 1% (0.88% - 1.57%). In the application site of the skin in the control group (delgocitinib ointment vehicle) and delgocitinib ointment 3 mg/g (1.2. mg/kg/day) there were occasional slight to mild, focal to diffuse red spots and erythema affecting no more than 25% of the dermal application site during the dosing period. No changes suggestive of systemic or target organ toxicity (including the testes, epididymides and prostate) were observed at up to the highest dose level, delgocitinib ointment 30 mg/g (12 mg/kg/day).

In nine-month dermal toxicity study in minipigs, at NOAEL of 20 mg/kg, some treated animals with skin lesions had higher systemic exposure to delgocitinib when compared with the other animals at the same dose levels, which increased mean AUC value in minipig plasma. The highest systemic exposure was measured in week 36 of the 9-month study in one high-dose male, with C_{max} 41 ng/mL and AUC_{0-24} 618 ng*h/mL. In comparison, the systemic exposure following the administration of lowest oral dose (0.01 mg/kg), which was observed to be pharmacologically active, in week 39 of the 9-month dog repeat-dose toxicity study was 41 ng/mL/172 ng*h/mL and 57 ng/mL/ 224 ng*h/mL (males/females respectively). Therefore, a few minipigs in the 9-month repeat-dose toxicity study had delgocitinib levels at which short-term systemic JAK inhibition (JAKi) could occur, which is likely attributed to fluctuation/variation in minipig exposure over the time course of treatment as compared to dogs which are dosed orally and were continuously exposed to delgocitinib. Repeat-dose toxicity studies in dogs suggest that JAKi-related effects are dependent not only on delgocitinib concentration, but on the duration of treatment, as well. These data are to some extent consistent with the values around 50 ng/mL (10-100 ng/ml range) obtained in *in vitro* functional cell-based IC_{50} values, in which the inhibitory effect of delgocitinib on cytokine signalling was examined (studies 10B052SG01 and 11B052SG01). Furthermore, the clinical relevance of high inter-individual differences in exposure seen in dermal toxicity study is estimated to be negligible. Contrary to minipigs, there was consistently low exposure (with a geometric mean of 0.21 ng/mL in study 1402) and minimal variation in humans following dermal application.

The animals with high systemic exposure had the skin findings on the dermal application sites on the days for measurement of plasma concentrations of delgocitinib, suggesting that the higher systemic exposure was related to the skin findings. Ulceration, epidermal hyperplasia and mixed inflammatory cell infiltration in the skin were seen at a relatively high incidence in groups 3 (12 mg/kg) and 4 (20 mg/kg). The applicant explained that more pronounced variation in exposure that was seen in minipigs treated dermally compared to dogs or rats treated orally was not unexpected due to some uncertainties related to actual topical dose. These include highly variable semi-occlusive effect of the dressing on the back of minipigs, high risk oral contamination from contaminated hay and small procedural lesions on the back of animals resulting in increased dermal absorption. Moreover, there may have been residual ointment even after washing of the treated skin area due to very sticky and greasy texture of the ointment especially in high dose groups. This conclusion is endorsed. It is obvious that the skin lesions seen in minipigs are related to semi-occlusion not mimicking the clinical dosing conditions and hence with very limited clinical relevance. In conclusion, in oral repeat-dose toxicity studies in rats and dogs, extensive exposure margins at NOAEL to human exposure following 7-day dermal application exist. In nine-month dermal toxicity study in minipigs, human multiples of 20 and 11 was obtained in males and females, respectively.

2.4.4.3. Genotoxicity

In *in vivo* chromosomal aberration test adequate systemic exposure was demonstrated in rats. In the *in vitro* chromosomal aberration test, delgocitinib had the potential to induce polyploidy in human peripheral blood lymphocytes but not chromosomal structural aberrations. 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. In conclusion, delgocitinib is not a genotoxic substance.

2.4.4.4. Carcinogenicity

Mouse

In the two-year dermal carcinogenicity study in mice with delgocitinib ointment (0, 1%, 3% and 5%), no treatment related neoplastic/preneoplastic changes were observed locally (skin) or systemically. The systemic exposure at the highest dose (strength) 30 mg/kg (5%) was approximately 600 times the exposure in patients with CHE treated with delgocitinib cream 20 mg/g ointment twice daily for 8 days.

The haematological changes including decrease of white blood cell counts, red blood cell counts lymphocyte, eosinophil, basophil and large unstained cell counts, haemoglobin concentration and haematocrit values were considered to be related to the JAK inhibition by delgocitinib because the proliferation/differentiation of leukocytes and the erythropoietin signals are suppressed through inhibition of the JAK members.

In dermal mouse study, increased adipocytes were observed in the sternal bone marrow (females at 5%) and femoral bone marrow (both sexes at 3% and above). No fatty changes were seen in the bone marrow or skin of mice treated with 1% delgocitinib ointment. At this dose the AUC was approximately 100-fold higher than the exposure seen in man. Increased dermal adipose tissue was observed in the inguinal skin (females at 5%) and dorsal treated/untreated skin (females at 3% and above), but due to a safety margin of approximately 100, it is unlikely that adipocytes will be increased in the skin following topical administration of delgocitinib 20 mg/g cream to man and the clinical relevance is thus considered to be negligible.

Rat

Dose-dependent increases in bone marrow adipocytes were seen in rats. In the sub-chronic oral toxicity studies of 13- and 26-weeks duration in rats, fatty infiltration was seen at doses ≥ 10 mg/kg and the NOAEL was 3 mg/kg. At this dose (3 mg/kg) the AUC was approximately 150-fold higher than exposure seen in man.

In the two-year oral carcinogenicity study in rats (0, 3, 10 and 30 mg/kg), the following treatment related neoplastic/preneoplastic changes were observed: thymoma/hyperplasia in females ≥10 mg/kg, Leydig cell tumour/hyperplasia in males ≥10 mg/kg and pancreatic acinar cell adenoma/hyperplasia and subcutaneous lipoma in males ≥3 mg/kg. These neoplastic/preneoplastic changes did not occur in mice at similar exposure levels. The applicant concludes that the changes excluding pancreatic acinar cell adenoma were directly or secondarily related to the pharmacological action of delgocitinib i.e., JAK inhibition. This is supported by the delgocitinib exposure levels that exceeded by far the IC_{50} values of JAK1, JAK2 and JAK3 at all dose levels.

Delgocitinib was negative in a standard battery of genotoxicity tests and all the above neoplastic/preneoplastic changes (except pancreatic acinar cell adenoma) were therefore considered to have occurred through a non-genotoxic mechanism.

Thymoma:

In the oral carcinogenicity study in rats, the incidence of thymoma (benign and malignant) was increased in females ≥10 mg/kg, and thymic hyperplasia was increased at a dose of 30 mg/kg.

The systemic exposure in female rats at 3 mg/kg, at which neither thymoma nor hyperplasia was observed, was approximately 158 times the exposure (AUC0-24 = 0.0074 µg·hr/mL) in CHE patients (study LP0133-2285) and the carcinogenic risk to humans receiving therapeutic exposure to delgocitinib is negligible.

Leydig Cell Tumour:

In the oral carcinogenicity study in rats, the incidence of Leydig cell tumours (benign) was increased in males at 30 mg/kg and Leydig cell hyperplasia was increased at ≥10 mg/kg. Dopamine agonists reduce plasma PRL levels, and the subsequent down-regulation of luteinising hormone (LH) receptors on Leydig cells along with a continuous increase in plasma LH induce Leydig cell hyperplasia and tumours. The applicant assumes that delgocitinib induced Leydig cell tumours and hyperplasia by inhibiting PRL signal transduction via JAK2 inhibition. Since human Leydig cells lack this PRL dependence for normal function, the rodent Leydig cell tumours are irrelevant for human health risk assessment.

The systemic exposure in male rats at 3 mg/kg, at which neither Leydig cell tumours nor hyperplasia were observed, was approximately 161 times the exposure (AUC0-24 = 0.0074 µg·hr/mL) in CHE patients and the carcinogenic risk to humans receiving therapeutic exposure to delgocitinib is negligible.

Pancreatic acinar cell adenoma:

In the oral carcinogenicity study in rats, the incidence of pancreatic acinar cell adenoma/hyperplasia was increased in males ≥ 3 mg/kg. In rats, induction of proliferative lesions of the pancreatic acinar cells is associated with increased plasma CCK levels related to direct or indirect trypsin inhibition. A weak trypsin-inhibitory effect of delgocitinib was demonstrated in an *in vitro* investigation. Furthermore, increased plasma CCK levels were observed at 3 mg/kg and above in the plasma samples from male rats in the oral carcinogenicity study of delgocitinib.

Based on the distinct species differences in the expression and sensitivity of the CCK receptors in the pancreatic acinar cells between humans and rats, the proliferative lesions of the rat pancreatic acinar cell caused by increased plasma CCK is generally considered to be of little human relevance. There were no proliferative lesions of the pancreatic acinar cells in the dermal carcinogenicity in mice, and systemic exposure in mice treated with delgocitinib ointment 5% exceeded 600 times the exposure (AUC_{0-24} = 0.074 µg·hr/mL) in CHE patients and the carcinogenic risk to humans receiving therapeutic exposure to delgocitinib is negligible.

2.4.4.5. Reproductive and developmental toxicity

The effects on the male and female fertility and early embryonic development (rats), and embryo-foetal development (rats and rabbits), and pre- and postnatal developmental (rats) were evaluated in oral dose studies.

In the male fertility and early embryonic development in rats, small spleen and small thymus, considered related to the pharmacological action of delgocitinib, were observed in males at 30 mg/kg and at 10 mg/kg and above, respectively, without any effects on male fertility or early embryonic development. The NOAEL for male fertility and early embryonic development was greater than 30 mg/kg. When using AUC_{0-24h} at the same NOAEL obtained in the 3 months repeat dose toxicity study in rats, exposure margin is 1729-fold to human AUC_{0-24h} obtained in dermal 7-day application study 2285.

In the female fertility and early embryonic development study in rats (study P110952), decrease in the number of corpora lutea and implantation and fertility index was observed in dams at 100 mg/kg. Post-implantation losses and a decrease in the live foetuses were observed at 10 mg/kg and 30 mg/kg, respectively. The NOAELs for the female fertility and early embryonic development in this study were 30 mg/kg and 3 mg/kg, respectively. At 3 mg/kg the post-implantation loss index was increased (8.36%) when compared with the control group (4.69%). The applicant did not consider this to be treatment-related, since

the incidence was within the range of the background data at the test facility. As the increased number of post-implantation loss was dose related, the applicant provided historic data of test facility to support that the effect in 3 mg/kg group is not considered as treatment-related.

In the oral embryo-foetal development study in rats, delgocitinib was not teratogenic at any dose level. Relevant findings in the embryos/foetuses included a decrease in foetal weights and an increase in wavy ribs, which is a skeletal variation, at 10 mg/kg and above, and a tendency toward an increase in the post-implantation loss index, increased skeletal variations, delayed sternum ossification and an increase in thymic remnants in the neck at 30 mg/kg. The NOAEL for embryo-foetal development in this study was 3 mg/kg, $AUC_{0\text{-}24h}$ providing 120-fold exposure margin to human $AUC_{0\text{-}24h}$ obtained in dermal 7-day application study.

In the embryo-foetal development study in rabbits, delgocitinib was not teratogenic at any dose level. In the embryos/foetuses, an increase in post-implantation loss index, a decrease in the number of live foetuses and a tendency towards a decrease in foetal weights were observed at 10 mg/kg (992 times expected clinical exposure). The NOAEL for embryo-foetal development in this study was 3 mg/kg, and $AUC_{0\text{-}24h}$ provides 194-fold exposure margin to human $AUC_{0\text{-}24h}$ obtained in dermal 7-day application study.

In the pre- and postnatal development study in rats, at 30 mg/kg, food consumption was decreased in the dams during the lactation period and changes suggestive of effects on the delivery and foetal viability were noted. In the newborns, a decrease in the viability and suppression of growth during the early post-natal period was noted at 30 mg/kg, however, there were no effects on the behaviour or the reproductive performance at any dose level. The NOAEL was considered to be 10 mg/kg/day for dams and liveborn pups. When using $AUC_{0\text{-}24h}$ obtained on Day 89 in 3-month repeat dose toxicity study in rats there is 536-fold exposure margin to human $AUC_{0\text{-}24h}$ obtained in dermal 7-day application study.

In proposed SmPC the applicant stated that orally administered delgocitinib in rats resulted in decreased foetal viability and reduced pup weights during the early postnatal period at exposures approximately 1 800 times the human exposure. Since TK analysis wasn't performed in the pre- and postnatal development study, the applicant used the average of combined male and female $AUC_{0\text{-}24h}$ at 30 mg/kg on Day 89 from 13-week repeat dose toxicology study in rats (M=12.807 µg·hr/mL, F=15.226 µg·hr/mL) to calculate this exposure margin. This is considered acceptable to the CHMP.

In the 10-week oral repeat dose toxicity study in juvenile rats, a decrease in ulnar length was observed from the lowest dose of 3 mg/kg (M:87x human exposure, F: 130x human exposure). This finding was associated with slight decreases in body weight gain and food consumption observed in same animals. As mentioned above, an increase in wavy ribs, an increase in skeletal variations (general) and delayed sternal ossification were seen in embryo-foetal development study in rats. They were considered as minor variations predictably seen in the presence of maternal toxicity and related to overall delayed foetal growth / development and not specifically related to JAK inhibition. Skeletal findings observed in the embryo-foetal development study are included under embryo-foetal development in section 5.3 of the SmPC.

2.4.4.6. Toxicokinetic data

All pivotal repeat-dose toxicity studies included TK analyses of delgocitinib. Generally, in oral repeat-dose toxicity studies systemic exposure (C_{max} and $AUC_{0\text{-}24}$) to delgocitinib increased dose-dependently with no gender differences. There were no effects with repeated dosing on the systemic exposure to delgocitinib. In oral repeat-dose toxicity studies in rats and dogs, extensive exposure margins at NOAEL to human exposure exist. In dermal repeat-dose toxicity studies in minipigs, lower but still acceptable margins exist. Any pathological findings in oral repeat-dose toxicity studies in rats and dogs were considered related to the

delgocitinib's pharmacological activity and were not observed with topically applied delgocitinib in minipigs due to in significantly lower systemic drug concentrations.

In 9-month study all animals treated with ≥ 3% delgocitinib ointment had detectable plasma delgocitinib concentrations from week 13. Dose-dependent systemic exposure was observed, and steady state was reached in week 13. There were no gender differences in systemic exposure.

2.4.4.7. Local Tolerance

In primary skin irritation study in rabbits, delgocitinib 30 mg/g ointment formulation and vehicle proved to be slightly irritative. However, the commercial product is a cream, therefore these results are only considered supportive. In comparison, in minipig's skin no test article-related skin or histopathological skin reactions were seen following application of the ointment or different cream formulations including formulation that was identical to the commercial formulation.

The potential of primary eye irritation of delgocitinib ointment 1%, 3% and placebo was evaluated in a bovine corneal opacity and permeability (BCOP) test. The three tested delgocitinib ointment formulations (delgocitinib ointment placebo, 1% and 3%) were identified having no irritant properties to the eye, and as not requiring classification for eye irritation or serious eye damage (UN GHS No Category). However, this application is for delgocitinib 20 mg/g cream and therefore, these results are only considered supportive.

In a skin sensitisation study in guinea pigs following a procedure comparable to a Guinea pig maximisation test, delgocitinib ointment 3 mg/g (0.3%), 10 mg/g (1%) or 30 mg/g (3%) and vehicle were judged to have no skin sensitisation potential. The applicant stated that the cream formulation is not expected to have skin sensitisation potential based on the nature and concentration of the excipients. A thorough evaluation of the local tolerance of delgocitinib 20 mg/g cream including all excipients has been evaluated and discussed by the applicant. The excipients used in the cream formulation all have a long history of safe use, are EU/US pharmacopeial excipients and listed in FDA's list of inactive ingredients at the same or higher potency. All of the excipients are already approved for use in other topical products for chronic skin diseases. Several clinical trials confirm that topical administration of delgocitinib cream 20 mg/g is well tolerated. In conclusion, no additional non-clinical local tolerance study is required for the cream.

In a skin photosensitisation study in guinea pigs, delgocitinib ointment 3 mg/g, 10 mg/g or 30 mg/g (0.3%, 1% and 3%, respectively) and vehicle were judged to have no skin photosensitisation potential. The cream 20 mg/g has not been tested for photosensitisation. However, in a clinical trial (1411 CTR) there was no clinical indication of any photosensitisation potential of the cream formulation in healthy volunteers.

2.4.4.8. Other toxicity studies

Delgocitinib was repeatedly administered orally once daily to SD rats (six weeks of age, both sexes) at the dose levels of 3, 10 and 30 mg/kg for 4 weeks to investigate the effects on the immune system.

The haematology examination showed dose-dependent decreases in white blood cells, lymphocytes and eosinophil counts in both sexes at all dose levels and a decrease in neutrophil counts in both sexes at 10 mg/kg and above. The organ weights of the thymus and spleen were decreased dose-dependently in both sexes from the lowest dose level. T-cell dependent antibody response assessment, the anti-sheep red blood cell antibody production was decreased dose-dependently from the lowest dose level in both sexes, and at the highest dose level (30 mg/kg), the anti-SRBC antibody production was markedly decreased to the minimum limit of detection in both sexes. In the peripheral blood lymphocyte subset analyses, dose-

dependent decreases in T cell, CD4+ T cell, CD8+ T cell, B cell and NK cell counts associated with a decrease in peripheral blood lymphocyte counts were observed in both sexes at all dose levels.

All the changes are considered to be attributable to the immunosuppressive effects of JAK inhibitor delgocitinib.

Single oral dose phototoxicity study in mice and a single dermal dose skin phototoxicity study in guinea pigs with delgocitinib ointment and ointment vehicle indicated that there is no phototoxicity potential.

No findings besides those related to JAK inhibition were seen in studies on impurities and there were no significant differences in the findings between animals that were treated with delgocitinib alone or when compared with delgocitinib + impurities.

2.4.5. Ecotoxicity/environmental risk assessment

Table 2 - Summary of main study results

Substance (INN/Invented Name): delgocitinib			
CAS-number (if available): 1263774-59-9			
PBT screening		Result	**Conclusion**
Bioaccumulation potential- log K_{ow}	OECD 107	Log K_{ow} (pH 2.0) -2.6 Log K_{ow} (pH 5.0) 0.2 Log K_{ow} (pH 7.0) 0.6 Log K_{ow} (pH 7.4) 0.7 Log K_{ow} (pH 9.0) 0.7 pKa 5.5	Not Potential PBT (log K_{ow} < 4.5)
PBT-assessment			
Parameter	**Result relevant for conclusion**		**Conclusion**
Bioaccumulation	log K_{ow}	Log K_{ow} (pH 2.0) -2.6 Log K_{ow} (pH 5.0) 0.2 Log K_{ow} (pH 7.0) 0.6 Log K_{ow} (pH 7.4) 0.7 Log K_{ow} (pH 9.0) 0.7	not B
	BCF	-	
Persistence	DT_{50} or ready biodegradability	$DT_{50\ Sediment}$ (12 °C): 299 d $DT_{50\ TotalSystem}$ (12 °C): 198 d	vP in total system and sediment
Toxicity	NOEC or CMR	-	not T
PBT-statement:	The compound is not considered as PBT nor vPvB		
Phase I			
Calculation	**Value**	**Unit**	**Conclusion**
PEC $_{surfacewater}$, default	300	ng/L (calculated with $DOSE_{ai}$)	> 10 ng/L threshold (Y)
Other concerns (e.g. chemical class)			N
Phase II Physical-chemical properties and fate			
Study type	**Test protocol**	**Results**	**Remarks**
Adsorption-Desorption	OECD 106	*Log* $K_{oc\ sandy,\ silt,\ loam\ soil}$ = 2.83 *Log* $K_{oc\ loamy,\ sand\ soil}$ = 3.05 *Log* $K_{oc\ clay\ soil}$ = 2.62 *Log* $K_{oc\ Activated\ sludge}$ = 1.63 *Log* $K_{oc\ Activated\ sludge}$ = 1.87	- slight potential for binding to sewage sludge

					- medium potential for binding to soil → OECD TG 201, 211, 210 and 209 studies to be conducted.
Ready Biodegradability Test	OECD 301	N/A*			OECD TG 308 study to be conducted.
Aerobic and Anaerobic Transformation in Aquatic Sediment systems	OECD 308	Lake water $DT_{50, water}$ = 16.9 days $DT_{50, sediment}$ = 297 days $DT_{50, whole\ system}$ = 120 days Pond water $DT_{50, water}$ = 32.7 $DT_{50, sediment}$ = 160 $DT_{50, whole\ system}$ = 77.5			Potential of adverse effects on sediment dwelling organisms → OECD TG 218 study to be conducted.
Phase IIa Effect studies					
Study type	**Test protocol**	**Endpoint**	**value**	**Unit**	**Remarks**
Algae, Growth Inhibition Test/ *Raphidocelis subcapitata*	OECD 201	NOErC EC_{10} NOEyC EyC10	32 43 18 20	mg/ L	Green alga
Daphnia sp. Reproduction Test	OECD 211	NOEC EC_{10} reproduction	1.0 1.3	mg/ L	
Fish, Early Life Stage Toxicity Test/ *Pimephales promelas*	OECD 210	NOEC post-hatch survival	>10	mg/ L	Fathead minnow; NOEC was the highest dose tested in all endpoints.
Activated Sludge, Respiration Inhibition Test	OECD 209	EC_{10} total respiration	501	mg/ L	at pH 7.2
Sediment-water chironomid toxicity test, spiked sediment / *Chironomus riparius*	OECD 218	NOEC reduction of emergence	1135	mg/ L	NOEC was the highest dose tested in all endpoints. o.c. 2.2%

o.c. = organic carbon

* Study deleted at the late phase of the assessment due to the failed GLP inspection of the test facility.

In the Phase I assessment of ERA, the applicant preformed the PBT screening based on the log K_{ow} value. The range of log D_{OW} values for delgocitinib were determined at room temperature within a pH-range of 2-9 according to the shake flask methodology (sfm). These studies were not conducted strictly according to the OECD TG 107, as the experiments were not repeated with volume ratios divided or multiplied by two. The dosing regimen is calculated using the maximum daily dose consumed per inhabitant, and default values of Fpen, WASTEWinhab and DILUTION were used in the calculation of PECsurfacewater. The outcome of the Phase I assessment is agreed with.

Delgocitinib was shown to be very persistent in total system and sediment. The CHMP consulted the NcWP if risk minimisation measures should be set on the PI to restrict delgocitinib entry to the aquatic systems. The

NcWP conclusions were that no specific RMM are warranted in the PI as no risk to the environment has been identified.

Phase II Tier A studies followed OEDC test protocols and were conducted in compliance with GLP. In addition, a study following OECD TG 218 (insects) was performed due to the high DT_{50} in the sediment observed in the sediment transformation study (OECD TG 308). The studies used the conditions specified in EMA Q&A on the Guideline on the ERA (EMA/CHMP/SWP/44609/2010 Rev. 1).

In the Aerobic Transformation in Aquatic Sediment Systems (OECD 308) study, delgocitinib showed persistence in sediment with DT_{50} values up to 140 days.

The PNEC calculation was performed with appropriate assessment factors and $PEC_{groundwater}$ was calculated as per the CHMP guideline on the ERA (EMEA/CHMP/SWP/4447/00 corr. 2). The ratios of PEC/PNEC in each compartment were below 1 and therefore it is agreed that the drug substance is unlikely to represent a risk to aquatic organisms in surface and groundwater or to microorganisms in STPs.

Delgocitinib is not expected to be an endocrine disrupting compound and therefore no additional investigations concerning these endpoints are required.

2.4.6. Discussion on non-clinical aspects

Overall, the primary pharmacodynamic studies provided adequate evidence that the proof of concept for delgocitinib in the intended indication is demonstrated *in vitro* with representative cell types and assays and *in vivo* with suitable animal models.

The general pharmacology studies showed decreased skin inflammation after oral and topical administration of delgocitinib, suppressing local swelling, histopathological changes (acanthosis, spongiosis and infiltration of inflammatory cells) and systemic IgE levels. Improvement of skin barrier function was also demonstrated, as well as inhibiting effect on the IL-31 induced scratching behaviours in mouse. No effect on skin thickness was observed in rats with no skin inflammation.

The safety pharmacology studies on CNS, cardiovascular, respiratory rate, gastrointestinal and renal/urinary system effects demonstrated inhibition of gastrointestinal transport and increase in urinary potassium excretion at the highest dose applied (30 mg/kg), with inhibition rates in the range with positive controls. The mechanism of decreased blood pressure in early timepoints observed in *in vivo* studies is partly unclear. Delgocitinib-induced urine potassium excretion, together with slight increase in urinary volume and Na^+ and Cl^- excretion were not discussed by the applicant. As calculated safety margins for clinical exposure exceed 1 000, these effects are not considered relevant in clinical settings.

The absorption, distribution, metabolism, excretion, and *in vitro* drug-drug interaction potential of delgocitinib were investigated in mice, rats, rabbits, dogs, and minipigs. Unlabelled delgocitinib and ^{14}C-labeled delgocitinib (^{14}C-delgocitinib) were used as the test articles.

For dermal application, ointment and/or cream containing delgocitinib or ^{14}C-delgocitinib was applied to rat, minipig/pig and *ex vivo* human skin. In dermal PK studies, mostly ointment formulation was used, however in a single dose or repeat-dose for seven days dermal PK study (crossover study design) ointment 30 mg/kg and cream 20 mg/kg were compared to bridge dermal PK data obtained with ointment formulation to cream.

The applicant acknowledges that the systemic exposure and bioavailability of the cream and ointment formulations are not necessarily fully comparable. Across the completed *in vivo*, *in vitro* and *ex vivo* studies,

the cream delivered at least as efficiently as the ointment with regards to skin penetration, and in the *ex vivo* human skin explants, the cream showed significantly higher delivery than ointment. The various penetration/permeation and open-flow microperfusion studies were not conducted to demonstrate comparability of exposure levels, but rather to assist in choosing the right formulation for further clinical development. To avoid excessive skin permeation, especially through lesional or barrier disrupted skin, no traditional skin penetration enhancers such as propylene glycol or polyethylene glycol were included in the cream formulation. This resulted in a general low bioavailability and negligible systemic exposure in both pigs and humans. Like in the minipigs there is comparable high variation in systemic exposure in humans. In the provided risk assessment, the applicant concludes that even the highest C_{max} value observed in CHE patients is below a concentration sufficient to have a meaningful systemic effect related to JAK inhibition. This is endorsed by the CHMP.

A comprehensive number of toxicology studies have been completed including genotoxicity, repeat dose toxicity (up to 6 months in rodents and 9 months in dogs [oral] and minipigs [dermal]) and reproductive toxicology (male and female fertility in rats, embryo-foetal development in rats and rabbits, and pre- and postnatal developmental study in rats). Special studies e.g., phototoxicity, skin and eye irritation, and immunotoxicology as well as juvenile and carcinogenicity studies (oral rat and dermal [ointment] mouse) have also been conducted. The studies except for the dermal dose skin micronucleus test in hairless mice and the preliminary one-month repeated dermal toxicity study in juvenile minipigs, were all conducted in compliance with the ICH guidelines and GLP principles as defined by the OECD.

The relevance of oral studies for the topical formulation was initially questioned. The potential adverse effects of pharmacological JAK-inhibitory action on immune response in laboratory animals (housed in clean environment) could be assessed to a limited degree. In dermal studies, in which no toxicity was observed up to 20 mg/kg/day of delgocitinib in minipigs [20 (M) and 11 (F)-fold higher exposure than human exposure], NOAEL was not identified. Therefore, there are no concerns on the potential issue of the relevance of NOAELs derived from oral studies for topical application of delgocitinib, as assessed by the CHMP.

In the one-month dermal dose toxicity study in juvenile minipigs the plasma delgocitinib concentration on day 1 of the dosing period was below the lower limit of quantification (0.5 ng/mL) in all the animals at all dose levels except for one female at the high dose level. On day 28 of the dosing period, the plasma delgocitinib concentration tended to increase dose-dependently, however, it remained low at all time points. Since plasma concentrations do not differ significantly across minipig studies and animal age, it can be assumed that the systemic bioavailability after dermal application in juvenile animals is similar to that determined in older minipigs i.e., approximately 1% (0.88% - 1.57%).

In the nine-month dermal toxicity study in minipigs, at NOAEL of 20 mg/kg some treated animals with skin lesions had higher systemic exposure to delgocitinib when compared with the other animals at the same dose levels, which increased mean AUC value in minipig plasma. The lack of JAKi-related effects in those minipigs despite the overlapping exposure with dogs for systemic JAK inhibition is likely attributed to variation in minipig exposure over the time course of treatment as compared to dogs which are dosed orally and were continuously exposed to delgocitinib. In comparison to human data, due to consistent low exposure and minimal variation in humans following dermal application, it can be concluded that there is no risk of clinically meaningful continuous systemic JAK inhibition with delgocitinib cream treatment.

In nine-month dermal dose toxicity study in minipigs, some animals with high systemic exposure had higher exposure to delgocitinib but it was shown that the skin lesions consequently seen were related to study conditions not mimicking the clinical dosing conditions and hence, have with very limited clinical relevance.

Dose-dependent increases in bone marrow adipocytes were seen in both rats and mice. In mice treated topically with delgocitinib for 2 years, increased dermal adipose tissue was observed in the inguinal skin (females at 5%) and dorsal treated/untreated skin (females at 3% and above). In rats treated orally with delgocitinib for 2 years, increased dermal adipose tissue was noted in the inguinal region at dose of ≥ 10 and ≥ 3 mg/kg in males and females respectively. These changes were considered non-adverse. Since fatty infiltration is related to the pharmacology of JAK inhibition, this finding would be of clinical relevance if sufficient exposure is obtained in human. Fatty infiltration of the bone marrow is, however, not considered to be clinically relevant for delgocitinib cream, due to 1) topical administration, 2) minimal exposure (declining over time), 3) no physiological JAK inhibition in human, and 4) safety margins of 100-150. Due to a safety margin of approximately 100, it is unlikely that adipocytes will be increased in the skin following topical administration of delgocitinib 20 mg/g cream to human and the clinical relevance of this observation is thus considered negligible by the CHMP.

In the oral carcinogenicity study in rats, the incidence of uncommon tumour thymoma was increased with unknown mechanisms that may be related to systemic JAK inhibition and prolactin inhibition. As the safety margin from NOEAL to expected clinical exposure was approximately 158, the carcinogenic risk to humans is considered negligible.

In the female fertility and early embryonic development study in rats (study P110952), decrease in the number of corpora lutea and implantation and fertility index were observed in dams at 100 mg/kg. Post-implantation losses and a decrease in the live foetuses were observed at 10 mg/kg and 30 mg/kg, respectively. The NOAELs for the female fertility and early embryonic development in this study were 30 mg/kg and 3 mg/kg, respectively. At 3 mg/kg the post-implantation loss index was increased (8.36%) when compared with the control group (4.69%). The applicant provided adequate historic data of the test facility to support not considering the effect in 3 mg/kg group as treatment-related. Skeletal findings observed in the embryo-foetal development study have been reflected in section 5.3 of the SmPC.

It can overall be agreed that the systemic absorption of delgocitinib cream is very low, and that the resulting safety margins are sufficiently high so that use during pregnancy does not need to be contraindicated and use during breastfeeding does not require restrictions. Nevertheless, as a precautionary measure, the applicant considers it preferable to avoid the use of delgocitinib cream 20 mg/g during pregnancy. This is agreed by CHMP. Section 4.6 of the SmPC adequately reflects this caution.

In addition, a thorough evaluation of the local tolerance of delgocitinib 20 mg/g cream including all excipients was provided and discussed by the applicant. Several clinical studies confirm that topical administration of delgocitinib cream 20 mg/g is well tolerated.

The current ERA data for delgocitinib cream do not suggest a potential risk to the environment. Delgocitinib is not a PBT substance and is not expected to pose a risk to the environment.

2.4.7. Conclusion on the non-clinical aspects

In conclusion, the applicant provided a comprehensive evaluation of pharmacologic, pharmacokinetic and toxicologic properties of delgocitinib. Overall, delgocitinib cream is therefore considered to be approvable from a non-clinical point.

2.5. Clinical aspects

2.5.1. Introduction

GCP aspects

The clinical trials were performed in accordance with GCP as claimed by the applicant.

The applicant has provided a statement to the effect that clinical trials conducted outside the Community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

- **Tabular overview of clinical studies**

Trial ID Phase Objectives	Trial status Type and location of report	Trial design	FSFV LSLV Number of sites and location	Planned/randomized or allocated/ exposed/subjects completed the trial Median age (range) Sex	Main inclusion criteria and diagnosis	IMPs, dose, route & regimen (n, exposed subjects)	Treatment duration	Primary endpoint(s)
Trials in chronic hand eczema								
2285 Phase 1 PK and safety.	Completed Full CTR M5.3.3.2 Trial 2285 CTR	Open-label, single-arm.	06-Sep-2022 22-Nov-2022 1 site in Germany.	≈22/16/16/15 39.0 years (22-69) M: 8 (50.0%) F: 8 (50.0%)	Adults (≥18 yrs) with moderate to severe CHE[1] (i.e. an IGA-CHE score of 3 or 4). Subjects with a documented recent history of inadequate response to treatment with TCS or for whom TCS is medically inadvisable.[2] Subjects adherent to standard non-medicated skin care including avoidance of known and relevant irritants and allergens.	Delgocitinib cream 20 mg/g (n=16). Topical application twice daily.	1 week.	AUC at Day 1 and Day 8 (0–12 hours post dose). C_{max} at Day 1 and Day 8 (0-12 hours post dose).
1180 Phase 2a Efficacy, safety, and PK/PD.	Completed Full CTR M5.3.5.1 Trial 1180 CTR	Randomized (2:1) vehicle-controlled, double-blind, proof-of-concept.	16-Feb-2016 30-Jun-2016 13 sites in Germany.	90/91/91/86 All randomized subjects: 44.0 years (18-65) M: 29 (31.9%) F: 62 (68.1%)	Adults (18-65 yrs) with mild to severe CHE.[1] Clinical diagnosis of CHE with or without atopic etiology/ background with a history of not adequately controlled disease activity with	Delgocitinib ointment 30 mg/g (n=60). Ointment vehicle (n=31). Topical application twice daily.	8 weeks.	Treatment success according to the PGA at Week 8.[3]

Trial ID Phase Objectives	Trial status Type and location of report	Trial design	FSFV LSLV Number of sites and location	Planned/randomized or allocated/ exposed/subjects completed the trial Median age (range) Sex	Main inclusion criteria and diagnosis	IMPs, dose, route & regimen (n, exposed subjects)	Treatment duration	Primary endpoint(s)
					cutaneously applied steroid. PGA of disease severity graded as at least mild at baseline (Week 0).			
1273 Phase 2b Efficacy, safety, and PK/PD.	Completed Full CTR M5.3.5.1 Trial 1273 CTR	Randomized (1:1:1:1:1), vehicle-controlled, double-blind, dose-ranging.	28-Nov-2018 20-Apr-2020 26 sites in 3 countries (Denmark, Germany, and United States).	250/258/258/204 All randomized subjects: 48.0 yrs (18-79) M: 100 (38.8%) F: 158 (61.2%)	Adults (≥18 yrs) with mild to severe CHE[1] (i.e. an IGA score of ≥2). Subjects with a recent history (within 1 year before the screening visit) of inadequate response to TCS treatment or TCS treatment being medically inadvisable.	Delgocitinib cream 1, 3, 8, 20 mg/g: (1 mg: n=52). (3 mg: n=51). (8 mg: n=52). (20 mg: n=53). Cream vehicle (n=50). Topical application twice daily.	16 weeks.	IGA-CHE TS at Week 16.
1401 Phase 3 Efficacy, safety, and PD.	Completed Full CTR M5.3.5.1 Trial 1401 CTR	Randomized (2:1), vehicle-controlled, double-blind.	10-May-2021 31-Oct-2022 51 sites in 6 countries (Canada, France, Germany, Italy, Poland, and United Kingdom).	470/487/487/459 All randomized subjects: 44.0 yrs (19-87) M: 181 (37.2%) F: 306 (62.8%)	Adults (≥18 yrs) with moderate to severe CHE[1] (i.e. an IGA-CHE score of 3 or 4). HESD itch score (weekly average) of ≥4 points at baseline. Subjects with a documented recent history of inadequate response to treatment with TCS or for whom	Delgocitinib cream 20 mg/g (n=325). Cream vehicle (n=162). Topical application twice daily.	16 weeks.	IGA-CHE TS at Week 16.

Trial ID Phase Objectives	Trial status Type and location of report	Trial design	FSFV LSLV Number of sites and location	Planned/randomized or allocated/ exposed/subjects completed the trial Median age (range) Sex	Main inclusion criteria and diagnosis	IMPs, dose, route & regimen (n, exposed subjects)	Treatment duration	Primary endpoint(s)
					TCS is medically inadvisable.[2] Subjects adherent to standard non-medicated skin care including avoidance of known and relevant irritants and allergens.			
1402 Phase 3 Efficacy, safety, and PK.	Completed Full CTR M5.3.5.1 Trial 1402 CTR	Randomized (2:1), vehicle-controlled, double-blind.	25-May-2021 06-Jan-2023 49 sites in 7 countries (Belgium, Canada, Denmark, Germany, the Netherlands, Poland, and Spain).	450/473/472/420 All randomized subjects: 44.0 yrs (18-86) M: 161 (34.0%) F: 312 (66.0%)	Adults (≥18 yrs) with moderate to severe CHE[1] (i.e. an IGA-CHE score of 3 or 4). HESD itch score (weekly average) of ≥4 points at baseline. Subjects with a documented recent history of inadequate response to treatment with TCS or for whom TCS is medically inadvisable.[2] Subjects' adherent to standard non-medicated skin care including avoidance of known and relevant irritants and allergens.	Delgocitinib cream 20 mg/g (n=313). Cream vehicle (n=159). Topical application twice daily.	16 weeks.	IGA-CHE TS at Week 16.
1403 Phase 3	Completed. Full CTR	Open-label extension trial of	23-Aug-2021 18-Sep-2023	≈600/801/779/661	All eligible subjects who completed the	Delgocitinib cream 20 mg/g (n=779).	36 weeks.	Number of treatment-emergent AEs from

Trial ID Phase Objectives	Trial status Type and location of report	Trial design	FSFV LSLV Number of sites and location	Planned/randomized or allocated/ exposed/subjects completed the trial Median age (range) Sex	Main inclusion criteria and diagnosis	IMPs, dose, route & regimen (n, exposed subjects)	Treatment duration	Primary endpoint(s)
Long-term safety and efficacy.	M5.3.5.2 Trial 1403	Trials 1401 and 1402.	99 sites in 10 countries (Belgium, Canada, Denmark, France, Germany, Italy, Netherlands, Poland, Spain, and United Kingdom).	45.0 yrs (18-86) M: 289 (36.1%) F: 512 (63.9%)	treatment period in Trials 1401 or 1402.	Topical application twice daily as needed. As needed defined as: If the subject has an IGA-CHE score of ≥2 (mild or worse), subject is to apply delgocitinib cream 20 mg/g twice daily until an IGA-CHE score of 0 (clear) or 1 (almost clear) is achieved.		baseline up to Week 38.
1426 Phase 3 Efficacy, safety, and PK. *Ongoing at the time of the MAA submission*	Ongoing NA	Randomized (3:1), vehicle-controlled, double-blind.	14-Jul-2022 NA Planned: Approximately 40 sites in Europe, Canada, and Australia.	92/NA/NA/NA NA	Adolescents (12-17 yrs) with moderate to severe CHE[1] (i.e. an IGA-CHE score of 3 or 4). Subjects with a documented recent history of inadequate response to treatment with TCS or for whom TCS is medically inadvisable.[2]	Planned subjects: Delgocitinib cream 20 mg/g (n=69). Cream vehicle (n=23). Topical application twice daily.	16 weeks.	IGA-CHE TS at Week 16.
1528 Phase 3 Efficacy, and safety.	Completed CTR not submitted (*the trial was ongoing at the time of the MAA submission)*	Randomized (1:1), assessor-blinded, active-controlled.	15-Jun-2022 05-Dec-2023 103 sites in 9 countries in Europe and Canada.	510/513/500/408 All randomized subjects: 45.0 yrs (18-77) M: 179 (34.9%) F: 334 (65.1%)	Adults (≥18 yrs) with severe CHE[1]. Subjects with a documented recent history of inadequate response to treatment with TCS or for whom TCS is medically inadvisable.[2]	Delgocitinib cream 20 mg/g (n=253). Topical application twice daily. Alitretinoin 30 (or 10) mg capsule (n=247). Oral administration once daily.	Delgocitinib cream 20 mg/g for 16-24 weeks. Alitretinoin 30 (or 10) mg capsule for 12-24 weeks.	Change in HECSI score from baseline to Week 12.
Trials in atopic dermatitis								
1181 Phase 1 Safety and PK (including maximum usage trial).	Completed Full CTR M5.3.5.4 Trial 1181 CTR	Open-label, single-arm. Part 1: Adults and adolescents. Part 2: Children. Parts 1 and 2 were separated by a safety evaluation.	20-Feb-2019 29-Oct-2021 14 sites in 2 countries (Canada and United States)	44/46/46/44 Part 1: 24/26/26/24 Part 2: 20/20/20/20 Adults: 37.5 yrs (18-77) M: 8 (57.1%) F: 6 (42.9%) Adolescents: 15.0 yrs (12-17) M: 4 (33.3%) F: 8 (66.7%) Children: 6.0 yrs (2-11) M: 13 (65.0%) F: 7 (35.0%)	Adults (≥18 yrs), adolescents (12-17 yrs), and children (2-11 yrs) with moderate to severe AD. Treatable body surface area Part 1: 25-50%. Part 2: ≥35%. History of AD Part 1: ≥12 mths. Part 2: ≥3 mths (children 2-5 yrs); ≥12 mths (children 6-11 yrs).	Part 1: Adults and adolescents. Delgocitinib cream 20 mg/g (n=26). Part 2: Children. Delgocitinib cream 20 mg/g (n=20). Topical application twice daily.	8 weeks.	AEs (number of AEs and number of subjects with AEs) from baseline to Week 8.
1275 Phase 2b	Completed Full CTR	Randomized (1:1:1:1:1), vehicle-controlled double-blind, dose-ranging, 5-arm, parallel-group.	29-Nov-2018 19-May-2020 31 sites in 3 countries	250/251/250/208 All randomized subjects: 37.0 yrs (18-82)	Adults (≥18 yrs) with mild to severe AD Treatable body surface area (5-50%). History of AD (≥1 yr).	Delgocitinib cream 1, 3, 8, 20 mg/g: (1 mg: n=49). (3 mg: n=50). (8 mg: n=50). (20 mg: n=51).	8 weeks.	Change from baseline to Week 8 in EASI score.

Trial ID Phase Objectives	Trial status Type and location of report	Trial design	FSFV LSLV Number of sites and location	Planned/randomized or allocated/ exposed/subjects completed the trial Median age (range) Sex	Main inclusion criteria and diagnosis	IMPs, dose, route & regimen (n, exposed subjects)	Treatment duration	Primary endpoint(s)
Efficacy, safety, and PK.	M5.3.5.4 Trial 1275 CTR		(Australia, Canada, and United States).	M: 79 (31.5%) F: 172 (68.5%)		Cream vehicle (n=50). Topical application twice daily.		
Trials in healthy subjects								
1408 Phase 1 Photo-toxicity and safety.	Completed Full CTR M5.3.5.4 Trial 1408 CTR	Randomized, vehicle-controlled, double-blind, 4-day, within-subject comparison.	23-Apr-2020 30-May-2020 1 site in Germany.	≈45/35/35/35 56.0 yrs (24-64) M: 14 (40.0%) F: 21 (60.0%)	Healthy adults (18-64 yrs). Fitzpatrick skin type of I, II, or III. Successful minimal erythemal dose determination prior to randomization.	Delgocitinib cream 1, 3, 8, 20 mg/g and cream vehicle. (n=35; all 4 strenghts of delgocitinib cream and cream vehicle). Single topical occlusive application.	24 hours.	Positive skin reaction at 24 hours or 48 hours after irradiation.
1409 Phase 1 QT/QTcF pro-longation, safety, and PK.	Completed Full CTR M5.3.4.1 Trial 1409 CTR	Randomized (1:1:1:1:1), double-blind, placebo-controlled, parallel-group, single-dose.	29-Sep-2021 04-Jan-2022 1 site in the United Kingdom.	40/40/40/40 All randomized subjects: 39.0 yrs (median of the medians) (20-60) M: 20 (50.0%) F: 20 (50.0%)	Healthy adults (18-60 yrs). Body mass index of ≥18.0 to <30.0 kg/m². In good general health, without any clinically relevant abnormal ECG findings.	Delgocitinib capsule 1.5, 3, 6, 12 mg: (1.5 mg: n=8). (3 mg: n=8). (6 mg: n=8). (12 mg: n=8). Delgocitinib capsule placebo (n=8). Single oral dose.	1 day.	ΔQTcF. Timeframe: predose to 24 hours postdose.
1411 Phase 1	Completed Full CTR	Randomized, vehicle-controlled, double-blind, within-subject comparison.	25-Mar-2021 30-Jul-2021 1 site in Germany.	≈60/60/60/57 50.0 yrs (24-64) M: 23 (38.3%) F: 37 (61.7%)	Healthy adults (18-64 yrs). Fitzpatrick skin type of I, II, or III.	Delgocitinib cream 20 mg/g and cream vehicle (n=60). Topical occlusive application twice weekly	Induction phase: 3 weeks. Challenge phase: 1 day.	Positive skin reaction at 72 hours after irradiation.

Trial ID Phase Objectives	Trial status Type and location of report	Trial design	FSFV LSLV Number of sites and location	Planned/randomized or allocated/ exposed/subjects completed the trial Median age (range) Sex	Main inclusion criteria and diagnosis	IMPs, dose, route & regimen (n, exposed subjects)	Treatment duration	Primary endpoint(s)
Photo-allergenicity and safety.	M5.3.5.4 Trial 1411 CTR		.			for 3 weeks (induction phase) and single application 2 weeks after induction phase (challenge phase).		
Trial in healthy subjects (conducted by Japan Tobacco Inc.)								
NBX1-1 Phase 1 Safety and PK.	Completed Full CTR M5.3.3.1 Trial NBX1-1 CTR	Randomized, placebo-controlled single-blind, single dose (Part 1) and multiple dose (Part 2).		Part 1: 40/40/40/40 Part 2: 24/24/24/24 Part 1: ≈24.5 yrs (median of the medians) (20-42) M: 40 (100%) Part 2: 29.0 yrs (median of the medians) (21-38) M: 24 (100%)	Healthy Japanese males (20-45 yrs). Body mass index of ≥18.5 to <25.0 kg/m².	Part 1 (single dose; oral) *Fasted conditions:* 1, 5, 25, 50, 100 mg delgocitinib (n=6 in each active group). Placebo oral (n=10). *Fed conditions:* 25 mg delgocitinib (n=6). Placebo oral (n=2). Part 2 (multiple dose; oral) *Once daily for 14 days:* 25, 50 mg delgocitinib (n=6 in each active group). Placebo oral (n=4). *Twice daily for 14 days:* 25 mg delgocitinib (n=6). Placebo oral (n=2).	Part 1: 1 day. Part 2: 14 days.	AEs and adverse drug reactions.

[1] CHE is defined as hand eczema that has persisted for more than 3 months or returned twice or more within the last 12 months.

[2] Subjects who have a documented recent history of inadequate response to treatment with TCS (at any time within 1 year before the screening visit) or for whom TCS are documented to be otherwise medically inadvisable (e.g. due to important side effects or safety risks)

[3] Subjects classified at baseline as having 'mild' disease according to PGA had to achieve 'clear' to be considered to have achieved treatment success. Subjects classified at baseline as having 'moderate' or 'severe' disease according to PGA had to achieve 'clear' or 'almost clear' to be considered to have achieved 'treatment success'.

Abbreviations: Δ = change from baseline; AD = atopic dermatitis; AE = adverse event; AUC_{0-12} = area under the concentration-time curve 0-12 hours post dose; CHE = chronic hand eczema; C_{max} = maximum observed plasma concentration; CTR = clinical trial report; EASI = Eczema Area and Severity Index; F = females; FSFV = first subject first visit; HECSI = Hand Eczema Severity Index; HESD = Hand Eczema Symptom Diary©; IGA-CHE = Investigator's Global Assessment for CHE (an instrument used in clinical trials to rate the severity of the subject's global CHE and is based on a 5-point scale ranging from 0 [clear] to 4 [severe]); IGA-CHE TS = IGA-CHE treatment success, i.e. an IGA-CHE score of 0 (clear) or 1 (almost clear) with a ≥2-step improvement from baseline; IMP = investigational medicinal product; LSLV = last subject last visit; M = males; MAA = marketing authorization application; mths = months; NA = not applicable; PD = pharmacodynamic(s); PGA = Physician's Global Assessment of Disease Severity; PK = pharmacokinetic(s); QTc = QT corrected for heart rate; QTcF = QT interval corrected using Fridericia's formula; TCS = topical corticosteroid(s); yrs = years.

2.5.2. Clinical pharmacology

2.5.2.1. Pharmacokinetics

The clinical studies providing PK and/or PD data are summarised in the above tabular overview of clinical studies. In studies 1180, 1273, 2285, 1401, and 1402, the enrolled population consisted of adult patients with CHE and these studies can be considered the most important for evaluation delgocitinib cream 20 mg/g PK and PD. Of note, in the study 1180, the formulation has been 30 mg/g ointment.

In addition to the cream formulation, tablet, and capsule formulations of delgocitinib have also been used during development (studies 1409 and NBX1-1) and delgocitinib cream PK has been also studied in patients with AD (studies 1181 and 1275). The PK data from these studies can be considered as a supportive information.

In addition, the applicant provided 'PBPK prediction of systemic exposure of delgocitinib in breastfeeding children' and additional analyses of PK data from two clinical studies (studies 1273 and 1402) with delgocitinib cream 20 mg/g in treatment of subjects with mild to severe CHE.

Bioanalytical methods

Delgocitinib concentrations in human plasma and urine samples were determined with four validated methods using LC-MS/MS analysis.

Interference of the analytical methods with delgocitinib metabolites was not investigated, which was acceptable since metabolism was determined to be minimal.

Absorption

Rate and extent of absorption after oral administration

NBX1-1 Study

The PK parameters after oral administration of delgocitinib after single dose administration at fasted conditions are summarised in Table 3. The PK parameters following multiple oral administrations for 14 days, were similar at Day 1 and Day 14 and no accumulation was observed for C_{max} and AUC_{tau}.

Table 3 - Pharmacokinetic parameters after oral administration of delgocitinib at single doses – study NBX1-1

	Delgocitinib				
Dose	**1 mg**	**5 mg**	**25 mg**	**50 mg**	**100 mg**
n	6	6	6	6	6
Plasma					
C_{max} (ng/mL)	11.0±2.43	56.5±9.85	313±94.6	619±115	956±129
AUC_{last} (ng×h/mL)	29±6	167±16	951±92	1799±339	3238±279
$AUC_{0\text{-}inf}$	NC	175±16	957±105[a]	1815±341	3257±273
t_{max} (hr)	0.75 (0.50-1.00)	1.00 (1.00-1.00)	1.00 (0.50-1.50)	1.00 (0.50-1.00)	1.00 (0.50-1.50)
$t_{1/2}$ (hr)	NC	2.71±0.32	3.82±0.83[a]	3.96±1.00	4.71±0.96
CL/F	NC	28.80±2.65	26.40±3.08[a]	28.35±5.15	30.88±2.45
V_z/F	NC	112.7±19.9	147.5±44.7 [a]	164.0±59.1	210.5±49.6

Notes: Numbers in panel are mean ± SD; [a] n = 5. For t_{max} median (min-max).

Abbreviations: $AUC_{0\text{-}inf}$ = area under the concentration-time curve from the time of dosing to infinity; AUC_{last} = area under the curve concentration-time from t=0 to the time corresponding the last measurable concentration; C_{max} = maximum plasma concentration; n = number of subjects; NC = not calculated; SD = standard deviation; t_{max} = time to peak concentration; $t_{1/2}$ = half-life; CL/F = apparent total plasma clearance;Vz/F = apparent volume of distribution during the terminal phase.

Study 1409

The PK parameters of delgocitinib are given in the Table 4.

Table 4 - PK parameters after oral single dose administration of delgocitinib – study 1409

	Delgocitinib 1.5 mg (N=8)	Delgocitinib 3 mg (N=8)	Delgocitinib 6 mg (N=8)	Delgocitinib 12 mg (N=8)
C_{max} (ng/mL)				
n	8	8	8	8
Geometric mean	7.22	18.4	51.0	99.3
CV (%)	89.6	42.6	41.9	17.0
Median	9.38	17.0	49.7	101
Min;Max	2.12;19.5	10.7;37.3	32.4;92.2	74.1;124
AUC_{last} (ng×h/mL)				
n	7	8	8	8
Geometric mean	19.4	55.8	193	389
CV (%)	123.8	39.1	37.9	22.1
Median	21.3	51.0	197	398
Min;Max	4.13;66.4	35.0;106	113;315	255;512
AUC_{0-inf} (ng×h/mL)				
n	5	8	8	8
Geometric mean	39.6	66.6	211	408
CV (%)	53.2	35.1	35.8	20.5
Median	40.6	61.5	215	412
Min;Max	23.5;78.6	41.8;120	133;334	276;530
t_{max} (h)				
n	8	8	8	8
Median	1.00	0.842	0.833	1.00
Min-max	0.667;1.33	0.667;1.67	0.667;1.72	0.667;1.33
$t_{½}$ (h)				
n	6	8	8	8
Geometric mean	2.02	2.32	2.85	2.75
CV (%)	39.9	11.5	15.7	25.4
Median	1.84	2.22	2.81	2.64
Min;Max	1.40;3.68	2.05;2.75	2.10;3.41	2.09;4.70
CL/F (L/h)				
n	5	8	8	8
Geometric mean	37.9	45.1	28.4	29.4
CV (%)	53.2	35.1	35.8	20.5
V_z/F (L)				
n	5	8	8	8
Geometric mean	118	151	117	117
CV (%)	30.0	34.8	29.1	31.7

Rate and extent of absorption after topical administration in subjects with atopic dermatitis

Study 1181

After topical administration in subjects with AD, delgocitinib absorption reached the peak concentration in median 1 to 2 hours after administration. Time to peak concentrations, t_{max} values for the individual subjects ranged between 0.83 to 12.22 h on Day 1 and from 0.00 to 12.03 h on Day 8, indicating variability in the absorption profiles.

The geometric mean C_{max} was 1.28 ng/ml (GM CV% 372.5%) after first administration and 1.20 ng/ml (GM CV% 188.27%) after one week of twice daily application in adult subjects. Overall, the exposures were low. Children (2-11 years of age) had higher geometric mean C_{max} 3.94 ng/ml (CV% 1312%) on Day 1 and 3.26 ng/ml (CV% 369.32%) on Day 8 after twice daily application. The large variability was observed due to high concentrations for some subjects. The exposures tended to increase with the treated body surface area. Few

subjects, mainly in the children group, had higher exposure, with values for C_{max} ranging from 0.01 to 79.80 ng/mL at Day 1 and from 0.04 to 54.70 ng/mL at Day 8. The review of the AEs reported in this study did not identify safety concerns for the subjects with higher exposure. In adults, the concentrations stayed mainly below 10 ng/ml. One adult patient (20-30 years of age, BSA 50%) had C_{max} of 15.8 ng/ml on the first day of the treatment.

Bioavailability

No bioavailability study has been conducted; however, the relative bioavailability (F_{rel}) of delgocitinib cream 20 mg/g was calculated by comparing the AUC after topical administration of delgocitinib cream 20 mg/g in patients with CHE (from study 2285) with the AUC after oral administration of delgocitinib (from studies NBX1-1 and 1409) and adjusting for dose. The relative bioavailability of delgocitinib cream 20 mg/g has been found to be low (approximately 0.5-0.6%).

Distribution

After oral administration, apparent volume of distribution during terminal (V_z/F) ranged from 112 L to 199 L (5 - 100 mg dose) and from 188.5 – 357 L (25 – 50 mg dose) after single and multiple dosing, respectively. The applicant did not report the volume of distribution after topical use of delgocitinib 20 mg/g cream. Plasma protein binding of delgocitinib was 22% to 29% at concentrations 30 ng/ml to 100 ng/ml, respectively. The blood/plasma concentration ratios in human blood *in vitro* ranged from 1.40 to 1.49. At concentration of 30 ng/ml, delgocitinib is distributed approximately 60% in blood cells in human blood *in vitro*.

Elimination

Urine excretion and metabolic profiling of delgocitinib has been evaluated after oral administration of delgocitinib in study NBX1-1. Renal excretion of delgocitinib has been investigated after single doses of 1 mg to 100 mg and after multiple doses of 25 mg once a day, 50 mg once a day or 25 mg twice day for 14 days.

After single oral dose, delgocitinib was observed to be excreted mainly as unchanged drug in urine. The fraction of systematically available drug excreted in urine over entire collection interval of 48 hours (fe_{total}) was 70.8% to 80.9% after single oral dose of 1 to 100 mg. The major fraction was excreted within the first 12 hours after administration of the oral dose. Renal clearance CL_r ranged from mean 21.15 L/h to mean 22.84 L/h after 5 mg to 100 mg oral single dose at fasted conditions.

After multiple dose administration of 25 mg once daily or 50 mg once daily for 14 days, CLr ranged from mean 17.62 L/hr to 21.47 L/hr and the fraction excreted in urine during the dosing interval (fe_{tau}) was approximately 66% to 69%.

Metabolite profiling was investigated semi-quantitatively on plasma samples of the six Japanese subjects who had received orally 50 mg QD for 14 days in the Part 2 of study NBX1-1. The plasma samples were pooled over the period of 0 to 24 hours on day 14. Parent drug was the major circulating compound in the human plasma. The delgocitinib-glucuronide conjugate (M5) was observed as major metabolite (1.7% of the average delgocitinib concentration) in the pooled human plasma over the 24 hours period after oral administration. Three oxidised metabolites were found as approximately 0.8% (M1), 0.4% (M3) and 0.7% (M4) of the average delgocitinib concentration (M2 was not detected).

Metabolism of delgocitinib has been investigated *in vitro* in human hepatocytes, human liver microsomes, human skin microsomes and with various recombinant CYP enzymes. Delgocitinib was slightly metabolised to M1, M2 and M3 when incubated with human liver microsomes. The *in vitro* incubation with various

recombinant CYP-enzymes suggested that CYP3A4 was the main metabolising enzyme of delgocitinib with CYP1A1, CYP2C19 and CYP2D6 contributing with minor extent. No metabolite was detected after incubation with CYP1A2, 2A6, 1B1, 2B6, 2C8, 2C9, 2E1, and 3A5. No metabolic degradation of delgocitinib was observed when incubated *in vitro* with human hepatocytes and human skin microsomes.

Dose proportionality and time dependencies

Study 1273

Delgocitinib showed low systemic exposure across all doses, although with a tendency to increase with dose (geometric mean range: 0.02–0.26 ng/ml). One subject in the delgocitinib 20 mg/g group had a plasma concentration of 20.8 ng/ml. The subject had severe CHE and was treated with delgocitinib 20 mg/g. The higher systemic exposure of the subject was originally speculated to be attributed to fissures on hands. However, subsequent analyses showed that the extent of fissures in this subject was unlikely to explain the observed exposure. A possible explanation for the observed outlying exposure level is IMP contamination at the site of phlebotomy for PK assessment.

Study 1275

Delgocitinib cream showed low systemic exposure in the subjects with AD, which increased with dose. The geometric mean plasma concentrations in the 4 delgocitinib cream treatment groups measured 2 to 6 hours post-dose at week 1 were 0.06 ng/mL (1 mg/g), 0.10 ng/mL (3 mg/g), 0.17 ng/mL (8 mg/g), and 0.40 ng/mL (20 mg/g group). One patient had a higher systemic exposure of 11.50 ng/ml. The subject had severe AD with a BSA of 46.6% at baseline and was treated with delgocitinib 20 mg/g cream.

Time dependency

The systemic exposure decreases over time based on PK data from patients with CHE in studies 1273, 2285 and 1402. The reason for decrease may be related to improved skin barrier integrity associated with delgocitinib cream treatment.

Intra- and inter-individual variability

The inter-individual variations in target population were calculated in studies 2285 and 1402. In study 2285, the inter-individual variations (coefficient of variation [CV%]) were in $AUC_{0\text{-}12}$ 134 on day 1 and 45 on day 8. The CV% in C_{max} was 513 on day 1 and 53 on day 8. In study 1402, the CV% in through concentrations was 210 at week 1, 239 at week 4, and 460 at week 16.

PK in target population

Study 2285

The arithmetic mean $AUC_{0–12}$ value was slightly higher on day 1 (6.1 h*ng/mL) compared with day 8 (4.2 h*ng/mL) due to a few subjects with higher delgocitinib plasma concentrations on day 1, thereby raising the mean. The geometric mean $AUC_{0–12}$ value was slightly higher on day 8 (3.7 h*ng/mL) compared with day 1 (2.5 h*ng/mL) (Table 5).

Table 5 - PK parameters on Day 1 and Day 8 (PK analysis set)-study 2285

Pharmacokinetic parameter	Delgocitinib cream 20 mg/g (N = 15[a])	
	Day 1	Day 8
C_{max} (ng/mL)		
n	15	15
Geometric mean (GSD)	0.50 (6.165)	0.46 (1.740)
Mean (SD)	1.53 (2.336)	0.53 (0.279)
CV, %	153.07	52.68
Min;Max	0.01;7.30	0.17;1.08
AUC_{0-12} (h×ng/mL)		
n	15	15
Geometric mean (GSD)	2.5 (5.21)	3.7 (1.74)
Mean (SD)	6.1 (8.14)	4.2 (1.88)
CV, %	134.4	45.1
Min;Max	0.0;30.7	1.0;7.6
$t_{max\ 0\text{-}12\ h}$ (h)		
n	15	15
Mean (SD)	3.4 (4.17)	6.4 (4.36)
Median (Q1;Q3)	0.9 (0.8;7.8)	7.9 (1.9;11.9)
Min;Max	0.8;11.8	0.0;12.1
$t_{½}$ (h)		
n	-	6[b]
Geometric mean (GSD)	-	20.3 (1.31)
Mean (SD)	-	21.0 (5.98)
CV, %	-	28.5
Min;Max	-	15.8;30.9

Notes: [a] One subject was excluded from the PK analysis set due to contamination. [b] 9 subjects were excluded from $t_{½}$ calculations due to non-achievement of the criteria for the regression quality.

Abbreviations: AUC_{0-12} = area under the concentration-time curve 0-12 hours post-dose at Day 1 and Day 8. C_{max} = maximum observed concentration (0-12 hours post-dose); CV = coefficient of variation; GSD = geometric standard deviation; Max = maximum; Min = minimum; N = number of subjects within a treatment group; n = number of subjects with data; SD = standard deviation; t_{max} = time to reach maximum observed concentration; $t_{½}$ = half-life (0-12 hours post-dose); Q1 = 1st quartile. Q3 = 3rd quartile.

Due to the large variation in delgocitinib concentrations, especially on day 1, it was not possible to draw any firm conclusions on whether there is an accumulation of delgocitinib in the systemic compartment from day 1 to day 8. However, based on the range of the data observed, any actual accumulation of delgocitinib would be limited.

Study 1180

In the 60 samples obtained from subjects treated with delgocitinib ointment 30 mg/g, plasma concentrations above lower limit of quantification (LLOQ) were measured in all subjects. The systemic exposure of delgocitinib was low—only a few samples were above 1 ng/ml.

The applicant's conclusion in relation to the PK was that systemic exposure of delgocitinib was low after one week treatment at steady state.

Study 1402 (DELTA 2)

Minimal systemic delgocitinib exposure levels were observed at all 3 sampling time points (weeks 1, 4, and 16). Geometric mean and median delgocitinib plasma concentrations were lower at week 16 compared with week 1 and 4 (Table 6).

Table 6 - Delgocitinib plasma concentration by visit (safety analysis set) - study 1402

Delgocitinib plasma concentration	Delgocitinib 20 mg/g (N=313)
Week 1	
n	287
Geometric mean, ng/mL	0.21
CV (%)	218.28
Min;Max	0.00;5.65
Week 4	
n	276
Geometric mean, ng/mL	0.21
CV (%)	239.82
Min;Max	0.00;29.20
Week 16	
n	262
Geometric mean, ng/mL	0.11
CV (%)	459.68
Min;Max	0.00;4.63

Abbreviations: CV = coefficient of variation; Max = maximum; Min = minimum; N = number of subjects within a treatment group; n = number of subjects with data.

Table 7 - Delgocitinib systemic exposure on day 8 across studies in CHE

Trial	Formulation and dose	Delgocitinib plasma concentration			
		n	Geometric mean (ng/mL)	Mean (ng/mL)	Min;Max
2285	Cream 20 mg/g	15	0.46[a]	0.53[a]	0.17;1.08
1402	Cream 20 mg/g	287	0.21[b]	0.42[b]	0.00;5.65
1273	Cream 20 mg/g	51	0.26[b]	NC	0.01;20.80
1180	Ointment 30 mg/g	60	NC	0.39[b]	0.005;2.720

Notes: [a] C_{max} from intense sampling (0-72 hours); [b] Single sample 2-6 hours after IMP application.
Abbreviations: CHE = chronic hand ezcema; Max = maximum; Min = minimum; n = number of subjects with data; NC = not calculated.

Special populations

No specific studies have been conducted is special populations. The applicant conducted the analysis of plasma concentrations of delgocitinib by baseline renal function in 96 mild/moderate CHE patients based on data from phase 3 study 1402. Based on the available results, no dose adjustments are needed in patients with mild or moderate renal impairment. Nonetheless, it is improbable that severe renal function would lead to changes in delgocitinib PK substantial enough to necessitate a dosage adjustment. The applicant also

conducted analysis of the delgocitinib plasma concentration in CHE patients stratified by their hepatic function (normal, mild, or moderate/severe) based on data from phase 3 study 1402. Up to 2-fold higher delgocitinib geometric mean plasma concentrations were observed in the only available patient with moderate/severe hepatic impairment when compared to the patients with normal hepatic function at weeks 1 and 4. Delgocitinib plasma concentrations decreased with a longer duration of use in patients with normal hepatic function as well as in patients with hepatic impairment, transitioning from week 1 to weeks 4 and 16. Since delgocitinib has low bioavailability and is primarily eliminated unchanged via renal excretion it is unlikely that impaired hepatic function would cause alterations in its pharmacokinetics that would warrant a dosage adjustment.

Pharmacokinetic interaction studies

No clinical interaction studies with delgocitinib after oral or topical administration have been conducted. The systemic exposure after topical administration is low, therefore, risk of clinically relevant drug-drug-interactions is minimal.

Delgocitinib has not been evaluated in combination with other topical medicinal products and co-application on the same skin area is not recommended.

Pharmacokinetics using human biomaterials

The *in vitro* studies with CYP450 enzymes indicated that delgocitinib has no inhibitory effect and has not a significant inducing effect on the enzymes at clinically relevant plasma concentrations. Ketoconazole, a specific CYP3A4/5 inhibitor, significantly inhibited delgocitinib metabolism in human liver microsomes (study B101265). In contrast, inhibitory effects were low with CYP2C9, CYP2C19, and CYP2D6 inhibitors. Since delgocitinib exhibits low bioavailability and low metabolism no safety concerns arising from CYP3A4 inhibition are expected.

The *in vitro* studies with transporters included evaluation of inhibitory potential of delgocitinib on kidney uptake transporters (OCT2, OAT1 and OAT2), liver update transporters (OATP1B1, OATP1B3), kidney efflux transporters (MATE1, MATE2-K), and efflux-transporters P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP). The results indicated that delgocitinib was a substrate of P-gp and a weak substrate of OCT2 and OAT3. Delgocitinib inhibited OAT1 and OAT3, albeit with IC50 values that exceeded the concentrations observed in plasma after the local application of the delgocitinib cream 20 mg/g. Delgocitinib did not show inhibitory effects on transporters *in vitro* at clinically relevant concentrations.

2.5.2.2. Pharmacodynamics

Mechanism of action

Delgocitinib is a pan-JAK inhibitor that targets the activity of all 4 members of the JAK family of enzymes consisting of JAK1, JAK2, JAK3, and TYK2 in a concentration dependent manner. Janus kinases are intracellular enzymes specifically associated to the different cytokine receptors in either a heterodimeric or homodimeric complex and are essential for cytokine signaling. JAKs are activated upon cytokine- receptor interaction and thereafter phosphorylate and activate signal transducers and activators of transcription (STATs). Activated STATs, in turn, activate the expression of cytokine-responsive genes to induce specific biological responses in target cells. Thus, the JAK/STAT signalling pathways provide direct translation of extracellular signals, cytokines, into specific transcriptional responses and play a key role in the immune system in driving the pathophysiology of chronic inflammatory skin diseases.

Primary and Secondary pharmacology

Pharmacodynamic biomarkers and *S. aureus* colonisation in relation to delgocitinib treatment were investigated as exploratory objectives in studies 1180, 1273, and 1401.

In study 1180, inflammatory markers including S100A8, S100A9, S100A12, PI3 and KLK6, keratinocyte differentiation marker K16, and key barrier integrity markers FLG, FLG2, SCEL (Sciellin), CLDN25, and LOR were investigated by micro-array gene expression profiling of biopsy samples.

In study 1273, biomarkers were histologically quantified from skin biopsies using preparative and staining methods together with digital image analysis, and included CK16 (cytokeratin 16), CD3 and filaggrin, and IL33, IL36, IL1RAP, IL1B and H4R. In addition, filaggrin mutations were investigated in blood samples derived from study participants. *S. aureus* skin colonisation was also assessed using qPCR of the femA gene (*S. aureus*) and general microbial diversity was assessed using cDNA sequencing.

In study 1401, samples containing mRNA were collected from a subset of subjects via tape stripping of lesional as well as non-lesional skin. Gene expression of preselected genes was assessed using quantitative polymerase chain reaction (qPCR). Data analysis and reporting of the expression of genes included for example various types of claudin and filaggrin, LOR, and S100A9.

The PD results from studies 1180, 1273 and 1401 suggested that delgocitinib may cause changes in expression of various genes in skin biopsies, e.g. upregulate claudins (CLDN3 and CLDN23) and downregulate SERPINB3 and S100A9, as well as reduce T cells (CD3+) and *S. Aureus* colonisation in the skin. These investigations had an exploratory character. However, the dose-proportional and statistically significant reduction in the *S. aureus* colonisation in study 1273 is noted.

2.5.3. Discussion on clinical pharmacology

Bioanalytical methods

The bioanalytical methods are generally well documented and overall acceptable. It is acknowledged that the quantification of delgocitinib in plasma samples after topical administration requires a highly sensitive method and thus, is analytically challenging. The validation of the method covering the low concentration range of delgocitinib (5 pg/mL - 5000 pg/mL) samples did not include stability of internal standard stock and working solution, and the corresponding bioanalysis results demonstrated a notable number of samples with decreased internal standard signal responses. Nevertheless, the majority of affected samples was reanalysed and met acceptance criteria.

Pharmacokinetics

The PK development programme of delgocitinib cream in the proposed indication (i.e., in patients with moderate to severe CHE) consisted of one phase 1 study (study 2285), two phase 2 studies (studies 1180 [ointment formulation] and 1273) and one phase 3 study (study 1402). The MAA dossier also included studies with tablet and capsule formulations (studies NBX1-1 and 1409) and studies in patients with AD (studies 1181 and 1275 with cream formulation). This was acceptable to the CHMP.

Absorption and bioavailability

Delgocitinib was initially developed as a 30 mg/g ointment for the treatment of AD in Japan. Subsequently, the applicant conducted a phase 2a study 1180 with delgocitinib ointment 30 mg/g in adults with moderate to severe CHE. To improve skin delivery and user-friendliness, a 20 mg/g cream formulation, corresponding

to the 30 mg/g ointment, was developed, and used in a phase 2b study 1273. In the commercial cream formulation, the content of the excipient disodium edetate was reduced. This modified formulation was used in the clinical development programme for moderate to severe CHE, including a phase 1 PK study 2285 and phase 3 clinical studies (1401, 1402, and 1403).

The applicant considers that altering the formulation did not affect the product's performance and was not expected to impact the PK of delgocitinib cream. Nonetheless, it is important to note that besides the sparse PK data from studies 1273 and 1402, the applicant did not provide further information about the similarity of the two formulations. However, the change in formulation did not substantially affect the sparse PK data, as systemic delgocitinib concentrations remained consistent, mainly up to 1 ng/ml, in studies with the initial and commercial delgocitinib 20 mg/g cream formulations. Therefore, this issue has not been further pursued.

The PK of delgocitinib cream was evaluated in study 2285 involving 15 adult patients 22 to 69 years of age with moderate to severe CHE. Patients applied on average 0.87 g delgocitinib 20 mg/g cream to the affected areas of the hands and wrists twice a day for 8 days.

The geometric mean ± GSD maximum plasma concentration (C_{max}) and area under the concentration curve from time 0 to 12 hours (AUC_{0-12}) on Day 8 was 0.46 ng/mL ± 1.74 and 3.7 ng*h/mL ± 1.74, respectively. Steady state was reached by Day 8. The systemic exposure (AUC and C_{max}) between Day 1 and Day 8 were similar. Compared to subjects with AD in study 1275, the geometric mean C_{max} of 0.40 ng/ml (N=51, min.-max. 0.01 to 11.50 ng/ml) indicated quite similar concentrations after one week of treatment with 20 mg/g cream twice a day.

Following twice daily application of delgocitinib 20 mg/g cream in study 1402 (DELTA 2), the geometric mean plasma concentration observed 2-6 hours after application at Day 113 was 48% lower than that at Day 8 (0.11 ng/mL and 0.21 ng/mL, respectively).

The PK of delgocitinib after oral administration has been characterised in two clinical studies (NBX1-1 and 1409). Absorption of delgocitinib was rapid after oral administration with median t_{max} of approximately 1 hour. The exposure increased in proportion to dose or slightly more than dose-proportionally after oral administration of 1 mg to 100 mg doses. The PK data for the study NBX1-1 has been used for evaluation of elimination of delgocitinib in human and calculation of relative bioavailability for the cream formulation.

No dedicated bioavailability study has been conducted; however, the relative bioavailability has been calculated. The relative bioavailability of delgocitinib cream 20 mg/g has been found to be low (approximately 0.5-0.6%) compared to administration *via* oral tablets.

Distribution and elimination

The apparent volume of distribution of 112 L to 199 L after oral administration suggests distribution of delgocitinib into tissues. At concentrations 30 ng/ml, the plasma protein binding of delgocitinib was approximately 29% and approximately 60% is distributed in blood cells in human blood *in vitro*.

After oral administration in the study NBX1-1, in approximately 70% to 80% of the administered dose was excreted as unchanged drug in urine over the collection interval of 48 hours. Overall, the results indicated that delgocitinib is not susceptible to significant metabolism in humans. Parent drug was the major circulating compound in human plasma. Excretion was not specifically examined after topical application. Nevertheless, it is anticipated that the excretion routes would be similar to those observed after oral administration.

Following repeated topical application of delgocitinib cream, the average half-life of delgocitinib was estimated to be 20.3 hours.

Hepatic metabolism was studied in 6 different *in vitro* studies and no metabolic degradation of delgocitinib was detected in human skin microsomes *in vitro*. Based on the *in vitro* studies, delgocitinib is metabolised primarily by CYP3A4/5 and to lesser extent by CYP2C19, CYP2D6 and CYP1A1.

Dose proportionality and time dependencies

In study 1273, four different delgocitinib cream concentrations were studied (i.e., 1, 3, 8, and 20 mg/g). Delgocitinib showed low systemic exposure across all doses, although with a tendency to increase with dose (geometric mean range: 0.02–0.26 ng/ml). One subject in the delgocitinib 20 mg/g group had a plasma concentration of 20.8 ng/ml. The subject had severe CHE and was treated with delgocitinib 20 mg/g. The reason for the outlier result was thought to be contamination of the studied product at the site of phlebotomy and the given reason can be considered adequate.

In study 1275, adult subjects with AD had the geometric mean C_{max} of 0.40 ng/ml (N=51, min.-max. 0.01 to 11.50 ng/ml) after one week of treatment with 20 mg/g cream. The systemic exposures tended to increase with dose and treated body surface area. The whole affected body surface areas (up to 50%) were treated in AD.

The exposure increased in proportion to dose after oral administration of 1 mg to 100 mg doses or slightly more than dose-proportionally after oral administration of 1.5 mg to 12 mg doses. PK parameters (C_{max} and AUC_{tau}) of delgocitinib following multiple oral administrations were quite similar at Day 1 and Day 14 and no accumulation was observed, however, no statistical evaluation of the data was presented.

Inter-individual variability

The inter-individual variability in target population was calculated in studies 2285 and 1402. In study 2285, the geometric coefficient variation (CV) for both AUC and C_{max} was notably high, exceeding 100%, following the first application of delgocitinib cream 20 mg/g (Day 1, 0-12 hours). However, there was a significant reduction in variability for both, the AUC and C_{max} at steady state after one week treatment (Days 8-11, 0-72 hours). The delgocitinib plasma concentrations measured in study 1402 demonstrated high variability (exceeding a 100% geometric CV) following the delgocitinib cream application of one week or longer. However, minimal systemic exposure of topical delgocitinib was demonstrated consistently across the clinical studies.

Special populations

PK parameters of delgocitinib were analysed in 96 patients with mild or moderate renal impairment (eGFR 30 to 89 ml/min/1.73 m^2) in study 1402 (DELTA 2). There were no clinically relevant differences in the PK observed in patients with mild or moderate renal impairment compared to the overall study population. Due to the minimal systemic exposure of topically applied delgocitinib, changes in renal function are unlikely to be of clinical importance. Therefore, no dose adjustment is recommended in patients with renal impairment. Similarly, due to the minimal systemic exposure of topically applied delgocitinib and limited metabolism of delgocitinib, changes in hepatic function are unlikely to have any effect on the elimination of delgocitinib. Therefore, no dose adjustment is recommended in patients with hepatic impairment. The SmPC reflects these findings.

Drug-drug interactions

No clinical interaction studies with delgocitinib after oral or topical administration have been conducted. The systemic exposure after topical administration is low, therefore, risk of clinically relevant drug-drug-interactions is minimal and no clinical drug-drug interaction studies are necessary.

The *in vitro* studies with CYP450 enzymes indicated that delgocitinib has no inhibitory effect and not a significant inducing effect on the enzymes at clinically relevant plasma concentrations. Moreover, the *in vitro* studies with transporters indicated that delgocitinib has no inhibitory effects at clinically relevant concentrations. Delgocitinib was a substrate of P-glycoprotein (P-gp) and a weak substrate of kidney uptake transporters, human organic cation transporter 2 (OCT2) and human organic anion transporter 3 (OAT3) *in vitro*.

Delgocitinib has not been evaluated in combination with other topical medicinal products and co-application on the same skin area is not recommended, as stated in the SmPC.

The PK of delgocitinib is considered to be sufficiently characterised after oral and topical administration in the applied indication of moderate to severe CHE.

2.5.4. Conclusions on clinical pharmacology

Delgocitinib exhibits low systemic bioavailability following topical application of a 20 mg/g cream to the hands and wrists of patients with moderate to severe CHE. Furthermore, delgocitinib has a low metabolic turnover and is predominantly excreted unchanged renally. A minimal systemic exposure of topical delgocitinib was demonstrated consistently across studies and the systemic exposure decreased over time. Overall, the PK of topically applied delgocitinib was adequately characterised. The information and results obtained in the clinical pharmacology programme have been adequately reflected in the SmPC.

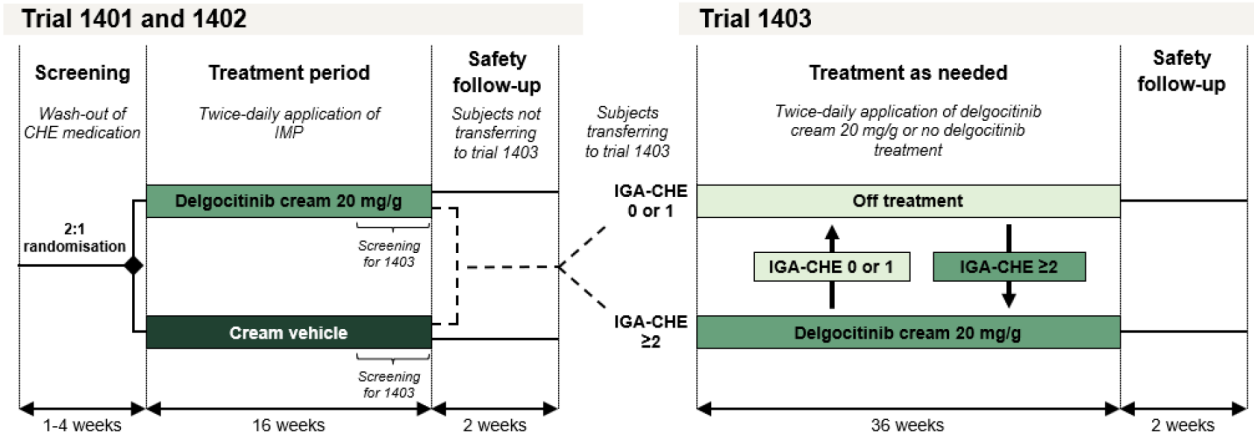
2.5.5. Clinical efficacy

The efficacy evaluation of delgocitinib in CHE is mainly based on the following studies:

- The pivotal studies 1401 and 1402 (16-week treatment period).
- Long-term extension study 1403 (up to 36-week as-needed treatment period).

The pivotal studies 1401 and 1402 were randomised, double-blind, vehicle-controlled studies in subjects with moderate to severe CHE. The long-term extension study 1403 was a non-controlled, open-label extension study in subjects who completed 16 weeks of treatment in studies 1401 and 1402 (Figure 2).

Figure 2 - Overview of the delgocitinib studies 1401, 1402 and 1403



Abbreviations: CHE = chronic hand eczema; IGA-CHE = Investigator's Global Assessment for chronic hand eczema; IMP = investigational medicinal product.

2.5.5.1. Dose response study

Study 1273

This was a phase 2b, double-blind, multi-centre, randomised, 5-arm, vehicle-controlled, parallel-group study, designed to establish dose-response, and to investigate the efficacy and safety of twice-daily topical application of delgocitinib cream in adult subjects with mild to severe CHE. Subjects were randomised to 4 different strengths of delgocitinib cream (1, 3, 8, or 20 mg/g) or cream vehicle and were adults with the diagnosis of CHE defined as hand eczema that has persisted for more than 3 months or returned twice or more within the last 12 months, disease severity graded as mild to severe according to IGA-CHE (i.e. an IGA-CHE score ≥2), and recent history (within 1 year before the screening visit) of inadequate response to topical corticosteroid treatment or topical corticosteroid treatment being medically inadvisable.

A total of 250 subjects were to be randomised in a 1:1:1:1:1 ratio to delgocitinib cream 1, 3, 8, or 20 mg/g or delgocitinib cream vehicle. The randomisation was stratified by the severity of CHE according to the Investigator's Global Assessment for CHE (IGA-CHE score of 2 [mild], 3 [moderate], or 4 [severe]) and region (Europe and North America).

The investigational medicinal products (IMPs) were administered as a twice daily cutaneous application for 16 weeks. The applications were performed approximately 12 hours apart. A thin layer of delgocitinib cream covering the affected areas on the hands was applied. The maximum use depended on the size of the affected area and the size of the hands. One tube of 15 g delgocitinib cream was considered maximum for treatment of the whole surface of both hands twice daily for 1 week.

The subjects were instructed to not change their usual skin care routine regarding use of emollients. However, the emollient was not allowed to be used within 2 hours before and after application of the IMP.

The primary objective was to establish the dose-response relationship of twice-daily applications of delgocitinib cream 1, 3, 8, and 20 mg/g compared with cream vehicle for 16 weeks in subjects with mild to severe CHE.

The primary endpoint was IGA-CHE TS, defined as IGA-CHE score of 0 (clear) or 1 (almost clear) with at least a 2-step improvement from baseline to Week 16.

The secondary endpoints were time to IGA-CHE TS and change in HECSI from baseline to Week 16.

Altogether 258 subjects were randomised to treatment: 52 to delgocitinib 1 mg/g, 51 to delgocitinib 3 mg/g, 52 to delgocitinib 8 mg/g, 53 to delgocitinib 20 mg/g, and 50 to vehicle.

Demographics and baseline characteristics are shown in Table 8.

Table 8 - Demographics and baseline characteristics – randomised subjects

	Delgocitinib				**Vehicle**	**All randomized**
	1 mg/g (N=52)	3 mg/g (N=51)	8 mg/g (N=52)	20 mg/g (N=53)	(N=50)	(N=258)
Female, n (%) Male, n (%)	37 (71.2%) 15 (28.8%)	28 (54.9%) 23 (45.1%)	32 (61.5%) 20 (38.5%)	34 (64.2%) 19 (35.8%)	27 (54.0%) 23 (46.0%)	158 (61.2%) 100 (38.8%)
Age (years), mean (SD)	44.3 (13.6)	46.1 (14.6)	47.9 (12.9)	43.9 (15.1)	47.8 (16.2)	46.0 (14.5)
Race, n (%): White Asian Other	 51 (98.1%) 1 (1.9%) 0	 51 (100%) 0 0	 50 (96.2%) 1 (1.9%) 1 (1.9%)	 52 (98.1%) 1 (1.9%) 0	 50 (100%) 0 0	 254 (98.4%) 3 (1.2%) 1 (0.4%)
Subtype of CHE, n (%): Allergic contact dermatitis Irritant contact dermatitis Contact urticaria/protein contact dermatitis Atopic hand eczema Pompholyx Hyperkeratotic eczema	 3 (5.8%) 21 (40.4%) 0 16 (30.8%) 4 (7.7%) 8 (15.4%)	 4 (7.8%) 13 (25.5%) 0 17 (33.3%) 3 (5.9%) 14 (27.5%)	 4 (7.7%) 14 (26.9%) 0 20 (38.5%) 8 (15.4%) 6 (11.5%)	 2 (3.8%) 12 (22.6%) 0 28 (52.8%) 2 (3.8%) 9 (17.0%)	 2 (4.0%) 20 (40.0%) 0 16 (32.0%) 3 (6.0%) 9 (18.0%)	 15 (5.8%) 80 (31.0%) 0 97 (37.6%) 20 (7.8%) 46 (17.8%)
IGA-CHE score, n (%): 0 (clear) 1 (almost clear) 2 (mild) 3 (moderate) 4 (severe)	 0 0 13 (25.0%) 29 (55.8%) 10 (19.2%)	 0 0 13 (25.5%) 29 (56.9%) 9 (17.6%)	 0 0 11 (21.2%) 29 (55.8%) 12 (23.1%)	 0 0 12 (22.6%) 31 (58.5%) 10 (18.9%)	 0 0 12 (24.0%) 27 (54.0%) 11 (22.0%)	 0 0 61 (23.6%) 145 (56.2%) 52 (20.2%)
Age at CHE onset (years), mean (SD)	32.7 (16.8)	35.8 (16.8)	36.3 (18.5)	29.8 (19.6)	33.8 (21.5)	33.6 (18.7)
Duration of CHE (years), mean (SD)	11.6 (12.8)	10.3 (10.2)	11.7 (11.7)	14.2 (14.9)	14.0 (13.7)	12.3 (12.8)
HECSI score, mean (SD)	59.0 (48.0)	52.4 (35.9)	49.5 (29.3)	65.7 (58.3)	52.7 (34.9)	55.9 (42.8)

Abbreviations: CHE = chronic hand eczema. HECSI = Hand Eczema Severity Index. IGA-CHE = Investigator's Global Assessment for chronic hand eczema. N = number of subjects within a treatment group. n = number of subjects with data. SD = standard deviation.

All 258 randomised subjects were included in the full analysis set (FAS).

Primary endpoint

For the primary endpoint IGA-CHE TS responders at week 16, delgocitinib 8 and 20 mg/g showed a statistically significant treatment effect against vehicle. The responder rates in the delgocitinib 8 and 20 mg/g groups were 36.54% and 37.74%, respectively, and 8.00% in the vehicle group.

In an exploratory analysis of subjects with baseline IGA-CHE score ≥3, the responder pattern was similar to the total population. Delgocitinib 8 and 20 mg/g showed a statistically significant treatment effect against vehicle. The responder rates in the 8 mg/g and 20 mg/g groups were 41.46% and 39.02%, respectively, and 10.53% in the vehicle group.

Secondary endpoints

Time to IGA-CHE TS: The rate of achieving IGA-CHE TS was statistically significant in the delgocitinib 1, 8 and 20 mg/g groups vs. the vehicle group. The estimated median time to IGA-CHE TS was 82 days for delgocitinib 8 mg/g and 98 days for delgocitinib 20 mg/g.

Change in HECSI from baseline to Week 16: The LSMean changes from baseline at week 16 were statistically significantly different from vehicle for all active delgocitinib groups. The difference vs. vehicle group was -20.29 in the delgocitinib 8 mg/g group and -15.59 in the delgocitinib 20 mg/g group.

In an exploratory analysis of subjects with baseline IGA-CHE score ≥3, the LSMean changes from baseline to Week 16 in the delgocitinib 1, 3, 8, and 20 mg/g groups were -46.8, -45.3, -56.2, and -50.0, respectively, and -29.5 in the vehicle group. The changes were statistically significantly different from vehicle for all active delgocitinib groups.

2.5.5.2. Main studies

The pivotal studies 1401 (DELTA 1) and 1402 (DELTA 2) were identical in design and are hence described together. Study 1403 (DELTA 3) was a long-term extension study for studies 1401 and 1402.

Title of studies

Study 1401: A phase 3 clinical trial to confirm efficacy and evaluate safety of twice-daily delgocitinib cream 20 mg/g compared with cream vehicle for a 16-week treatment period in adult subjects with moderate to severe chronic hand eczema (DELTA 1).

Study 1402: A phase 3 clinical trial to confirm efficacy and evaluate safety of twice-daily delgocitinib cream 20 mg/g compared with cream vehicle for a 16-week treatment period in adult subjects with moderate to severe chronic hand eczema (DELTA 2).

Study 1403: A phase 3 extension trial of DELTA 1 and DELTA 2 to evaluate the long-term safety of a twice-daily treatment with delgocitinib cream 20 mg/g as needed for up to 36 weeks in adult subjects with chronic hand eczema (DELTA 3).

Methods

- **Study design**

Studies 1401 and 1402

Studies 1401 and 1402 were randomised, double-blind, vehicle-controlled trials in adult subjects with moderate to severe CHE. The screening period lasted 1-4 weeks depending on the need for wash-out of previous CHE treatment. Subjects were randomised 2:1 to delgocitinib cream 20 mg/g or cream vehicle to be applied twice daily throughout the 16-week treatment period. If rescue treatment was initiated to control intolerable CHE symptoms, treatment with IMP was discontinued and not allowed to be re-started. The studies included a 2-week off-treatment follow-up period for assessments of safety. Subjects who transferred to long-term study 1403 did not complete the safety follow-up period in their parent study before transferring. The follow-up visit was performed as a phone visit unless a site visit was needed.

Study 1403

Study 1403 was an open-label extension trial for the parent studies 1401 and 1402. The study included a screening period (weeks -4 to week 0), with baseline visit (Day 1) at the same time as the end of treatment visit (week 16) in the parent study, a treatment period (week 0 to week 36) during which the subjects received delgocitinib cream 20 mg/g twice daily as needed, and a safety follow-up period (week 36-38).

- **Study Participants**

Studies 1401 and 1402

The eligibility criteria for the pivotal studies 1401 and 1402 were designed to include subjects with moderate to severe CHE who had a recent history of inadequate response to TCS or for whom TCS was medically inadvisable.

The eligibility criteria for the studies 1401 and 1402 were identical.

Inclusion criteria

1. Signed and dated informed consent has been obtained prior to any protocol-related procedures.

2. Age 18 years or above at screening.

3. Diagnosis of CHE, defined as hand eczema that has persisted for more than 3 months or returned twice or more within the last 12 months.

4. Disease severity graded as moderate to severe at screening and baseline according to IGA-CHE (i.e. an IGA-CHE score of 3 or 4).

5. HESD itch score (weekly average) of ≥4 points at baseline. The baseline weekly average was calculated from daily assessments of itch severity during the 7 days immediately preceding the baseline visit (Day -7 to Day -1). A minimum of 4 itch scores out of the 7 days is required to calculate the baseline average score.

6. Subjects who have a documented recent history of inadequate response to treatment with TCS or for whom TCS are documented to be otherwise medically inadvisable.

- Inadequate response is defined as a history of failure to achieve and maintain a low disease activity state (comparable to an IGA-CHE score of ≤2) despite treatment with a daily regimen of TCS of class III-IV (potent to very potent) for Europe and class IV-I (medium potency to very/ultra-high potency)

for Canada, applied for at least 28 days or for the maximum duration by the product prescribing information, whichever is shorter.

- Important side effects or safety risks are those that outweigh the potential treatment benefits and include intolerance to treatment, hypersensitivity reactions, and significant skin atrophy as assessed by the physician.

7. Subjects adherent to standard non-medicated skin care including avoidance of known and relevant irritants and allergens.

8. A woman of childbearing potential must use an acceptable method of birth control throughout the trial up until the last application of IMP.

Exclusion criteria

1. Concurrent skin diseases on the hands, e.g. tinea manuum.

2. Active AD requiring medical treatment in regions other than the hands and feet.

3. Active psoriasis on any part of the body.

4. Hyperkeratotic hand eczema in combination with a history of psoriasis on any part of the body.

5. Clinically significant infection (e.g. impetiginised hand eczema) on the hands.

6. Systemic treatment with immunosuppressive drugs (e.g. methotrexate, cyclosporine, azathioprine), immunomodulating drugs, retinoids (e.g. alitretinoin), or corticosteroids within 28 days prior to baseline (steroid eyedrops and inhaled or intranasal steroids corresponding to up to 1 mg prednisolone for allergic conjunctivitis, asthma, or rhinitis are allowed).

7. Use of tanning beds, phototherapy (e.g. UVB, UVA1, PUVA), or bleach baths on the hands within 28 days prior to baseline.

8. Previous or current treatment with JAK inhibitors (including delgocitinib), systemic or topical.

9. Cutaneously applied treatment with immunomodulators (e.g. PDE-4 inhibitors, pimecrolimus, tacrolimus) or TCS on the hands within 14 days prior to baseline.

10. Use of systemic antibiotics or cutaneously applied antibiotics on the hands within 14 days prior to baseline.

11. Other transdermal or cutaneously applied therapy on the hands (except for the use of subject’s own emollients) within 7 days prior to baseline.

12. Cutaneously applied treatments in regions other than the hands, which could interfere with clinical trial evaluations or pose a safety concern within 7 days prior to baseline.

13. Treatment with any marketed biological therapy or investigational biologic agents (including immunoglobulin, anti-IgE, and dupilumab).

14. Treatment with any non-marketed drug substance (that is, an agent that has not yet been made available for clinical use following registration) within the last 28 days prior to baseline or 5 half-lives, whichever is the longest.

15. Clinically significant infection within 28 days prior to baseline which, in the opinion of the investigator, may compromise the safety of the subject in the trial, interfere with evaluation of the IMP, or reduce the subject's ability to participate in the trial.

16. History of any known primary immunodeficiency disorder including a positive HIV virus test at screening, or the subject taking antiretroviral medications as determined by medical history and/or subject's verbal report.

17. Major surgery within 8 weeks prior to screening, or planned in-patient surgery or hospitalisation during the trial period.

18. History of cancer.

19. Any disorder which is not stable and could affect the safety of the subject throughout the trial or impede the subject's ability to complete the trial.

20. Any abnormal finding which may put the subject at risk because of their participation in the trial or influence the subject's ability to complete the trial.

21. Positive hepatitis B surface antigen or hepatitis C virus antibody serology at screening.

22. ALT or AST level ≥2.0×ULN at screening.

23. Known or suspected hypersensitivity to any component(s) of the IMP.

24. Current participation in any other interventional clinical trial.

25. Previously randomised in this clinical trial.

26. Current or recent chronic alcohol or drug abuse, or any other condition associated with poor compliance as judged by the investigator.

27. Employees of the trial site, or any other individuals directly involved with the planning or conduct of the trial, or immediate family members of such individuals.

28. Subjects who are legally institutionalised.

29. Women who are pregnant or lactating.

Classification of CHE

The classification of CHE was to be done by the investigator according to the definition shown in Table 9 and to standard clinical practice, which could vary across regions and countries. In Europe, the classification included mandatory diagnostic patch testing with at least a relevant baseline series including the most important contact allergens relevant to the locality of the site. For subjects who had a diagnostic patch test performed within 3 years prior to screening, the results from the most recent patch test could be used for the classification. For subjects who had not a patch test within 3 years prior to screening, a patch test was to be performed. The patch test was to be completed preferably prior to the baseline visit, but no later than the week 8 visit.

Table 9 - Definition of subtypes of hand eczema

Subtype	Definition
Allergic contact dermatitis	Hand eczema caused by relevant contact allergens or cross-reactors identified by patch testing. Relevance means that there is a current exposure of the allergens to the hands.
Irritant contact dermatitis	Hand eczema with documented irritant exposure, which is quantitatively likely to cause dermatitis. No relevant contact allergy (no current exposure to allergens to which the patient has reacted positive in patch test).
Contact urticaria/protein contact dermatitis	Hand eczema in patients exposed to proteins (food, latex, and other biological material) with a positive prick test, or proven specific IgE, to suspected items. A considerable proportion of patients with contact urticaria will also have atopic symptoms.
Atopic hand eczema	Hand eczema in a patient with a medical history of atopic eczema, previous or current. No documented irritant exposure and/or relevant contact allergen likely to cause eczema.
Vesicular hand eczema (pompholyx)	Recurrent hand eczema with vesicular eruptions. No relevant contact allergy, no documented irritant exposure likely to cause dermatitis.
Hyperkeratotic eczema (hyperkeratotic dermatitis of the palms)	Chronic eczema with hyperkeratosis in the palms, or pulpitis, and no vesicles or pustules. No documented irritant exposure to the involved skin areas, likely to cause irritant exposure.

Reference: Adapted from (1). Note that the terms eczema and dermatitis are used interchangeably in the referenced publication.
Abbreviation: IgE = immunoglobulin E.

Study 1403

Inclusion criteria

1. Signed and dated informed consent has been obtained prior to any protocol-related procedures.

2. The baseline visit in this extension trial must coincide with the Week 16 (end-of-treatment) visit in the parent trial.

3. Subjects must have met eligibility criteria at screening and baseline in the parent trial.

4. Subjects must have completed the treatment period in the parent trial (to be assessed at baseline visit in this extension trial).

5. Subjects must have complied with the clinical trial protocol in the parent trial to the satisfaction of the investigator.

6. A woman of childbearing potential must use an acceptable method of birth control throughout the trial up until the end-of-treatment/early termination visit.

Exclusion criteria

1. Subjects who prematurely discontinued treatment with IMP or initiated rescue treatment in the parent trial.

2. Subjects who experienced any adverse event (AE) during participation in the parent trial, which precludes further treatment with delgocitinib cream 20 mg/g in the judgement of the investigator.

3. Any medical or psychiatric condition that could put the subject at undue risk by participating in the trial, or which, by the investigator's judgment, makes the subject inappropriate for the trial.

4. Current participation in any other interventional clinical trial, except for parent trial.

- **Treatments**

Studies 1401 and 1402

The IMP (delgocitinib cream 20 mg/g or cream vehicle) was to be applied as a topical application twice daily, approximately 12 hours apart, for 16 weeks. The IMP application on initially affected areas and new lesions was to be continued regardless of clearance status until Week 16.

The IMP was to be applied to clean, dry hands, fingers, fingertips, and wrists in a thin layer covering the affected areas. One tube of 15 g delgocitinib cream was considered sufficient for treatment of the whole surfaces.

The first application of IMP occurred at the study site. The subjects were advised to contact the investigator before initiating treatment of new lesions.

The subjects were to continue with their usual skin care routine for the hands regarding the use of emollients. However, emollients were not to be used on the affected areas within 2 hours before and after application of the IMP. Emollients were not considered concomitant medication and were not recorded as such.

Rescue treatment was defined as treatment initiated to treat intolerable CHE symptoms during the treatment and follow-up periods. Rescue treatment for CHE could be prescribed at the discretion of the investigator. If rescue treatment was initiated, the subject had to stop treatment with IMP and was not allowed to restart the treatment.

Study 1403

At baseline (Day 1), subjects were evaluated by the investigator to determine the severity of their CHE. Subjects with IGA-CHE score of 0 or 1 were not assigned treatment with delgocitinib, but continued to use their routine skin care emollient, if applicable. Subjects with IGA-CHE score ≥2 started treatment with twice-daily delgocitinib cream 20 mg/g and continued until IGA-CHE score of 0 or 1 was achieved.

If a subject experienced worsening of CHE signs and symptoms while off-treatment, the subject was to contact the trial site. If a scheduled visit was not planned within a reasonable timeframe, an unscheduled visit was to be planned as soon as possible. If an IGA-CHE score ≥2 was attested, the subject was dispensed delgocitinib cream 20 mg/g and the investigator instructed the subject to start treatment with twice-daily applications.

If the subject observed that CHE signs and symptoms were resolved while on treatment, they were to contact the study site. If a scheduled visit was not planned within a reasonable timeframe, an unscheduled visit was to be planned as soon as possible. If IGA-CHE score of 0 or 1 was achieved, the subject was instructed to stop treatment and return all opened and unopened tubes to the site.

Rescue treatment for CHE could be provided to subjects at the discretion of the investigator, in which case the delgocitinib cream was discontinued and the subject was withdrawn from the study.

- **Objectives**

Studies 1401 and 1402

Primary objective: To confirm the efficacy of twice-daily applications of delgocitinib cream 20 mg/g compared with cream vehicle in the treatment of adult subjects with moderate to severe CHE.

Secondary objectives: To confirm the health-related quality of life and efficacy (selected key efficacy endpoints), and safety of twice-daily applications of delgocitinib cream 20 mg/g compared with cream vehicle in the treatment of adult subjects with moderate to severe CHE.

Study 1403

The key objectives of the study 1403 were to evaluate the long-term safety (primary objective) and efficacy (secondary objective) of an as-needed treatment with twice-daily applications of delgocitinib cream 20 mg/g.

- **Outcomes/endpoints**

Studies 1401 and 1402

Primary endpoint:

- IGA-CHE TS at week 16

Key secondary efficacy endpoints:

- HECSI-75 at Weeks 8 and 16.
- HECSI-90 at Week 16.
- IGA-CHE TS at Weeks 4 and 8.
- Percentage change in HECSI score from baseline to Week 16.
- Reduction of HESD itch score (weekly average) of ≥4 points from baseline at Weeks 2, 4, 8 and 16 (among subjects with a baseline HESD itch score (weekly average) ≥4 points).
- Reduction of HESD score (weekly average) of ≥4 points from baseline at Weeks 4, 8 and 16 (among subjects with a baseline HESD score (weekly average) ≥4 points).
- Reduction of HESD pain score (weekly average) of ≥4 points from baseline at Weeks 4, 8 and 16 (among subjects with a baseline HESD pain score (weekly average) ≥4 points).
- Reduction of DLQI score of ≥4 points from baseline at Week 16 (among subjects with a baseline DLQI score ≥4 points).
- Change in HESD itch score (weekly average) from baseline to Week 16.
- Change in HESD score (weekly average) from baseline to Week 16.
- Change in HESD pain score (weekly average) from baseline to Week 16.
- Change in HEIS score from baseline to Week 16.
- Change in HEIS PDAL score from baseline to Week 16.
- Change in DLQI score from baseline to Week 16.

Definitions of endpoints and development of key instruments used in the efficacy and QoL assessment in pivotal phase 3 studies

IGA-CHE TS

The Investigator Global Assessment for chronic hand eczema (IGA-CHE) is a single item clinician-reported outcome (ClinRO) that allows investigators to assess global disease severity at one given timepoint. IGA-CHE has been developed and validated by the applicant. The subject's disease is scored on a 5-point scale ranging from 0 (clear) to 4 (severe), and scoring is based on the clinical characteristics of erythema, scaling, hyperkeratosis/lichenification, vesiculation, oedema and fissures. Treatment success (IGA-CHE TS) is defined as an IGA-CHE score of 0 or 1 (clear or almost clear) with at least a 2-step improvement from baseline.

IGA-CHE was assessed by the investigator at each visit in studies 1401 and 1402, i.e. at screening, baseline and at Weeks 1, 2, 4, 8, 12 and 16.

Development and validation of IGA-CHE:

IGA-CHE scale was derived from the Physician Global Assessment for CHE (PGA), which was as used in the phase 2a proof-of-concept study in subjects with CHE (study 1180), and the modified Total Lesion Symptom Score to incorporate the descriptors of disease severity into a single global scale. IGA-CHE scale was used in the phase 2b study 1273 and slightly changed to comply with a request from health authorities before the initiation of the phase 3 program. To support the evaluation of the measurement properties and interpretation of IGA-CHE scores, the applicant conducted a separate analysis of IGA-CHE using blinded data from the phase 3 study 1401, pooled across treatment groups, including evaluation of the following:

- Quality of completion
- Reliability and validity of scores
    - Score reliability using test-retest methods.
- To evaluate construct-related validity of IGA-CHE scores (e.g., convergent validity, known-groups methods for validity, ability to detect change).
- Interpretation IGA-CHE scores
    - To aid interpretation of scores by producing estimates for within-subject responder definition thresholds for improvement and worsening. Anchor and distribution-based approaches were employed.

Summary of results

The psychometric analysis population comprised the first 280 subjects randomised and exposed to treatment with an IGA-CHE completion at both Baseline and Week 16. All 280 subjects were included in the full analysis set (psychometric analysis population).

Quality of completion

Quality of completion was 100% completion at both Baseline and Week 16 (due to the way the analysis population was defined), and never falling below 97.1% for any other visit.

Test-retest reliability

Test-retest reliability was calculated to evaluate the degree to which IGA-CHE scores were similar over time in a subset of subjects defined as having stable CHE between Week 2 and Week 4, as well as between Week 4 and Week 8 according to the PaGA, HESD PGI-S, and HECSI. Kappa coefficient (k) estimates greater than 0.75 or so were taken to represent excellent agreement, values below 0.40 or so were taken to represent poor agreement, and values between 0.40 and 0.75 were taken to represent fair to good agreement.

The k estimates for the PaGA, HESD PGI-S, and HECSI scores ranged between 0.63 to 0.69 for Week 2 to 4 and were 0.76 for Week 4 to 8 for PaGA, HASD PGI-S and HECSI. All lower bounds of the associated 95% CIs exceeded 0.40.

Construct validity results: Convergent validity

Convergent validity was evaluated by examining correlations at Week 4 in the psychometric analysis population between the IGA-CHE score and the PaGA, HESD PGI-S and HECSI scores. Correlations of <0.50 were defined as 'weak', those ≥0.50 and <0.70 as 'moderate, those ≥0.70 and <0.90 as 'strong', and those ≥0.90 were considered 'very strong'.

Convergent validity assessments based on Week 4 data showed moderate or strong correlations (range: 0.65-0.72) with other, theoretically related measures of CHE symptoms, namely the PaGA, HESD PGI-S and HECSI total score.

Construct validity results: Known-groups comparisons

IGA-CHE score at Week 4 was compared among groups of subjects who differed on other assessments of CHE symptom severity (PaGA, and HESD PGI-S). The magnitude of score differences between groups was evaluated using between-group effect size (ES) estimates and the magnitude of effect sizes were interpreted using predefined thresholds. The statistical significance of overall differences in scores among groups was also calculated using one-way ANOVAs.

The pattern of monotonic increase of higher IGA-CHE scores for the groups that included subjects with more severe CHE symptoms or disease severity was observed. The between-group effect sizes comparing between adjacent groups ranged from 0.44 to 1.11; all were moderate to large except for the comparison between the HESD PGI-S "Mild" group and "none" (i.e. indicating no symptoms) which had a small effect size, but only just below the threshold for moderate. The differences in IGA-CHE scores among severity groups were statistically significant (all p<0.001).

Ability to detect change

The IGA-CHE was evaluated in terms of its ability to detect change where change exists. This was evaluated by assessing changes in the IGA-CHE score from Baseline to Week 16 in subjects who had rated themselves (or by clinician) to have experienced change over this time period. The anchor measures used for defining change were the PaGA, HESD PGI-S, HESD PGI-C and HECSI total score.

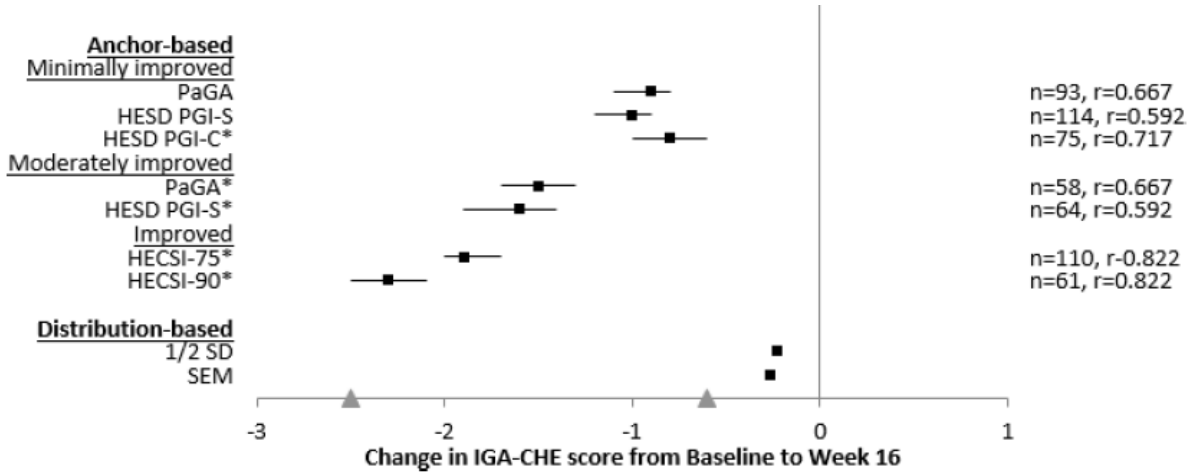
Changes in IGA-CHE scores between Baseline and Week 16 were compared among the "improved", "stable" and "worsened" groups defined for each anchor in the primary analysis population. Within- and between-group eSs were interpreted according to the defined cut-offs and between-group change was assessed by the statistical significance of a one-way ANOVA. The following cut-offs were used to interpret the magnitude of each ES: small change (ES=0.20), moderate change (ES=0.50) and large change (ES=0.80).

The IGA-CHE score was able to detect improvement, with large eSs (>2.79 in magnitude) for the improved group for all anchors from Baseline to Week 16. In all cases the eSs for the stable group were smaller than the improved group, with moderate to large eSs for all anchors when looking at stable subjects. Between-groups eSs were also large between those defined as improved and stable subjects. Mean changes were significantly different (p<0.001) between improved, stable, and worsened groups for all anchors used.

Establishing thresholds for clinically meaningful change and responder definitions for the IGA-CHE

Both anchor-based and distribution-based approaches were conducted to establish thresholds for clinically meaningful change, with a focus on within-group anchor-based change. Analyses were conducted for change from Baseline to Week 16. The results suggested that the IGA-CHE score has a meaningful change threshold of between -0.8 and -2.3 for the psychometric analysis population (Figure 3). A correlation weighted average, taking into account the strength of each anchor's correlation with the target score, suggested a single value of -1.7.

Figure 3 - Forest plot showing within-group mean change and distribution-based meaningful change estimates for the IGA-CHE



*indicates anchor groups that were considered of primary interest to confirm a responder definition and were included in the triangulation of estimates

HECSI

Hand Eczema Severity Index (HECSI) is a validated clinician reported outcome (ClinRO) measure used to assess the severity and extent of CHE. To calculate a score on the HECSI, the subject's hand is divided into 5 areas (fingertips, fingers [except fingertips], palms of hands, back of hands, and wrists). For each hand area, the intensity of each of 6 clinical signs (erythema, induration/papulation, vesicles, fissures, scaling, and edema) is scored using the following scale: 0='none/absent', 1='mild', 2='moderate', and 3='severe'. Furthermore, the extent (percentage) of the area affected within each hand area is scored using the following scale: 0=0%, 1=1–25%, 2=26–50%, 3=51–75%, and 4=76–100%. This extent score is then multiplied by the sum of intensity scores for each hand area. The total HECSI score is the sum of the combined scores for each hand area and ranges from 0 to 360, with higher scores indicating a greater severity of HE.

HECSI was assessed by the investigator in studies 1401 and 1402 at baseline and at Weeks 1, 2, 4, 8, 12 and 16.

HESD

Hand Eczema Symptom Diary (HESD) is a 6-item PRO instrument, developed and validated by the applicant, in which subjects assess the worst severity of their itch, pain, cracking, redness, dryness, and flaking over the past 24 hours. Subjects score each item on an 11-point numeric rating scale where 0='no (symptom)' and 10='severe (symptom)'. The HESD score is derived as an average of the 6 items. The HESD score as well as individual item scores, e.g. HESD itch score and HESD pain score, range from 0 to 10, where a high score is indicative of a high severity (Table 10).

Table 10 - HESD

Hand Eczema Symptom Scale	Rate the severity of any **itch** on your hands, at its worst, over the past 24 hours
	Rate the severity of any **pain** on your hands, at its worst, over the past 24 hours
	Rate the severity of any **cracking of the skin** on your hands, at its worst, over the past 24 hours
	Rate the severity of any **redness of the skin** on your hands, at its worst, over the past 24 hours
	Rate the severity of any **dryness of the skin** on your hands, at its worst, over the past 24 hours
	Rate the severity of any **flaking of the skin** on your hands, at its worst, over the past 24 hours

Subjects were to complete HESD daily in an electronic diary from at least 7 days prior to baseline in studies 1401 and 1402.

HEIS

Hand eczema impact scale (HEIS) is a 9-item PRO instrument, developed and validated by the applicant, in which subjects assess how much their CHE impacts their daily activities (HEIS PDAL), embarrassment with appearance of their hands, frustration with CHE, sleep, work, and physical functioning over the past 7 days. Each item is scored on a 5-point scale (0='not at all', 1='a little', 2='moderately', 3='a lot', 4='extremely'). The HEIS score is the average of the 9 items, and 6 domain scores can be calculated for HEIS PDAL (average of 3 items), embarrassment with the appearance of the hands (average of 2 items), frustration with CHE (1 item), sleep (1 item), work (1 item), and physical functioning (1 item) (Table 11).

Table 11 - HEIS

Hand Eczema Impact Scale	Proximal Daily Activities Limitation (PDAL)	Over the past 7 days, how has your hand eczema impacted your ability to **use soaps/cleaning products**?
		Over the past 7 days, how much has your hand eczema made it hard to do **housework** that involved your **hands getting wet** (e.g. washing dishes)?
		Over the past 7 days, how much has your hand eczema made it hard to **wash yourself**?
	Embarrasment with the appearance of the hands	Over the past 7 days, how **embarrased** have you felt about how your hands look due to your hand eczema?
		Over the past 7 days, how much have you disliked the **appearance of your hands**?
	Frustration with chronic hand eczema	Over the past 7 days, how much has your hand eczema made you feel **frustrated**?
	Sleep	Over the past 7 days, how much has your hand eczema impacted the **quality of your sleep**?
	Work	Over the past 7 days, how much has your hand eczema made it hard to **work** (e.g. paid work or voluntary)?
	Physical funtioning	Over the past 7 days, how much has your hand eczema made it hard to **hold or grip objects** (e.g. a cell phone, a pen, or a pencil)?

Subjects were to complete the HEIS questionnaire at site at each scheduled visit in studies 1401 and 1402.

DLQI

DLQI is a validated PRO instrument consisting of 10 items addressing the subjects' perception of the impact of their skin disease over the last 7 days, addressing dermatology-related symptoms and feelings, daily social and leisure activities, work or school, personal relationships, and time spent on treatment of the disease. Each item is scored on a 4-point Likert scale (0='not at all /not relevant'; 1='a little'; 2='a lot'; 3='very much'). The DLQI score is derived as the sum of the 10 items and can range from 0 to 30, with a high score indicative of a poor health-related quality of life. A 4-point reduction of DLQI score has been shown to correspond to the threshold for a clinically relevant improvement in health-related quality of life.

Subjects were to complete the DLQI questionnaire at site at each scheduled visit (except at Week 2).

Study 1403

The primary endpoint was number of treatment-emergent AEs from baseline up to Week 36. The key secondary endpoints included the following:

- IGA-CHE score at each scheduled visit from baseline up to Week 36.
- IGA-CHE score of 0 (clear) or 1 (almost clear) at each scheduled visit from baseline up to Week 36.
- HECSI score at each scheduled visit from baseline up to Week 36.
- HECSI-75 at each scheduled visit from baseline up to Week 36.

- HECSI-90 at each scheduled visit from baseline up to Week 36.

Other/exploratory endpoints included e.g. the following:

- Number of days on-treatment with delgocitinib cream 20 mg/g from baseline up to Week 36.
- Number of on-treatment periods from baseline up to Week 36.
- Proportion of response days from baseline up to Week 36.
- Mean duration of on-treatment periods per subject from baseline up to Week 36.
- Time to first IGA-CHE score ≥2 in subjects previously treated with delgocitinib cream 20 mg/g in the parent trial and who achieved IGA-CHE TS at Week 16 in the parent trial.
- Time to first response (IGA-CHE score of 0 [clear] or 1 [almost clear]) in subjects who did not achieve IGA-CHE TS at Week 16 in the parent trial.
- Time to response (IGA-CHE score of 0 [clear] or 1 [almost clear]) following treatment re-initiation after first off-treatment period in subjects previously treated with delgocitinib cream 20 mg/g in the parent trial.
- Reduction of HESD score, HESD itch score, and HESD pain score, (weekly averages) of ≥4 points from parent baseline at each nominal week from baseline up to Week 36.

- **Sample size**

Studies 1401 and 1402:

A total of 470 subjects in study 1401 and 450 subjects in study 1402 were to be randomised 2:1 to delgocitinib cream 20 mg/g or cream vehicle.

With a one-sided significance level of 2.5%, a sample size of 470 subjects randomised in study 1401 and 450 subjects randomised in study 1402 provided at least 99% power for detecting a treatment difference for the primary endpoint, assuming an IGA-CHE TS response rate at week 16 of 40% vs. 10% for delgocitinib cream 20 mg/g and cream vehicle, respectively. The assumptions on response rates were based on results from the phase 2b dose-ranging study (LP0133-1273).

Study 1403:

The expected sample size for this trial was approximately 600 subjects. No formal sample size was calculated, as the primary objective for the trial was to evaluate safety, which is reflected by the open-label trial design. No comparative analyses were performed in this trial. The expected sample size was based on the population size of the parent trials (920 subjects) and assumptions regarding completion rates in the parent trials.

- **Randomisation**

Studies 1401 and 1402:

Subjects who were found to comply with all the inclusion criteria and not to violate any of the exclusion criteria were randomised at baseline (Day 1) in a 2:1 ratio to receive treatment with either delgocitinib cream 20 mg/g or cream vehicle. The randomisation was stratified by region (Europe or North America) and baseline IGA-CHE score (3 or 4).

The IRT system was used to control randomisation and stratification factors, along with IMP supply chain and expiry tracking.

Study 1403:

- Not applicable.

Blinding (masking)

Study 1401 and 1402:

These were double-blind trials. The packaging and labelling of the IMPs contained no evidence of their identity. It was not considered possible to differentiate between the IMPs solely by sensory evaluation.

Study 1403:

Not applicable.

- **Statistical methods**

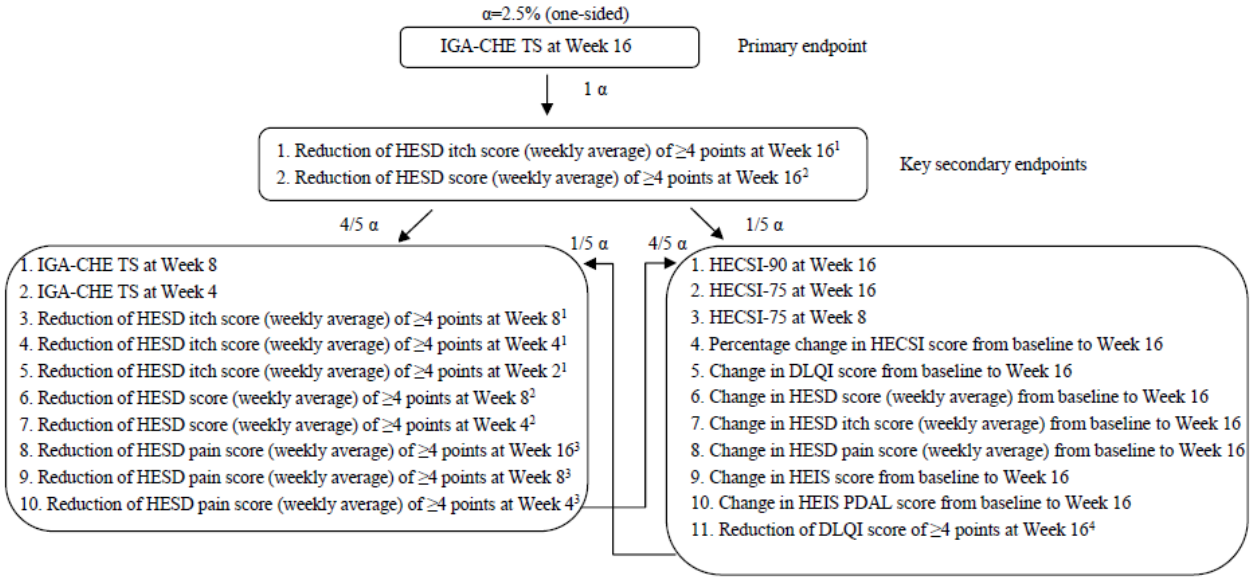
Studies 1401 and 1402:

Testing hierarchy

For the primary and key secondary endpoints, confirmatory one-sided (superiority) hypotheses were tested for delgocitinib cream 20 mg/g vs. cream vehicle based on the primary analysis for the primary estimand. A closed testing procedure with hierarchical tests, alpha splitting and alpha recycling was used to control the overall type I error at a nominal one-sided 2.5% level. The statistical testing strategy was built on the principle that the IGA-CHE TS superiority at week 16 was to be established before testing for additional benefits (key secondary endpoints) related to efficacy and health-related quality of life.

The first hypothesis to be tested was superiority of delgocitinib cream 20 mg/g in terms of IGA-CHE TS at week 16. It was to be tested at the overall one-sided significance level of 2.5%. If a test was significant, the significance level was reallocated according to the weight and the direction of the arrows as specified in Figure 4. Each of the following hypotheses were to be tested at their local significance level (α-local). This process was to be repeated until no further tests were significant.

Figure 4 - Graphical display of testing procedure for primary and key secondary endpoints



1) From baseline among subjects with a baseline HESD itch score (weekly average) ≥4 points.
2) From baseline among subjects with a baseline HESD score (weekly average) of ≥4.
3) From baseline among subjects with a baseline HESD pain score (weekly average) of ≥4.
4) From baseline among subjects with a baseline DLQI score of ≥4.

Trial analysis sets

The FAS (all subjects randomised and exposed to IMP) was used to analyse endpoints related to the efficacy objectives, and the SAF (all subjects who were exposed to IMP) was used to analyse the endpoints and assessments related to safety.

For analyses of safety all subjects who had at least one application with delgocitinib 20 mg/g were analysed in the delgocitinib 20 mg/g treatment group. This was done to ensure that no drug reactions to delgocitinib 20 mg/g treatment was erroneously assigned to the vehicle treatment group.

General principles

All significance tests specified in the testing hierarchy were one-sided using the assigned significance level (alpha). Operationally, the one-sided (superiority) hypotheses were evaluated by deriving the two-sided p value; the null hypothesis was rejected if the p value was smaller than 2*alpha and if the point estimate was in favor of the alternative hypothesis.

Baseline measurements were defined as the latest available observation at or prior to the date of randomisation. Subjects without a baseline measurement for a given efficacy score were excluded from the corresponding analysis.

In case of randomisation in wrong stratum with respect to baseline IGA-CHE score, the statistical analyses used the baseline IGA-CHE score confirmed by the investigator in the eCRF. This is due to the fact that the disease severity according to baseline IGA-CHE score is considered to be a strong prognostic factor for the treatment effect.

Intercurrent events (IE)

The following IE were defined to describe the treatment effect that was targeted with the different estimand strategies:

• Initiation of rescue treatment: This IE occurs when a subject initiates rescue treatment, at the discretion of the investigator. If rescue treatment is initiated, regardless of relatedness to the COVID-19 pandemic, the subject must stop treatment with IMP immediately and will not be allowed to restart treatment with IMP. The date of the IE is the start date of initiation of the rescue treatment. This IE is handled without assessing relatedness to the pandemic.

• Permanent discontinuation of IMP independent of the COVID-19 pandemic: This IE occurs when a subject permanently discontinues IMP independent of the pandemic, at the subject's own initiative, at the discretion of the investigator or the sponsor, or if the subject is lost to follow-up. The date of the IE is the date following the date of last application of IMP.

• Permanent discontinuation of IMP related to the COVID-19 pandemic: This IE occurs when a subject permanently discontinues IMP due to circumstances related to the pandemic; not attributed to lack of efficacy or randomised treatment features considered unacceptable by the subject. The date of the IE is the date following the date of last application of IMP.

If a subject experienced more than one IE, the first IE occurring was used when addressing IEs in the statistical analyses. If the IEs occur on the same day, the IE related to the COVID-19 pandemic was used when addressing handling of data for IEs. The 2 iEs permanent discontinuation of IMP independent of the COVID-19 pandemic and permanent discontinuation of IMP related to the COVID-19 pandemic are mutually exclusive, and a subject cannot experience both IEs.

The phrase 'permanent discontinuation of IMP' covered both IEs related to permanent discontinuation of IMP regardless of relation to the COVID-19 pandemic, i.e., the 2 IEs permanent discontinuation of IMP independent of COVID-19 pandemic and permanent discontinuation of IMP related to the COVID-19 pandemic.

The number of IEs and type of IEs were summarised by treatment group and visit interval.

Estimands

Three estimands were defined for binary and continuous endpoints: the primary estimand 'composite' strategy, the first supplementary estimand 'pandemic modified composite' strategy, and the second supplementary estimand 'treatment policy' strategy. For the 'composite' and 'treatment policy' strategy, sensitivity analyses were also defined. For time-to-event endpoints a 'while on treatment' strategy was used, that evaluated the response to treatment prior to the occurrence of the IEs of interest i.e., initiation of rescue treatment or permanent discontinuation of IMP.

Primary estimand - 'composite'

This primary estimand 'composite' strategy evaluated the treatment effect in adult subjects with moderate to severe CHE, without initiation of rescue treatment or permanent discontinuation of IMP. The population level summary for binary endpoints was the difference in response rates between delgocitinib cream 20 mg/g and cream vehicle.

For each primary and key secondary binary endpoint assessment missing data at each visit and the presence of IEs prior to or on the visit were summarised by treatment group. The difference in response rates between

the two treatment groups were analysed using the CMH test stratified by region and baseline IGA-CHE score. The difference in response rates with 95% CI was calculated by the Mantel-Haenszel method stratified by region and baseline IGA-CHE score.

For continuous endpoints the population level summary was the difference in mean change (or percentage change) from baseline to the endpoint of interest between delgocitinib cream 20 mg/g and cream vehicle. Non-response imputation according to the same criteria as for binary endpoints, was done using WOCF (including the baseline value).

The change (or percentage change) from baseline to the endpoint of interest was analysed using an ANCOVA model with effects of treatment group, region, baseline IGA-CHE score, and baseline value (endpoint of interest). LSMeans were estimated using observed margins. The difference in the LSMeans between the treatment groups were presented along with the corresponding 95% CI and nominal p-value.

Analysis of time-to-event endpoints

The timepoints of the 25th percentile, median and the 75th percentile of the estimated cumulative incidence function and 95% CI were presented by treatment group.

Analysis of exploratory efficacy endpoints

The analysis of exploratory endpoints resembled the primary analysis for the primary estimand related to a specific endpoint type: binary, continuous, or time-to-event.

Other analyses - PRO
The 3 PGI-S scores (Itch PGI-S, Pain PGI-S, and HESD PGI-S), the 3 PGI-C scores (Itch PGI-C, Pain PGI-C, and HESD PGI-C), and PaGA score were summarised by visit for each treatment group.

Results

- **Participant flow**

Studies 1401 and 1402:

Overall, 566 and 557 subjects were screened, and 487 and 473 subjects were randomised in study 1401 and 1402, respectively. All randomised subjects were included in the full analysis set (FAS). The subject disposition of studies 1402 and 1402 is shown in Table 12.

Table 12 - Subject disposition (study 1401 and 1402)

	Trial 1401		Trial 1402	
	Delgocitinib 20 mg/g (N=325) n (%)	Vehicle (N=162) n (%)	Delgocitinib 20 mg/g (N=314) n (%)	Vehicle (N=159) n (%)
Randomized	325 (100.0)	162 (100.0)	314 (100.0)	159 (100.0)
Randomized in error	8 (2.5)	5 (3.1)	16 (5.1)	7 (4.4)
Exposed to IMP	325 (100.0)	162 (100.0)	313 (99.7)	159 (100.0)
Full analysis set	325 (100.0)	162 (100.0)	313 (99.7)	159 (100.0)
Completed treatment	305 (93.8)	141 (87.0)	291 (92.7)	122 (76.7)
Without rescue treatment	305 (93.8)	141 (87.0)	291 (92.7)	120 (75.5)
Completed trial	311 (95.7)	148 (91.4)	293 (93.3)	127 (79.9)
Without rescue treatment	305 (93.8)	144 (88.9)	293 (93.3)	120 (75.5)
Transferred to extension Trial 1403				
Yes	293 (90.2)	134 (82.7)	267 (85.0)	107 (67.3)
No	32 (9.8)	28 (17.3)	47 (15.0)	52 (32.7)
Discontinuation of IMP or did not complete trial	21 (6.5)	21 (13.0)	25 (8.0)	38 (23.9)
Discontinuation of IMP	20 (6.2)	21 (13.0)	22 (7.0)	37 (23.3)
Death				
Pregnancy			2 (0.6)	
Adverse event	2 (0.6)	6 (3.7)	1 (0.3)	6 (3.8)
Lack of efficacy	5 (1.5)	7 (4.3)	6 (1.9)	14 (8.8)
Lost to follow-up		2 (1.2)	2 (0.6)	1 (0.6)
Withdrawal by subject	11 (3.4)	5 (3.1)	10 (3.2)	16 (10.1)
Other	2 (0.6)	1 (0.6)	1 (0.3)	

Abbreviations: IMP = investigational medicinal product. N = number of subjects. n = number of subjects with observation. % = percentage of subjects with observation.

Study 1403: Overall, 810 were screened and 801 enrolled into the long-term extension study 1403. The subject disposition of study 1403 is shown in Table 13.

Table 13 - Disposition of subjects (study 1403)

	Previous Delgocitinib 20 mg/g (N=560) n (%)	Previous Vehicle (N=241) n (%)	Total (N=801) n (%)
Enrolled	560 (100.0)	241 (100.0)	801 (100.0)
Enrolled in error	7 (1.3)	4 (1.7)	11 (1.4)
Exposed to IMP	544 (97.1)	235 (97.5)	779 (97.3)
Safety analysis set	560 (100.0)	241 (100.0)	801 (100.0)
Subjects excluded from SAF			
Completed treatment	472 (84.3)	192 (79.7)	664 (82.9)
Completed trial	469 (83.8)	192 (79.7)	661 (82.5)
Without rescue treatment	455 (81.3)	189 (78.4)	644 (80.4)
Attended safety follow-up visit	526 (93.9)	224 (92.9)	750 (93.6)
After completing treatment	469 (83.8)	192 (79.7)	661 (82.5)
After discontinuation of IMP	57 (10.2)	32 (13.3)	89 (11.1)
Discontinuation of IMP or did not complete trial	91 (16.3)	49 (20.3)	140 (17.5)
Discontinuation of IMP	88 (15.7)	49 (20.3)	137 (17.1)
Death	1 (0.2)		1 (0.1)
Pregnancy	3 (0.5)	1 (0.4)	4 (0.5)
Adverse event	2 (0.4)	5 (2.1)	7 (0.9)
Lack of efficacy	38 (6.8)	17 (7.1)	55 (6.9)
Lost to follow-up	4 (0.7)	5 (2.1)	9 (1.1)
Withdrawal by subject	35 (6.3)	17 (7.1)	52 (6.5)
Other	5 (0.9)	4 (1.7)	9 (1.1)
Discontinuation of IMP related to COVID-19 pandemic			
Yes	1 (0.2)		1 (0.1)
No	87 (15.5)	49 (20.3)	136 (17.0)
Did not complete trial	91 (16.3)	49 (20.3)	140 (17.5)
Death	1 (0.2)		1 (0.1)
Adverse event	2 (0.4)	5 (2.1)	7 (0.9)
Lack of efficacy	38 (6.8)	16 (6.6)	54 (6.7)
Lost to follow-up	7 (1.3)	6 (2.5)	13 (1.6)
Withdrawal by subject	35 (6.3)	17 (7.1)	52 (6.5)
Other	8 (1.4)	5 (2.1)	13 (1.6)
Did not complete trial related to COVID-19 pandemic			
Yes	1 (0.2)		1 (0.1)
No	90 (16.1)	49 (20.3)	139 (17.4)
Completed treatment but did not complete trial	3 (0.5)		3 (0.4)

Abbreviations: COVID-19 = coronavirus disease 2019. IMP = investigational medicinal product. N= number of subjects. n = number of subjects with observation. SAF = safety analysis set. % = percentage of subjects with observation.
Notes: Completed trial is defined as completed marked on both the End of treatment form and the End of trial form.

- **Recruitment**

Study 1401:

Date of first subject first visit: 10 May 2021, date of last subject last visit: 31 October 2022, and data lock point: 17 November 2022.

Study 1402:

Date of first subject first visit: 25 May 2021, date of last subject last visit: 06 January 2023 and data lock point: 25 January 2023.

Study 1403:

Date of first subject first visit: 23 August 2021, date of last subject last visit: 18 September 2023 and data lock point: 10 October 2023.

- **Conduct of the study**

Protocol amendments

Studies 1401 and 1402

The original protocol (Protocol version 3.0) was dated 4 February 2021.

One substantial protocol amendment was made (20 August 2021). This amendment was made to comply with request from health authorities, to accommodate for the conduct of the trial in Russia, and to proceed with administrative and editorial changes. However, due to operational challenges, Russian sites were not initiated.

Study 1403:

The original protocol was dated 25 March 2021.

Three amendments were made to the original protocol. Two of these were considered non-substantial.

One substantial amendment was made (23 August 2021), to accommodate for the conduct of the trial in Russia, to add photography of hands at certain visits, and to proceed with administrative and editorial changes. However, due to operational challenges, Russian sites were not initiated.

Protocol deviations

Study 1401:

No important protocol deviations were reported at trial-level, country-level or at site-level.

Altogether 118 important protocol deviations were reported at subject-level, including 14 cases related to the violation of the eligibility criteria. In addition, 94 important subject-level protocol deviations not related to eligibility criteria were considered to impact results for the individual subjects.

None of the protocol deviations led to exclusion from any trial analysis set.

Study 1402:

No important protocol deviations were reported at trial-level or country level. Two protocol deviations occurred at site-level, but these were unrelated to the assessment of the primary or secondary efficacy endpoints.

Altogether 115 important protocol deviations were reported at subject-level, including 23 related to the violation of the eligibility criteria. 83 important subject-level protocol deviations not related to eligibility criteria were considered to impact results for the individual subjects.

One important protocol violation led to exclusion from the FAS and the SAF (subject randomised in error and not treated).

Study 1403:

Altogether 204 important protocol deviations were reported, 2 at trial-level, 9 at site-level and 193 at subject-level.

14 important subject-level protocol deviations were considered to impact results for the individual subjects, out of which 9 were related to missing/late primary endpoint assessment. 5 important site-level PDs were considered to impact the results. These concerned 34 subjects. All were categorised as "other": all were related to blood pressure assessments with a sphygmomanometer (blood pressure device) without a calibration certificate. 2 important trial-level PDs resulted from a high number of repeated non-important PDs for subjects incorrectly or not answering the eDiary question: "Did you apply trial cream today?".

- **Baseline data**

Studies 1401 and 1402:

Demographic and other baseline characteristics

The baseline demographics of studies 1401 and 1402 by treatment group are summarised in Table 14.

Table 14 - Baseline demographics (studies 1401 and 1402) – randomised subjects

	Trial 1401		Trial 1402	
	Delgocitinib 20 mg/g (N=325)	Vehicle (N=162)	Delgocitinib 20 mg/g (N=314)	Vehicle (N=159)
Age (years)				
Mean (SD)	44.3 (14.3)	42.9 (14.1)	45.3 (14.6)	42.6 (14.3)
Min;max	19;87	20;73	18;83	18;86
Age group, n (%)				
18 to <65 years	297 (91.4)	154 (95.1)	286 (91.1)	150 (94.3)
65 to <85 years	27 (8.3)	8 (4.9)	28 (8.9)	8 (5.0)
>=85 years	1 (0.3)			1 (0.6)
Sex, n (%)				
Male	123 (37.8)	58 (35.8)	110 (35.0)	51 (32.1)
Female	202 (62.2)	104 (64.2)	204 (65.0)	108 (67.9)
Race, n (%)				
White	283 (87.1)	144 (88.9)	295 (93.9)	146 (91.8)
Black or African American	3 (0.9)	1 (0.6)	2 (0.6)	1 (0.6)
Asian other	13 (4.0)	5 (3.1)	8 (2.5)	6 (3.8)
Asian Chinese	1 (0.3)			1 (0.6)
American Indian or Alaska Native	1 (0.3)			
Native Hawaiian or Other Pacific Islander			1 (0.3)	
Other	2 (0.6)		5 (1.6)	1 (0.6)
Multiple	2 (0.6)	1 (0.6)	1 (0.3)	3 (1.9)
Not reported	20 (6.2)	11 (6.8)	2 (0.6)	1 (0.6)
Ethnicity, n (%)				
Hispanic or Latino	14 (4.3)	4 (2.5)	2 (0.6)	5 (3.1)
Not Hispanic or Latino	292 (89.8)	147 (90.7)	310 (98.7)	152 (95.6)
Not reported	19 (5.8)	11 (6.8)	2 (0.6)	2 (1.3)
Region, n (%)				
Europe	260 (80.0)	130 (80.2)	250 (79.6)	126 (79.2)
North America	65 (20.0)	32 (19.8)	64 (20.4)	33 (20.8)
Weight[1] (kg)				
n	325	162	314	158
Mean (SD)	77.35 (17.55)	78.11 (19.72)	78.83 (17.90)	81.10 (18.25)
Min;max	47.6;133.0	41.1;151.0	42.0;135.0	46.7;143.9
BMI[1] (kg/m2)				
n	325	162	314	158
Mean (SD)	26.83 (5.46)	27.19 (6.05)	27.26 (5.44)	28.11 (5.84)
Min;max	15.9;46.0	15.6;53.6	16.8;47.0	18.2;46.7

1: Baseline measurements are defined as the latest available observation at or prior to the date of randomization
Abbreviations: N = number of subjects. BMI = body mass index. n = number of subjects with observation. SD = standard deviation. % = percentage of subjects with observation.

Baseline disease characteristics

The baseline disease characteristics of studies 1401 and 1402 by treatment group are summarised in Table 15.

Table 15 - Baseline disease characteristics (studies 1401 and 1402) – randomised subjects

	Trial 1401		Trial 1402	
	Delgocitinib 20 mg/g (N=325)	Vehicle (N=162)	Delgocitinib 20 mg/g (N=314)	Vehicle (N=159)
IGA-CHE score, n (%)				
n	325 (100.0)	162 (100.0)	314 (100.0)	159 (100.0)
Clear				
Almost clear				
Mild				
Moderate	218 (67.1)	109 (67.3)	239 (76.1)	121 (76.1)
Severe	107 (32.9)	53 (32.7)	75 (23.9)	38 (23.9)
HECSI score				
n	325	162	313	159
Mean (SD)	77.6 (46.4)	77.3 (53.6)	64.3 (37.9)	67.7 (39.5)
Min;max	10;275	12;280	7;272	8;213
HESD itch score (weekly average)				
n	324	162	312	157
Mean (SD)	7.13 (1.64)	7.23 (1.69)	6.99 (1.55)	6.98 (1.51)
Min;max	1.9;10.0	3.3;10.0	2.3;10.0	2.6;10.0
HESD itch score (weekly average)				
n	324 (100.0)	162 (100.0)	312 (100.0)	157 (100.0)
<4	1 (0.3)	1 (0.6)	3 (1.0)	1 (0.6)
>=4	323 (99.7)	161 (99.4)	309 (99.0)	156 (99.4)
HESD pain score (weekly average)				
n	324	162	312	157
Mean (SD)	6.83 (2.00)	6.84 (2.03)	6.62 (1.81)	6.46 (1.96)
Min;max	0.8;10.0	0.9;10.0	0.0;10.0	1.0;10.0
HESD score (weekly average)				
n	324	162	312	157
Mean (SD)	7.15 (1.66)	7.16 (1.68)	6.97 (1.46)	6.91 (1.51)
Min;max	1.4;10.0	2.6;10.0	2.8;10.0	2.1;10.0
DLQI score				
n	321	158	310	159
Mean (SD)	12.8 (6.0)	12.9 (6.8)	12.1 (6.2)	12.2 (6.6)
Min;max	0;30	2;30	1;28	2;30
HEIS score				
n	321	158	310	159
Mean (SD)	2.50 (0.77)	2.49 (0.89)	2.42 (0.79)	2.46 (0.84)
Min;max	0.0;4.0	0.0;4.0	0.4;4.0	0.2;4.0
HEIS PDAL score				
n	321	158	310	159
Mean (SD)	2.57 (0.89)	2.57 (0.94)	2.54 (0.90)	2.56 (0.94)
Min;max	0.0;4.0	0.0;4.0	0.0;4.0	0.0;4.0

Abbreviations: DLQI = Dermatology Life Quality Index. HECSI = Hand Eczema Severity Index. HEIS = Hand Eczema Impact Scale. HESD = Hand Eczema Symptom Diary. IGA-CHE = Investigator's Global Assessment for chronic hand eczema. N = number of subjects. n = number of subjects with observation. PDAL = Proximal Daily Activity Limitations. SD = standard deviation. % = percentage of subjects with observation.
Notes: Baseline measurements are defined as the latest available observation at or prior to the date of randomization. Baseline weekly average is defined as the average of the daily observations during the 7 days preceding the baseline visit.

The duration of CHE, age at onset of CHE, distribution of CHE subtypes (main diagnosis) and number of additional diagnoses in studies 1401 and 1402 by treatment group are summarised in Table 16.

Table 16 - CHE history and subtype of hand eczema (studies 1401 and 1402) – randomised subjects

	Trial 1401		Trial 1402	
	Delgocitinib 20 mg/g (N=325)	Vehicle (N=162)	Delgocitinib 20 mg/g (N=314)	Vehicle (N=159)
Duration of CHE (years)				
Mean (SD)	10.3 (11.2)	10.6 (11.9)	8.8 (10.6)	9.3 (10.3)
Median	6.0	5.5	4.0	5.0
Min;max	0;61	0;53	0;59	0;52
Age at onset of CHE (years)				
Mean (SD)	34.0 (17.0)	32.2 (16.7)	36.5 (16.9)	33.3 (16.9)
Median	33.0	30.0	35.0	32.0
Min;max	0;87	0;72	0;83	0;77
Main diagnosis, n (%)				
Allergic contact dermatitis	51 (15.7)	33 (20.4)	27 (8.6)	22 (13.8)
Irritant contact dermatitis	49 (15.1)	26 (16.0)	75 (23.9)	38 (23.9)
Contact urticaria/ protein contact dermatitis				1 (0.6)
Atopic hand eczema	143 (44.0)	74 (45.7)	82 (26.1)	46 (28.9)
Vesicular hand eczema (pompholyx)	25 (7.7)	9 (5.6)	44 (14.0)	9 (5.7)
Hyperkeratotic eczema	57 (17.5)	20 (12.3)	86 (27.4)	43 (27.0)
Number of additional diagnoses, n (%)				
No additional diagnoses	232 (71.4)	114 (70.4)	230 (73.2)	118 (74.2)
1 additional diagnosis	82 (25.2)	36 (22.2)	65 (20.7)	34 (21.4)
2 additional diagnoses	6 (1.8)	9 (5.6)	16 (5.1)	6 (3.8)
3 or more additional diagnoses	5 (1.5)	3 (1.9)	3 (1.0)	1 (0.6)

Abbreviations: CHE = chronic hand eczema. N = number of subjects. n = number of subjects with observation. SD = standard deviation. % = percentage of subjects with observation.
Notes: Duration of CHE is calculated as the year of screening minus year of CHE diagnosis. Age at onset of CHE is calculated as the age of the subject minus the duration of CHE (years).

The previous treatments in studies 1401 and 1402 by treatment group are summarised in Table 17.

Table 17 - CHE treatment history (studies 1401 and 1402) – randomised subjects

	Trial 1401		Trial 1402	
	Delgocitinib 20 mg/g (N=325)	Vehicle (N=162)	Delgocitinib 20 mg/g (N=314)	Vehicle (N=159)
Subjects with any previous CHE treatments, n (%)	325 (100.0)	161 (99.4)	314 (100.0)	158 (99.4)
Topical corticosteroids (TCS)				
Treatment with TCS medically inadvisable, n (%)				
Yes	79 (24.3)	39 (24.1)	48 (15.3)	29 (18.2)
No	246 (75.7)	123 (75.9)	266 (84.7)	130 (81.8)
Subjects having inadequate response to TCS during the last 12 months, n (%)				
Yes	323 (99.4)	161 (99.4)	311 (99.0)	155 (97.5)
No	2 (0.6)	1 (0.6)	3 (1.0)	4 (2.5)
Highest potency, n (%)				
Very potent (Group IV)	138 (42.5)	80 (49.4)	127 (40.4)	66 (41.5)
Potent (Group III)	174 (53.5)	70 (43.2)	173 (55.1)	86 (54.1)
Moderately potent (Group II)	10 (3.1)	10 (6.2)	7 (2.2)	2 (1.3)
Weak (Group I)			1 (0.3)	1 (0.6)
Other	1 (0.3)	1 (0.6)	4 (1.3)	3 (1.9)
Topical calcineurin inhibitors, n (%)				
Yes	121 (37.2)	53 (32.7)	113 (36.0)	62 (39.0)
No	203 (62.5)	109 (67.3)	198 (63.1)	95 (59.7)
Oral corticosteroids, n (%)				
Yes	46 (14.2)	13 (8.0)	50 (15.9)	28 (17.6)
No	279 (85.8)	149 (92.0)	262 (83.4)	131 (82.4)
Oral retinoids, n (%)				
Yes	45 (13.8)	22 (13.6)	52 (16.6)	24 (15.1)
No	280 (86.2)	140 (86.4)	260 (82.8)	134 (84.3)

Abbreviations: ATC = Anatomical Therapeutic Chemical (classification system). CHE = chronic hand eczema. N = number of subjects. n = number of subjects with observation. Q1 = first quartile. TCS = topical corticosteroids. % = percentage of subjects with observation.
Notes: CHE treatment history includes previous treatments for CHE. For TCS only treatments during the last 12 months prior to screening were collected. TCS potency is classified according to ATC classification system.

Study 1403:

Demographic and other baseline characteristics

The baseline demographics of study 1403 by parent trial treatment are summarised in Table 18.

Table 18 - Demographics at parent trial baseline, by parent trial treatment – SAF

	Previous Delgocitinib 20 mg/g (N=560)	Previous Vehicle (N=241)	Total (N=801)
Age (years)			
n	560	241	801
Mean (SD)	45.8 (14.4)	43.3 (14.2)	45.0 (14.4)
Median (Q1;Q3)	46.0 (34.0;56.0)	44.0 (31.0;55.0)	45.0 (33.0;56.0)
Min;max	18;83	18;86	18;86
Age group, n (%)			
n	560 (100.0)	241 (100.0)	801 (100.0)
18 to <65 years	505 (90.2)	230 (95.4)	735 (91.8)
65 to <85 years	55 (9.8)	10 (4.1)	65 (8.1)
>=85 years		1 (0.4)	1 (0.1)
Sex, n (%)			
n	560 (100.0)	241 (100.0)	801 (100.0)
Male	205 (36.6)	84 (34.9)	289 (36.1)
Female	355 (63.4)	157 (65.1)	512 (63.9)
Race, n (%)			
n	560 (100.0)	241 (100.0)	801 (100.0)
White	513 (91.6)	219 (90.9)	732 (91.4)
Black or African American	3 (0.5)	1 (0.4)	4 (0.5)
Asian other	15 (2.7)	8 (3.3)	23 (2.9)
Asian Chinese		1 (0.4)	1 (0.1)
American Indian or Alaska Native	1 (0.2)		1 (0.1)
Native Hawaiian or Other Pacific Islander			
Other	7 (1.3)		7 (0.9)
Multiple	2 (0.4)	2 (0.8)	4 (0.5)
Not reported	19 (3.4)	10 (4.1)	29 (3.6)
Ethnicity, n (%)			
n	560 (100.0)	241 (100.0)	801 (100.0)
Hispanic or Latino	14 (2.5)	7 (2.9)	21 (2.6)
Not Hispanic or Latino	527 (94.1)	225 (93.4)	752 (93.9)
Not reported	19 (3.4)	9 (3.7)	28 (3.5)
Region, n (%)			
n	560 (100.0)	241 (100.0)	801 (100.0)
Europe	447 (79.8)	192 (79.7)	639 (79.8)
North America	113 (20.2)	49 (20.3)	162 (20.2)
Country, n (%)			
n	560 (100.0)	241 (100.0)	801 (100.0)
Belgium	10 (1.8)	9 (3.7)	19 (2.4)
Canada	113 (20.2)	49 (20.3)	162 (20.2)
Denmark	18 (3.2)	2 (0.8)	20 (2.5)
France	43 (7.7)	25 (10.4)	68 (8.5)
Germany	149 (26.6)	66 (27.4)	215 (26.8)
Italy	27 (4.8)	13 (5.4)	40 (5.0)
Netherlands	12 (2.1)	4 (1.7)	16 (2.0)
Poland	129 (23.0)	51 (21.2)	180 (22.5)
Spain	40 (7.1)	18 (7.5)	58 (7.2)
United Kingdom	19 (3.4)	4 (1.7)	23 (2.9)

Abbreviations: N = number of subjects. n = number of subjects with observation. Q1 = first quartile. Q3 = third quartile. SAF = safety analysis set. SD = standard deviation. % = percentage of subjects with observation.

Baseline disease characteristics

The disease characteristics, i.e. IGA-CHE and HECSI scores at parent trial baseline and extension trial baseline are shown in Table 19 and Table 20, respectively.

Table 19 - CHE characteristics at parent trial baseline, by parent trial treatment – SAF

	Previous delgocitinib 20 mg/g (N=560)	Previous vehicle (N=241)	Total (N=801)
IGA-CHE score, n (%)			
n	560 (100.0)	241 (100.0)	801 (100.0)
0 – Clear	0	0	0
1 – Almost clear	0	0	0
2 – Mild	0	0	0
3 – Moderate	395 (70.5)	165 (68.5)	560 (69.9)
4 – Severe	165 (29.5)	76 (31.5)	241 (30.1)
HECSI score			
n	560	241	801
Mean (SD)	72.5 (43.3)	74.6 (47.4)	73.1 (44.6)
Median (Q1; Q3)	63.0 (41.0; 91.0)	63.0 (43.0; 97.0)	63.0 (41.0; 92.0)
Min; max	7; 275	8; 234	7; 275

Abbreviations: HECSI = Hand Eczema Severity Index; IGA-CHE = Investigator's Global Assessment for chronic hand eczema; max = maximum; min = minimum; N = number of subjects; n = number of subjects with observation; Q1 = first quartile; Q3 = third quartile; SD = standard deviation.

Table 20 - CHE characteristics at extension trial baseline, by parent trial treatment – SAF

	Previous delgocitinib 20 mg/g (N=560)	Previous vehicle (N=241)	Total (N=801)
IGA-CHE score, n (%)			
n	560 (100.0)	241 (100.0)	801 (100.0)
0 – Clear	70 (12.5)	7 (2.9)	77 (9.6)
1 – Almost clear	68 (12.1)	15 (6.2)	83 (10.4)
2 – Mild	256 (45.7)	89 (36.9)	345 (43.1)
3 – Moderate	145 (25.9)	98 (40.7)	243 (30.3)
4 – Severe	21 (3.8)	32 (13.3)	53 (6.6)
HECSI score			
n	560	241	801
Mean (SD)	23.9 (29.1)	46.8 (46.0)	30.8 (36.5)
Median (Q1; Q3)	13.0 (4.0; 33.0)	36.0 (14.0; 62.0)	20.0 (6.0; 43.0)
Min; max	0; 194	0; 276	0; 276

Abbreviations: HECSI = Hand Eczema Severity Index; IGA-CHE = Investigator's Global Assessment for chronic hand eczema; max = maximum; min = minimum; N = number of subjects; n = number of subjects with observation; Q1 = first quartile; Q3 = third quartile; SD = standard deviation.

- **Numbers analysed**

Studies 1401 and 1402:

All randomised subjects in study 1401 and all, except one subject in study 1402 who was randomised in error and not treated, were included in the full analysis set (FAS).

Study 1403:

All 801 enrolled subjects were included in the safety analysis set (SAF), 664 completed 36 weeks of as needed treatment, 661 completed trial and 140 withdrew from the study.

- **Outcomes and estimation**

Studies 1401 and 1402:

The efficacy results for the primary and all key secondary endpoints using the primary estimand (composite) is summarised in Table 21.

Table 21 - Efficacy results for the primary and key secondary endpoints (studies 1401 and 1402)

Assessment Binary endpoints[1]	Trial 1401			Trial 1402		
	Delgocitinib cream 20 mg/g Responders (%)	Cream vehicle Responders (%)	Estimated treatment difference (95% CI); p-value	Delgocitinib cream 20 mg/g Responders (%)	Cream vehicle Responders (%)	Estimated treatment difference (95% CI); p-value
Primary endpoint						
IGA-CHE	N=325	N=162		N=313	N=159	
IGA-CHE TS at W16	64 (19.7)	16 (9.9)	9.8 (3.6,16.1); 0.006	91 (29.1)	11 (6.9)	22.2 (15.8,28.5); <0.001
Key secondary endpoints						
IGA-CHE	N=325	N=162		N=313	N=159	
IGA-CHE TS at W8	74 (22.8)	17 (10.5)	12.3 (5.7,18.9); 0.001	101 (32.3)	15 (9.4)	22.9 (16.0,29.8); <0.001
IGA-CHE TS at W4	50 (15.4)	8 (4.9)	10.4 (5.3,15.6); <0.001	46 (14.7)	13 (8.2)	6.5 (0.8,12.3); 0.043
HECSI	N=325	N=162		N=313	N=159	
HECSI-90 at W16	96 (29.5)	20.0 (12.3)	17.2 (10.1,24.3); <0.001	97 (31.0)	14 (8.8)	22.2 (15.4,29.0); <0.001
HECSI-75 at W16	160 (49.2)	38 (23.5)	25.7 (17.2,34.3); <0.001	155 (49.5)	29 (18.2)	31.3 (23.1,39.5); <0.001
HECSI-75 at W8	163 (50.2)	42 (25.9)	24.2 (15.5,33.0); <0.001)	158 (50.5)	31 (19.5)	31.0 (22.7,39.3); <0.001
HESD itch	N=323	N=161		N=309	N=156	
Reduction of HESD itch score of ≥4 points from baseline at W16	152 (47.1)	37 (23.0)	24.1 (15.5,32.6); <0.001	146 (47.2)	31 (19.9)	27.4 (19.0,35.8); <0.001
Reduction of HESD itch score of ≥4 points from baseline at W8	138 (42.7)	35 (21.7)	21.0 (12.6,29.4); <0.001	131 (42.4)	21 (13.5)	29.0 (21.3,36.7); <0.001
Reduction of HESD itch score of ≥4 points from baseline at W4	99 (30.7)	18 (11.2)	19.5 (12.5,26.5); <0.001	94 (30.4)	19 (12.2)	18.3 (11.0,25.6); <0.001
Reduction of HESD itch score of ≥4 points from baseline at W2	50 (15.5)	10 (6.2)	9.3 (3.8,14.7); 0.004	40 (12.9)	10 (6.4)	6.6 (1.1,12.0); 0.031

HESD pain	N=291	N=149		N=294	N=141	
Reduction of HESD pain score of ≥4 points from baseline at W16	143 (49.1)	41 (27.5)	21.7 (12.4,30.9); <0.001	143 (48.6)	32.0 (22.7)	26.0 (17.0,35.1); <0.001
Reduction of HESD pain score of ≥4 points from baseline at W8	134 (46.0)	33 (22.1)	23.9 (15.2,32.7); <0.001	124 (42.2)	18 (12.8)	29.6 (21.7,37.4); <0.001
Reduction of HESD pain score of ≥4 points from baseline at W4	100 (34.4)	22 (14.8)	19.6 (11.8,27.5); <0.001	91 (31.0)	15 (10.6)	20.5 (13.1,27.8); <0.001
HESD	N=309	N=156		N=308	N=153	
Reduction of HESD score of ≥4 points from baseline at W16	146 (47.2)	38 (24.4)	22.8 (14.0,31.7); <0.001	137 (44.5)	32 (20.9)	23.7 (15.1,32.2); <0.001
Reduction of HESD score of ≥4 points from baseline at W8	123 (39.8)	27 (17.3)	22.5 (14.4,30.6); <0.001	115 (37.3)	19 (12.4)	25.0 (17.5,32.5); <0.001
Reduction of HESD score of ≥4 points from baseline at W4	92 (29.8)	16 (10.3)	19.5 (12.5,26.5); <0.001	80 (26.0)	14 (9.2)	16.9 (10.2,23.7); <0.001
DLQI	N=305	N=148		N=299	N=153	
Reduction of DLQI score of ≥4 points from baseline to W16	227 (74.4)	74 (50.0)	24.5 (15.0,33.9); <0.001	216 (72.2)	70 (45.8)	26.4 (17.0,35.9); <0.001
HECSI	N=325	N=162		N=313	N=159	
Percentage change in HECSI from baseline to W16	-56.5 (3.4)	-21.2 (4.8)	-35.2 (-46.7,-23.8); <0.001	-58.9 (3.2)	-13.4 (4.5)	-45.5 (-56.4,-34.6); <0.001
HESD	N=324	N=162		N=312	N=157	
Change in HESD itch score from baseline to W16	-3.6 (0.2)	-1.9 (0.2)	-1.7 (-2.3,-1.2); <0.001	-3.4 (0.2)	-1.4 (0.2)	-2.0 (-2.5,-1.4); <0.001
Change in HESD pain score from baseline to W16	-3.4 (0.2)	-1.8 (0.2)	-1.6 (-2.1,-1.0); <0.001	-3.3 (0.2)	-1.3 (0.2)	-2.0 (-2.6,-1.5); <0.001
Change in HESD score from baseline to W16	-3.4 (0.1)	-1.7 (0.2)	-1.7 (-2.2,-1.2); <0.001	-3.2 (0.1)	-1.4 (0.2)	-1.9 (-2.4,-1.4); <0.001
DLQI	N=321	N=158		N=310	N=159	
Change in DLQI score from baseline to W16	-7.6 (0.3)	-3.9 (0.4)	-3.6 (-4.7,-2.6); <0.001	-7.0 (0.3)	-3.1 (0.5)	-3.9 (-5.0,-2.8); <0.001
HEIS	N=321	N=158		N=310	N=159	
Change in HEIS score from baseline to W16	-1.46 (0.05)	-0.82 (0.08)	-0.64 (-0.83,-0.45); <0.001	-1.45 (0.06)	-0.64 (0.08)	-0.81 (-0.99,-0.62); <0.001
Change in HEIS PDAL score from baseline to W16	-1.46 (0.06)	-0.86 (0.08)	-0.60 (-0.79,-0.40); <0.001	-1.48 (0.06)	-0.66 (0.08)	-0.82 (-1.01,-0.62); <0.001

[1] Endpoints are not presented in the order of the testing hierarchy.
Abbreviations: CI = confidence interval. DLQI = Dermatology Life Quality Index. FAS = full analysis set. HECSI = Hand Eczema Severity Index. HECSI-75 = at least 75% improvement in HECSI score from baseline. HECSI-90 = at least 90% improvement in HECSI score from baseline. HEIS = Hand Eczema Impact Scale. HESD = Hand Eczema Symptom Diary. IGA-CHE = Investigator's Global Assessment for chronic hand eczema. IGA-CHE TS = IGA-CHE treatment success, i.e. an IGA-CHE score of 0 (clear) or 1 (almost clear) with a ≥2-step improvement from baseline. LSMean=least squares mean. N=number of subjects with data available at baseline. PDAL = Proximal Daily Activity Limitations. SE = standard error. W = week.

Table 22 and Table 23 show the primary estimand and supportive analyses for IGA-CHE TS in study 1401 and 1402.

Table 22 - IGA-CHE TS at weeks 16 in study 1401 (CMH, FAS)

IGA-CHE TS at Week 16	Delgocitinib 20 mg/g (N=325) Responders (%)	Vehicle (N=162) Responders (%)	Difference in percentage (95% CI) #a	p-value #b
Primary estimand: Composite #c				
Primary analysis #d	64.0 (19.7)	16.0 (9.9)	9.8 (3.6,16.1)	0.006
1st sensitivity p=0.1 #e	64.1 (19.7)	16.0 (9.9)	9.9 (3.6,16.1)	0.002
1st sensitivity p=0.2 #f	64.2 (19.7)	16.0 (9.9)	9.9 (3.6,16.2)	0.002
First supplementary estimand: Pandemic-modified composite #g				
Primary analysis #h	64.0 (19.7)	16.0 (9.9)	9.8 (3.6,16.1)	0.006
Second supplementary estimand: Treatment policy #i				
Primary analysis #j	68.9 (21.2)	21.2 (13.1)	8.1 (1.1,15.2)	0.024
Sensitivity analysis #k	66.0 (20.3)	19.0 (11.7)	8.6 (2.0,15.2)	0.018

Abbreviations: CI = confidence interval. COVID-19 = coronavirus disease 2019. FAS = full analysis set. IGA-CHE = Investigator's Global Assessment for chronic hand eczema. IGA-CHE TS = IGA-CHE treatment success i.e. an IGA-CHE score of 0 (clear) or 1 (almost clear) with a >= 2-step improvement from baseline. IMP = investigational medicinal product. MAR = missing at random. MI = multiple imputation. MNAR = missing not at random. N = number of subjects with data available at baseline. % = percentage of subjects.
Notes: #a = Mantel-Haenszel risk difference, stratified by region and baseline IGA-CHE score. #b = Cochran-Mantel-Haenszel test, stratified by region and baseline IGA-CHE score. #c = Data considered non-response after initiation of rescue treatment or after permanent discontinuation of IMP. #d = Missing data imputed as non-response. #e = Missing data imputed from a Bernoulli distribution with parameter p=0.1 using MI. #f = Missing data imputed from a Bernoulli distribution with parameter p=0.2 using MI. Results from the second sensitivity analysis (tipping point analysis) are presented separately. #g = Data considered non-response after initiation of rescue treatment of after permanent discontinuation of IMP not related to COVID-19 pandemic. Data considered missing after permanent discontinuation of IMP related to COVID-19 pandemic. #h = Missing data related to COVID-19 pandemic imputed using MI assuming MAR. Data missing for other reasons imputed as non-response. #i = All data used as observed, except data collected after permanent discontinuation of IMP due to COVID-19 pandemic which is treated as missing. #j = Missing data for subjects who experienced intercurrent events not related to COVID-19 pandemic imputed using MI assuming MNAR (copy-reference). Data missing for other reasons imputed using MI assuming MAR. #k = Missing data related to COVID-19 pandemic imputed using MI assuming MAR. Data missing for other reasons is imputed as non-response.

Table 23 - IGA-CHE TS at weeks 16 in study 1402 (CMH, FAS)

IGA-CHE TS at Week 16	Delgocitinib 20 mg/g (N=313) Responders (%)	Vehicle (N=159) Responders (%)	Difference in percentage (95% CI) #a	p-value #b
Primary estimand: Composite #c				
Primary analysis #d	91.0 (29.1)	11.0 (6.9)	22.2 (15.8,28.5)	<.001
1st sensitivity p=0.1 #e	91.0 (29.1)	11.1 (7.0)	22.1 (15.7,28.5)	<.001
1st sensitivity p=0.2 #f	91.0 (29.1)	11.2 (7.1)	22.0 (15.6,28.4)	<.001
First supplementary estimand: Pandemic-modified composite #g				
Primary analysis #h	91.0 (29.1)	11.0 (6.9)	22.2 (15.8,28.5)	<.001
Second supplementary estimand: Treatment policy #i				
Primary analysis #j	95.1 (30.4)	14.0 (8.8)	21.6 (14.5,28.7)	<.001
Sensitivity analysis #k	92.0 (29.4)	11.0 (6.9)	22.5 (16.1,28.9)	<.001

Abbreviations: CI = confidence interval. COVID-19 = coronavirus disease 2019. FAS = full analysis set. IGA-CHE = Investigator's Global Assessment for chronic hand eczema. IGA-CHE TS = IGA-CHE treatment success i.e. an IGA-CHE score of 0 (clear) or 1 (almost clear) with a >= 2-step improvement from baseline. IMP = investigational medicinal product. MAR = missing at random. MI = multiple imputation. MNAR = missing not at random. N = number of subjects with data available at baseline. % = percentage of subjects.
Notes: #a = Mantel-Haenszel risk difference, stratified by region and baseline IGA-CHE score. #b = Cochran-Mantel-Haenszel test, stratified by region and baseline IGA-CHE score. #c = Data considered non-response after initiation of rescue treatment or after permanent discontinuation of IMP. #d = Missing data imputed as non-response. #e = Missing data imputed from a Bernoulli distribution with parameter p=0.1 using MI. #f = Missing data imputed from a Bernoulli distribution with parameter p=0.2 using MI. Results from the second sensitivity analysis (tipping point analysis) are presented separately. #g = Data considered non-response after initiation of rescue treatment of after permanent discontinuation of IMP not related to COVID-19 pandemic. Data considered missing after permanent discontinuation of IMP related to COVID-19 pandemic. #h = Missing data related to COVID-19 pandemic imputed using MI assuming MAR. Data missing for other reasons imputed as non-response. #i = All data used as observed, except data collected after permanent discontinuation of IMP due to COVID-19 pandemic which is treated as missing. #j = Missing data for subjects who experienced intercurrent events not related to COVID-19 pandemic imputed using MI assuming MNAR (copy-reference). Data missing for other reasons imputed using MI assuming MAR. #k = Missing data related to COVID-19 pandemic imputed using MI assuming MAR. Data missing for other reasons is imputed as non-response.

Treatment compliance

In studies 1401 and 1402, respectively, 22.8% and 16.0% of subjects in the delgocitinib group and 21.0% and 18.9% of subjects in the vehicle group had no days with missed IMP application, and 50.5% and 50.8% of subjects in the delgocitinib group and 52.5% and 52.2% of subjects in the vehicle group had at most 10% days with missed IMP application or missing compliance data.

In both studies and in both treatment groups, treatment compliance showed a slightly decreasing trend over time.

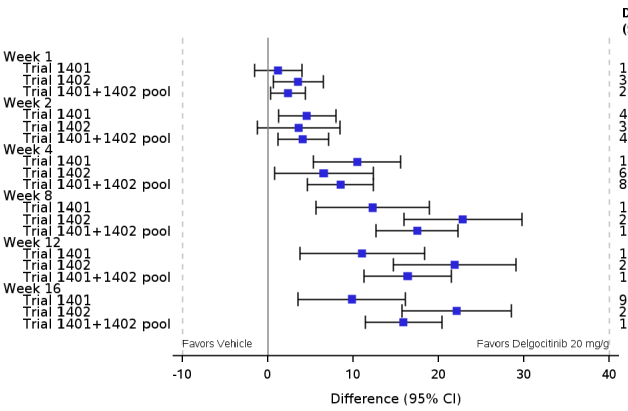
Rescue treatments

Any rescue treatment was used by 7 (2.2%) and 3 (1.0%) of subjects in the delgocitinib group and by 7 (4.3%) and 12 (7.5%) of subjects in the vehicle group in studies 1401 and 1402, respectively. The most frequently used rescue treatment were TCSs.

Onset of efficacy

The efficacy results (treatment comparisons) by visit for the relevant secondary endpoints (studies 1401, 1402 and pooled) are described in Figures below.

Figure 5 - IGA-CHE TS, treatment comparison by visit (Trials 1401, 1402 and pooled)

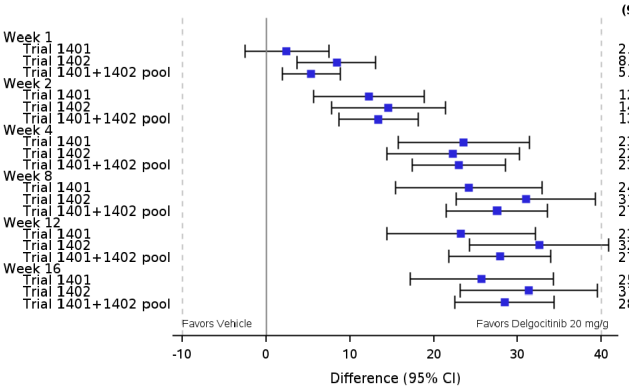


	Difference (95% CI)	Delgocitinib 20 mg/g Responders/N (%)	Vehicle Responders/N (%)	p-value
Week 1				
Trial 1401	1.2 (-1.6,4.0)	10/325 (3.1)	3/162 (1.9)	0.433
Trial 1402	3.5 (0.6,6.5)	15/313 (4.8)	2/159 (1.3)	0.052
Trial 1401+1402 pool	2.4 (0.3,4.4)	25/638 (3.9)	5/321 (1.6)	0.048
Week 2				
Trial 1401	4.6 (1.2,8.0)	21/325 (6.5)	3/162 (1.9)	0.027
Trial 1402	3.6 (-1.2,8.5)	29/313 (9.3)	9/159 (5.7)	0.173
Trial 1401+1402 pool	4.1 (1.2,7.1)	50/638 (7.8)	12/321 (3.7)	0.014
Week 4				
Trial 1401	10.4 (5.3,15.6)	50/325 (15.4)	8/162 (4.9)	<.001
Trial 1402	6.5 (0.8,12.3)	46/313 (14.7)	13/159 (8.2)	0.043
Trial 1401+1402 pool	8.5 (4.7,12.4)	96/638 (15.0)	21/321 (6.5)	<.001
Week 8				
Trial 1401	12.3 (5.7,18.9)	74/325 (22.8)	17/162 (10.5)	0.001
Trial 1402	22.9 (16.0,29.8)	101/313 (32.3)	15/159 (9.4)	<.001
Trial 1401+1402 pool	17.5 (12.7,22.3)	175/638 (27.4)	32/321 (10.0)	<.001
Week 12				
Trial 1401	11.0 (3.8,18.3)	84/325 (25.8)	24/162 (14.8)	0.006
Trial 1402	21.9 (14.7,29.1)	104/313 (33.2)	18/159 (11.3)	<.001
Trial 1401+1402 pool	16.4 (11.3,21.5)	188/638 (29.5)	42/321 (13.1)	<.001
Week 16				
Trial 1401	9.8 (3.6,16.1)	64/325 (19.7)	16/162 (9.9)	0.006
Trial 1402	22.2 (15.8,28.5)	91/313 (29.1)	11/159 (6.9)	<.001
Trial 1401+1402 pool	15.9 (11.4,20.4)	155/638 (24.3)	27/321 (8.4)	<.001

Abbreviations: CI = confidence interval. FAS = full analysis set. IGA-CHE = Investigator's Global Assessment for chronic hand eczema. IGA-CHE TS = IGA-CHE treatment success i.e. an IGA-CHE score of 0 (clear) or 1 (almost clear) with a >= 2-step improvement from baseline. IMP = investigational medicinal product. N = number of subjects with data available at baseline.

Notes: Responders were defined as subjects who achieved IGA-CHE TS. Composite estimand: Data considered non-response if observed after initiation of rescue treatment or after permanent discontinuation of IMP. Missing data imputed as non-response. For trial 1401 and 1402: Mantel-Haenszel risk difference stratified by region and baseline IGA-CHE score and Cochran-Mantel-Haenszel test stratified by region and baseline IGA-CHE score. For the trial 1401+1402 pool: Mantel-Haenszel risk difference stratified by trial ID, region and baseline IGA-CHE score and Cochran-Mantel-Haenszel test stratified by trial ID, region and baseline IGA-CHE score.

Figure 6 - HECSI-75, treatment comparison by visit (Studies 1401, 1402 and pooled)

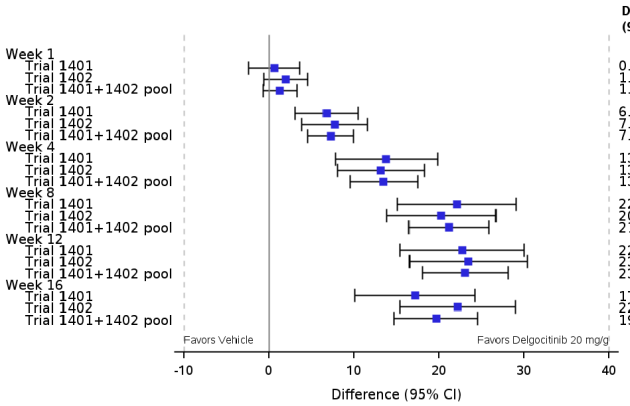


	Difference (95% CI)	Delgocitinib 20 mg/g Responders/N (%)	Vehicle Responders/N (%)	p-value
Week 1				
Trial 1401	2.4 (-2.6,7.4)	30/325 (9.2)	11/162 (6.8)	0.362
Trial 1402	8.4 (3.7,13.1)	38/313 (12.1)	6/159 (3.8)	0.003
Trial 1401+1402 pool	5.4 (1.9,8.8)	68/638 (10.7)	17/321 (5.3)	0.006
Week 2				
Trial 1401	12.3 (5.7,18.8)	74/325 (22.8)	17/162 (10.5)	0.001
Trial 1402	14.6 (7.8,21.4)	79/313 (25.2)	17/159 (10.7)	<.001
Trial 1401+1402 pool	13.4 (8.7,18.1)	153/638 (24.0)	34/321 (10.6)	<.001
Week 4				
Trial 1401	23.6 (15.8,31.4)	129/325 (39.7)	26/162 (16.0)	<.001
Trial 1402	22.3 (14.4,30.2)	119/313 (38.0)	25/159 (15.7)	<.001
Trial 1401+1402 pool	23.0 (17.4,28.5)	248/638 (38.9)	51/321 (15.9)	<.001
Week 8				
Trial 1401	24.2 (15.5,33.0)	163/325 (50.2)	42/162 (25.9)	<.001
Trial 1402	31.0 (22.7,39.3)	158/313 (50.5)	31/159 (19.5)	<.001
Trial 1401+1402 pool	27.6 (21.5,33.6)	321/638 (50.3)	73/321 (22.7)	<.001
Week 12				
Trial 1401	23.3 (14.4,32.1)	168/325 (51.7)	46/162 (28.4)	<.001
Trial 1402	32.6 (24.3,40.9)	163/313 (52.1)	31/159 (19.5)	<.001
Trial 1401+1402 pool	27.9 (21.8,34.0)	331/638 (51.9)	77/321 (24.0)	<.001
Week 16				
Trial 1401	25.7 (17.2,34.3)	160/325 (49.2)	38/162 (23.5)	<.001
Trial 1402	31.3 (23.1,39.5)	155/313 (49.5)	29/159 (18.2)	<.001
Trial 1401+1402 pool	28.5 (22.6,34.4)	315/638 (49.4)	67/321 (20.9)	<.001

Abbreviations: CI = confidence interval. FAS = full analysis set. HECSI = Hand Eczema Severity Index. HECSI-75 = at least 75% improvement in HECSI score from baseline. IMP = investigational medicinal product. N = number of subjects with data available at baseline.

Notes: Responders were defined as subjects who achieved HECSI-75. Composite estimand: Data considered non-response if observed after initiation of rescue treatment or after permanent discontinuation of IMP. Missing data imputed as non-response. For trial 1401 and 1402: Mantel-Haenszel risk difference stratified by region and baseline IGA-CHE score and Cochran-Mantel-Haenszel test stratified by region and baseline IGA-CHE score. For the trial 1401+1402 pool: Mantel-Haenszel risk difference stratified by trial ID, region and baseline IGA-CHE score and Cochran-Mantel-Haenszel test stratified by trial ID, region and baseline IGA-CHE score.

Figure 7 - HECSI-90, treatment comparison by visit (Studies 1401, 1402 and pooled)

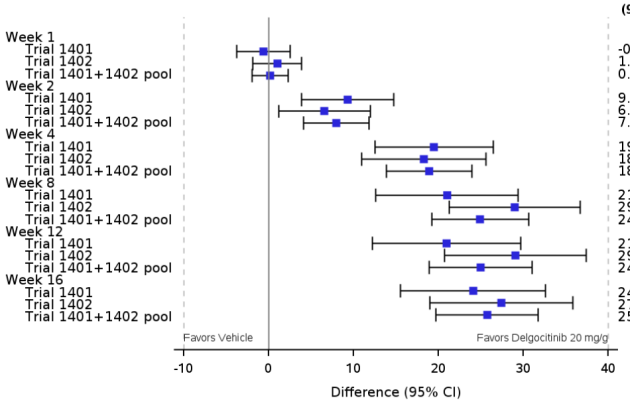


	Difference (95% CI)	Delgocitinib 20 mg/g Responders/N (%)	Vehicle Responders/N (%)	p-value
Week 1				
Trial 1401	0.6 (-2.4,3.6)	10/325 (3.1)	4/162 (2.5)	0.708
Trial 1402	1.9 (-0.7,4.6)	10/313 (3.2)	2/159 (1.3)	0.205
Trial 1401+1402 pool	1.3 (-0.7,3.3)	20/638 (3.1)	6/321 (1.9)	0.255
Week 2				
Trial 1401	6.8 (3.1,10.5)	28/325 (8.6)	3/162 (1.9)	0.004
Trial 1402	7.7 (3.8,11.6)	30/313 (9.6)	3/159 (1.9)	0.002
Trial 1401+1402 pool	7.2 (4.5,9.9)	58/638 (9.1)	6/321 (1.9)	<.001
Week 4				
Trial 1401	13.8 (7.8,19.8)	69/325 (21.2)	12/162 (7.4)	<.001
Trial 1402	13.2 (8.1,18.3)	53/313 (16.9)	6/159 (3.8)	<.001
Trial 1401+1402 pool	13.5 (9.5,17.5)	122/638 (19.1)	18/321 (5.6)	<.001
Week 8				
Trial 1401	22.1 (15.2,29.0)	104/325 (32.0)	16/162 (9.9)	<.001
Trial 1402	20.3 (13.9,26.7)	87/313 (27.8)	12/159 (7.5)	<.001
Trial 1401+1402 pool	21.2 (16.5,25.9)	191/638 (29.9)	28/321 (8.7)	<.001
Week 12				
Trial 1401	22.7 (15.4,30.0)	114/325 (35.1)	20/162 (12.3)	<.001
Trial 1402	23.5 (16.5,30.4)	103/313 (32.9)	15/159 (9.4)	<.001
Trial 1401+1402 pool	23.1 (18.1,28.1)	217/638 (34.0)	35/321 (10.9)	<.001
Week 16				
Trial 1401	17.2 (10.1,24.3)	96/325 (29.5)	20/162 (12.3)	<.001
Trial 1402	22.2 (15.4,29.0)	97/313 (31.0)	14/159 (8.8)	<.001
Trial 1401+1402 pool	19.7 (14.7,24.6)	193/638 (30.3)	34/321 (10.6)	<.001

Abbreviations: CI = confidence interval. FAS = full analysis set. HECSI = Hand Eczema Severity Index. HECSI-90 = at least 90% improvement in HECSI score from baseline. IMP = investigational medicinal product. N = number of subjects with data available at baseline.

Notes: Responders were defined as subjects who achieved HECSI-90. Composite estimand: Data considered non-response if observed after initiation of rescue treatment or after permanent discontinuation of IMP. Missing data imputed as non-response. For trial 1401 and 1402: Mantel-Haenszel risk difference stratified by region and baseline IGA-CHE score and Cochran-Mantel-Haenszel test stratified by region and baseline IGA-CHE score. For the trial 1401+1402 pool: Mantel-Haenszel risk difference stratified by trial ID, region and baseline IGA-CHE score and Cochran-Mantel-Haenszel test stratified by trial ID, region and baseline IGA-CHE score.

Figure 8 - Reduction of HESD itch score (weekly average) of ≥4 points, treatment comparison by week (Studies 1401, 1402 and pooled)

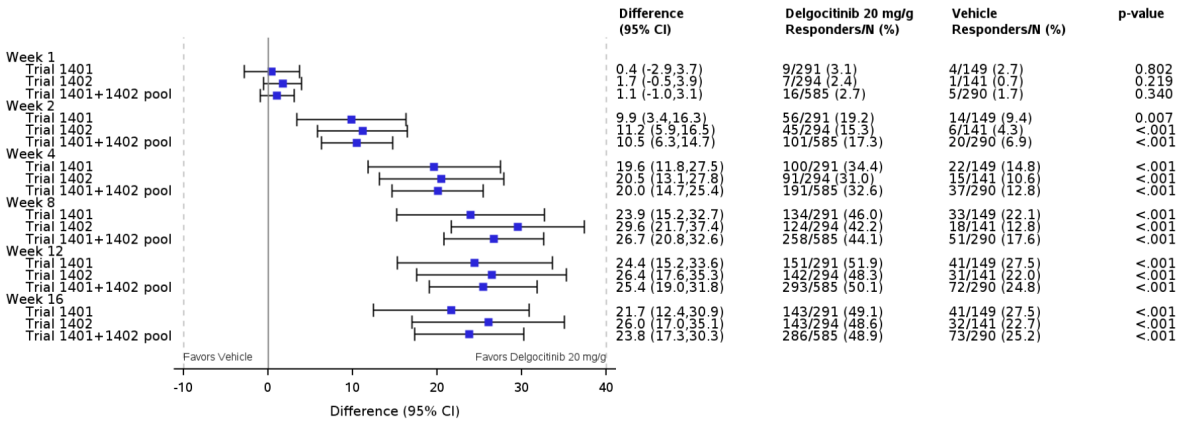


	Difference (95% CI)	Delgocitinib 20 mg/g Responders/N (%)	Vehicle Responders/N (%)	p-value
Week 1				
Trial 1401	-0.6 (-3.8,2.5)	8/323 (2.5)	5/161 (3.1)	0.688
Trial 1402	1.0 (-1.9,3.9)	9/309 (2.9)	3/156 (1.9)	0.522
Trial 1401+1402 pool	0.2 (-2.0,2.3)	17/632 (2.7)	8/317 (2.5)	0.877
Week 2				
Trial 1401	9.3 (3.8,14.7)	50/323 (15.5)	10/161 (6.2)	0.004
Trial 1402	6.6 (1.1,12.0)	40/309 (12.9)	10/156 (6.4)	0.031
Trial 1401+1402 pool	7.9 (4.1,11.8)	90/632 (14.2)	20/317 (6.3)	<.001
Week 4				
Trial 1401	19.5 (12.5,26.5)	99/323 (30.7)	18/161 (11.2)	<.001
Trial 1402	18.3 (11.0,25.6)	94/309 (30.4)	19/156 (12.2)	<.001
Trial 1401+1402 pool	18.9 (13.8,24.0)	193/632 (30.5)	37/317 (11.7)	<.001
Week 8				
Trial 1401	21.0 (12.6,29.4)	138/323 (42.7)	35/161 (21.7)	<.001
Trial 1402	29.0 (21.3,36.7)	131/309 (42.4)	21/156 (13.5)	<.001
Trial 1401+1402 pool	24.9 (19.2,30.6)	269/632 (42.6)	56/317 (17.7)	<.001
Week 12				
Trial 1401	21.0 (12.2,29.7)	150/323 (46.4)	41/161 (25.5)	<.001
Trial 1402	29.0 (20.7,37.4)	149/309 (48.2)	30/156 (19.2)	<.001
Trial 1401+1402 pool	24.9 (18.9,31.0)	299/632 (47.3)	71/317 (22.4)	<.001
Week 16				
Trial 1401	24.1 (15.5,32.6)	152/323 (47.1)	37/161 (23.0)	<.001
Trial 1402	27.4 (19.0,35.8)	146/309 (47.2)	31/156 (19.9)	<.001
Trial 1401+1402 pool	25.7 (19.7,31.7)	298/632 (47.2)	68/317 (21.5)	<.001

Abbreviations: CI = confidence interval. FAS = full analysis set. HESD = Hand Eczema Symptom Diary. IMP = investigational medicinal product. N = number of subjects with baseline score >= 4.

Notes: Responders were defined as subjects who achieved reduction in HESD itch score (weekly average) of >= 4 points. Composite estimand: Data considered non-response if observed after initiation of rescue treatment or after permanent discontinuation of IMP. Missing data imputed as non-response. For trial 1401 and 1402: Mantel-Haenszel risk difference stratified by region and baseline IGA-CHE score and Cochran-Mantel-Haenszel test stratified by region and baseline IGA-CHE score. For the trial 1401+1402 pool: Mantel-Haenszel risk difference stratified by trial ID, region and baseline IGA-CHE score and Cochran-Mantel-Haenszel test stratified by trial ID, region and baseline IGA-CHE score.

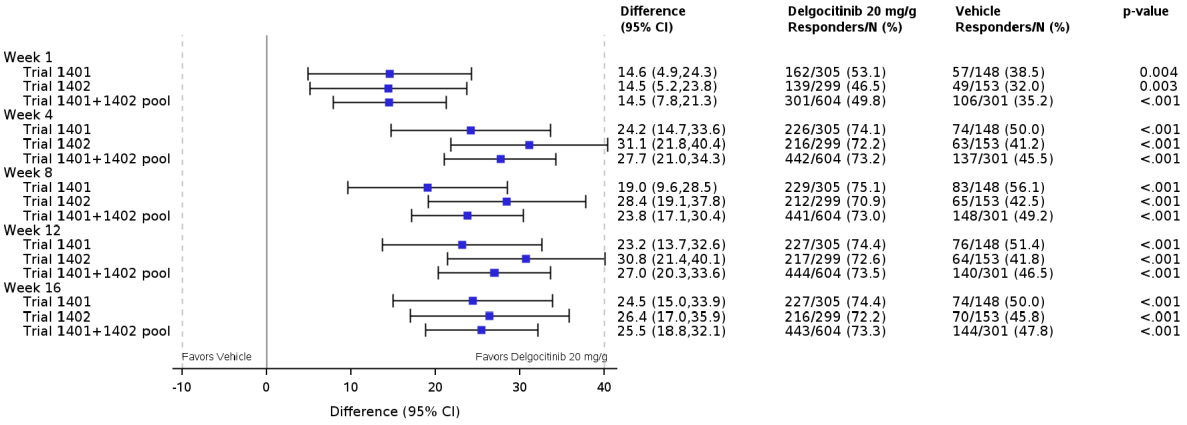
Figure 9 - Reduction of HESD pain score (weekly average) of ≥4 points, treatment comparison by week (Trials 1401, 1402 and pooled)



Abbreviations: CI = confidence interval. FAS = full analysis set. HESD = Hand Eczema Symptom Diary. IMP = investigational medicinal product. N = number of subjects with baseline score >= 4.

Notes: Responders were defined as subjects who achieved reduction in HESD pain score (weekly average) of >= 4 points. Composite estimand: Data considered non-response if observed after initiation of rescue treatment or after permanent discontinuation of IMP. Missing data imputed as non-response. For trial 1401 and 1402: Mantel-Haenszel risk difference stratified by region and baseline IGA-CHE score and Cochran-Mantel-Haenszel test stratified by region and baseline IGA-CHE score. For the trial 1401+1402 pool: Mantel-Haenszel risk difference stratified by trial ID, region and baseline IGA-CHE score and Cochran-Mantel-Haenszel test stratified by trial ID, region and baseline IGA-CHE score.

Figure 10 - Reduction of DLQI score of ≥4 points, treatment comparison by visit (Trials 1401, 1402 and pooled)



Abbreviations: CI = confidence interval. DLQI = Dermatology Life Quality Index. FAS = full analysis set. IMP = investigational medicinal product. N = number of subjects with baseline score >= 4.

Notes: Responders were defined as subjects who achieved reduction in DLQI score of >= 4 points. Composite estimand: Data considered non-response if observed after initiation of rescue treatment or after permanent discontinuation of IMP. Missing data imputed as non-response. For trial 1401 and 1402: Mantel-Haenszel risk difference stratified by region and baseline IGA-CHE score and Cochran-Mantel-Haenszel test stratified by region and baseline IGA-CHE score. For the trial 1401+1402 pool: Mantel-Haenszel risk difference stratified by trial ID, region and baseline IGA-CHE score and Cochran-Mantel-Haenszel test stratified by trial ID, region and baseline IGA-CHE score.

Study 1403:

Exposure

In the extension study 1403, the number of on-treatment periods and the duration of on-treatment periods were similar for subjects treated with delgocitinib and with vehicle in the pivotal studies. The number of days in response and proportion of days in response was slightly higher for subjects treated with delgocitinib (46.2 days and 18.9%) compared with subjects treated with vehicle in the pivotal studies (39.7 days and 16.4%) (Table 24).

Table 24 - Summary of exposure (study 1403) – SAF

	Previous delgocitinib 20 mg/g (N=560)	Previous vehicle (N=241)	Total (N=801)
Number of on-treatment periods			
n[1]	560	241	801
Mean (SD)	1.5 (0.9)	1.6 (0.9)	1.5 (0.9)
Median (Q1; Q3)	1.0 (1.0;2.0)	1.0 (1.0;2.0)	1.0 (1.0;2.0)
Min; max	0; 6	0;4	0; 6
Rate per 100 PYO	143.9	149.1	145.4
Duration of on-treatment periods (days)			
n[2]	850	375	1225
Mean (SD)	122.6 (89.7)	119.1 (87.5)	121.5 (89.0)
Median (Q1; Q3)	86.0 (39.0;230.0)	87.0 (36.0;205.0)	86.0 (36.0;226.0)
Min; max	3;275	1;265	1;275
Number of days in response			
n[3]	559	240	799
Mean (SD)	46.2 (64.6)	39.7 (57.8)	44.3 (62.7)
Median (Q1; Q3)	13.0 (0.0;83.0)	0.0 (0.0;59.5)	10.0 (0.0;80.0)
Min; max	0;259	0;274	0;274
Proportion of days in response (%)			
n[3]	559	240	799
Mean (SD)	18.90 (26.48)	16.44 (24.03)	18.16 (25.78)
Median (Q1; Q3)	5.00 (0.00;32.80)	0.00 (0.00;26.80)	4.30 (0.00;31.60)
Min; max	0.0; 100.0	0.0;100.0	0.0; 100.0

[1]Number of subjects.

[2]Number of on-treatment periods.

[3] Number of subjects with at least one post-baseline IGA-CHE assessment.

Abbreviations: max = maximum. min = minimum. N = number of subjects within a treatment group. PYO = patient years of observation. Q1 = first quartile. Q3 = third quartile. SAF = safety analysis set. SD = standard deviation.

Notes: An on-treatment period is defined from the day treatment is re-initiated (IGA-CHE score >=2) to the day treatment is stopped (IGA-CHE score of 0 or 1). Rate per 100 PYO is calculated as: (Number of on-treatment periods/PYO) x 100. PYO is based on observed time in treatment period. Proportion of response days is calculated as number of response days (i.e. IGA-CHE score of 0 or 1) divided by total number of days in the treatment period. Response days are defined as the sum of days where the subject is in response periods defined as the period from the day IGA-CHE score of 0 (clear) or 1 (almost clear) is observed to the day IGA-CHE score >= 2 is observed.

The mean cumulative number of days where subjects had IGA-CHE score of 0 or 1 was 111.3 days among IGA-CHE TS responders and 24.9 days among IGA-CHE TS non-responders who were treated with delgocitinib in the pivotal study, and 136.3 days among IGA-CHE TS responders and 30.0 days among IGA-CHE TS non-responders who were treated with vehicle in the pivotal study (Table 25).

Table 25 - Proportion and number of days in response, by parent trial treatment and baseline IGA-CHE TS – SAF

	Previous Delgocitinib 20 mg/g		Previous Vehicle		Total
	IGA-CHE 0/1 (N=138)	IGA-CHE>=2 (N=422)	IGA-CHE 0/1 (N=22)	IGA-CHE>=2 (N=219)	All (N=801)
Proportion of response days (%)					
n	138	421	22	218	799
Mean (SD)	46.45 (29.61)	9.87 (17.72)	59.15 (33.30)	12.13 (18.03)	18.16 (25.78)
Median (Q1;Q3)	43.50 (21.70;66.00)	0.00 (0.00;11.10)	53.15 (33.20;100.00)	0.00 (0.00;21.10)	4.30 (0.00;31.60)
Min;max	3.9;100.0	0.0;88.2	10.7;100.0	0.0;88.5	0.0;100.0
Number of response days					
n	138	421	22	218	799
Mean (SD)	111.3 (72.0)	24.9 (44.9)	136.3 (80.7)	30.0 (44.8)	44.3 (62.7)
Median (Q1;Q3)	110.0 (52.0;155.0)	0.0 (0.0;28.0)	121.0 (83.0;216.0)	0.0 (0.0;52.0)	10.0 (0.0;80.0)
Min;max	7;259	0;217	27;274	0;224	0;274

Abbreviations: IGA-CHE = Investigator's Global Assessment for chronic hand eczema. IGA-CHE TS = IGA-CHE treatment success, i.e. an IGA-CHE score of 0 (clear) or 1 (almost clear) at baseline (Day 1). N = number of subjects. n = number of subjects with at least one post-baseline IGA-CHE assessment. Q1 = first quartile. Q3 = third quartile. SAF = safety analysis set. SD = standard deviation.
Notes: Proportion of response days is calculated as number of response days divided by total number of days in the treatment period. Response days are defined as the sum of days where the subject is in response periods defined as the period from the day IGA-CHE score of 0 (clear) or 1 (almost clear) is observed to the day IGA-CHE score >= 2 is observed.

A summary of key efficacy endpoints is shown in Table 26.

Table 26 - Summary of efficacy endpoints (study 1403) - SAF

		Extension trial baseline Week 0	Extension trial Week 36
	N	n (%)	n (%)
Key secondary endpoints			
IGA-CHE score of 0 (clear) or 1 (almost clear)			
Delgocitinib cream 20 mg/g in parent trial	560	138 (24.6)	168 (30.0)
Cream vehicle in parent trial	241	22 (9.1)	71 (29.5)
HECSI-90			
Delgocitinib cream 20 mg/g in parent trial	560	178 (31.8)	205 (36.6)
Cream vehicle in parent trial	241	29 (12.0)	86 (35.7)
HECSI-75			
Delgocitinib cream 20 mg/g in parent trial	560	290 (51.8)	328 (58.6)
Cream vehicle in parent trial	241	57 (23.7)	124 (51.5)
Key exploratory endpoints			
HESD itch score (≥4 points reduction)			
Delgocitinib cream 20 mg/g in parent trial	557	282 (50.6)	292 (52.4)
Cream vehicle in parent trial	240	63 (26.3)	99 (41.3)
HESD pain score (≥4 points reduction)			
Delgocitinib cream 20 mg/g in parent trial	516	268 (51.9)	286 (55.4)
Cream vehicle in parent trial	217	70 (32.3)	94 (43.3)
HESD score (≥4 points reduction)			
Delgocitinib cream 20 mg/g in parent trial	541	267 (49.4)	281 (51.9)
Cream vehicle in parent trial	233	67 (28.8)	94 (40.3)

Abbreviations: % = percentage of subjects with observation. HESD = Hand Eczema Symptom Diary. HECSI = Hand Eczema Severity Index. HECSI-75 = at least 75% improvement in HECSI score from baseline. HECSI-90 = at least 90% improvement in HECSI score from baseline. IGA-CHE = Investigator's Global Assessment for chronic hand eczema. N = number of subjects within a treatment group. n = number of subjects with observation. SAF = safety analysis set.

Notes: The baseline visit (Day 1) in the extension trial coincided with the end of treatment visit (Week 16) in the parent trials. In the derivation of HECSI-90 and HECSI-75, the baseline HECSI score from the parent trial was used.

IGA-CHE TS responders treated with delgocitinib in the pivotal study started the extension study off treatment (n=138). While being off treatment, the estimated median time to first IGA-CHE score of ≥2 for these subjects was 4 weeks. While being off treatment, the estimated proportion of subjects maintaining IGA-CHE score of 0 or 1 was 40.6% at Week 4, and 28.3% at Week 8.

IGA-CHE TS non-responders treated with delgocitinib in the pivotal study started the extension study on treatment (n=422). For these subjects, estimated cumulative proportion of subjects with IGA-CHE score of 0 or 1 was 48.1% at the end of the treatment period.

For IGA-CHE TS non-responders treated with vehicle in the pivotal study (n=219), the estimated cumulative proportion of subjects with IGA-CHE score of 0 or 1 was 54.4% at the end of the treatment period.

Of the 138 IGA-CHE TS responders treated with delgocitinib in the pivotal study, 122 subjects re-initiated delgocitinib treatment upon getting an IGA-CHE score of ≥2 during the first off-treatment period. For these subjects, the estimated median time to regain IGA-CHE score of 0 or 1 was 8 weeks. The estimated cumulative proportion of subjects having regained an IGA-CHE score of 0 or 1 was 80.7% at the end of the treatment period.

Of the 422 IGA-CHE TS non-responders treated with delgocitinib in the pivotal study, 127 subjects re-initiated treatment upon getting an IGA-CHE score of ≥2 after their first off-treatment period. For these subjects the estimated median time to achieve an IGA-CHE score of 0 or 1 was 12 weeks. The estimated cumulative proportion of subjects having regained an IGA-CHE score of 0 or 1 was 94.5% at the end of the treatment period.

Analysis on IGA-CHE TS responders who retained or lost IGA-CHE score of 0 or 1 while off-treatment by CHE subtype, baseline IGA-CHE score and duration of CHE is shown in Table 27.

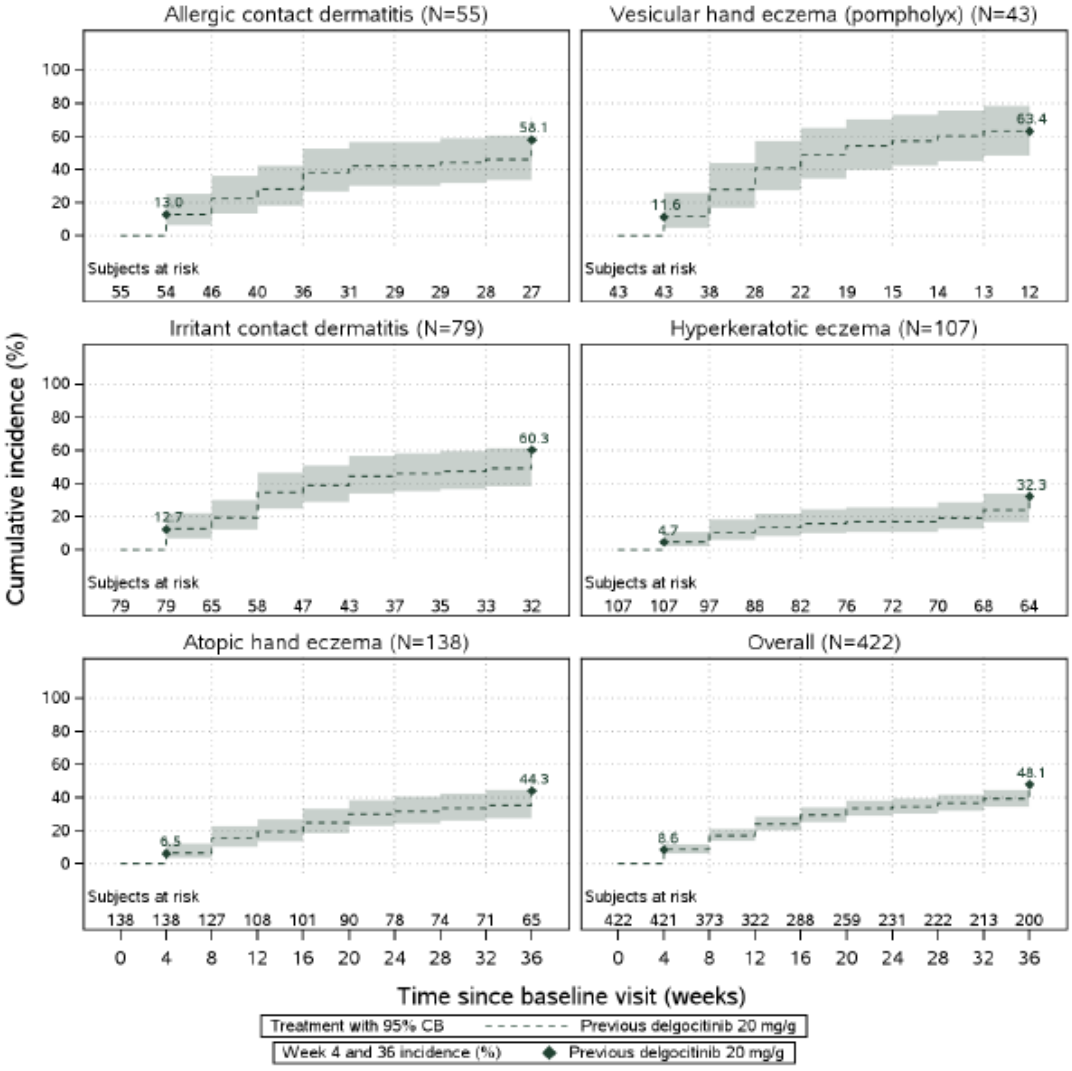
Table 27 - Subjects who retained or lost IGA-CHE score of 0 or 1 while off treatment, by CHE subtype main diagnosis and other factors, based on Kaplan-Meier estimate – Trial 1403 – subjects in SAF previously treated with delgocitinib cream 20 mg/g who achieved IGA-CHE TS at Week 16 in parent trials.

By subtypes and other factors	Subjects who retained IGA-CHE score of 0 or 1 (%)		Subjects who lost IGA-CHE score of 0 or 1 (%)
	Week 4	Week 8	Week 4
Subjects who achieved IGA-CHE TS at Week 16 in parent trials (N=138)	40.6%	28.3%	59.4%
CHE subtypes			
Allergic contact dermatitis (N=19)	57.9%	52.6%	42.1%
Irritant contact dermatitis (N=32)	40.6%	25.0%	59.4%
Atopic hand eczema (N=54)	33.3%	20.4%	66.7%
Vesicular hand eczema (N=20)	50.0%	35.0%	50.0%
Hyperkeratotic eczema (N=13)	30.8%	23.1%	69.2%
Baseline IGA-CHE score			
Moderate (N=109)	44.0%	30.3%	56.0%
Severe (N=29)	27.6%	20.7%	72.4%
Duration of CHE			
<5 years (N=61)	50.8%	36.1%	49.2%
5 to <15 years (N=43)	30.2%	16.3%	69.8%
≥15 years (N=34)	35.3%	29.4%	64.7%

Note: Baseline IGA-CHE score and CHE duration data refer to parent trial baseline data. CHE subtype contact urticaria/protein contact dermatitis is not included in the table above since none of the subjects previously treated with delgocitinib cream 20 mg/g in the parent trials had this as the CHE subtype (main diagnosis).

The cumulative proportion of subjects achieving IGA-CHE score of 0 or 1 in IGA-CHE TS non-responders by CHE subtype is shown in Figure 11.

Figure 11 - Time to first IGA-CHE score of 0 or 1 by CHE subtype main diagnosis – Trial 1403 treatment period – subjects in SAF previously treated with delgocitinib cream 20 mg/g who did not achieve IGA-CHE TS at Week 16 in parent trials.



Abbreviations: CB = confidence band. CHE = chronic hand eczema. IGA-CHE = Investigator's Global Assessment for chronic hand eczema. IGA-CHE TS = IGA-CHE treatment success i.e. an IGA-CHE score of 0 (clear) or 1 (almost clear) with a >= 2-step improvement from baseline. IMP = investigational medicinal product. N = number of subjects. SAF = safety analysis set.
Notes: Cumulative incidence (%) = 1 minus the Kaplan Meier estimate of having event at Week X expressed as a percentage. An event is defined as first time achieving response (IGA-CHE 0/1). Subjects completing treatment period, discontinuing IMP or initiating rescue treatment are censored at the day of the event, whichever occur first.

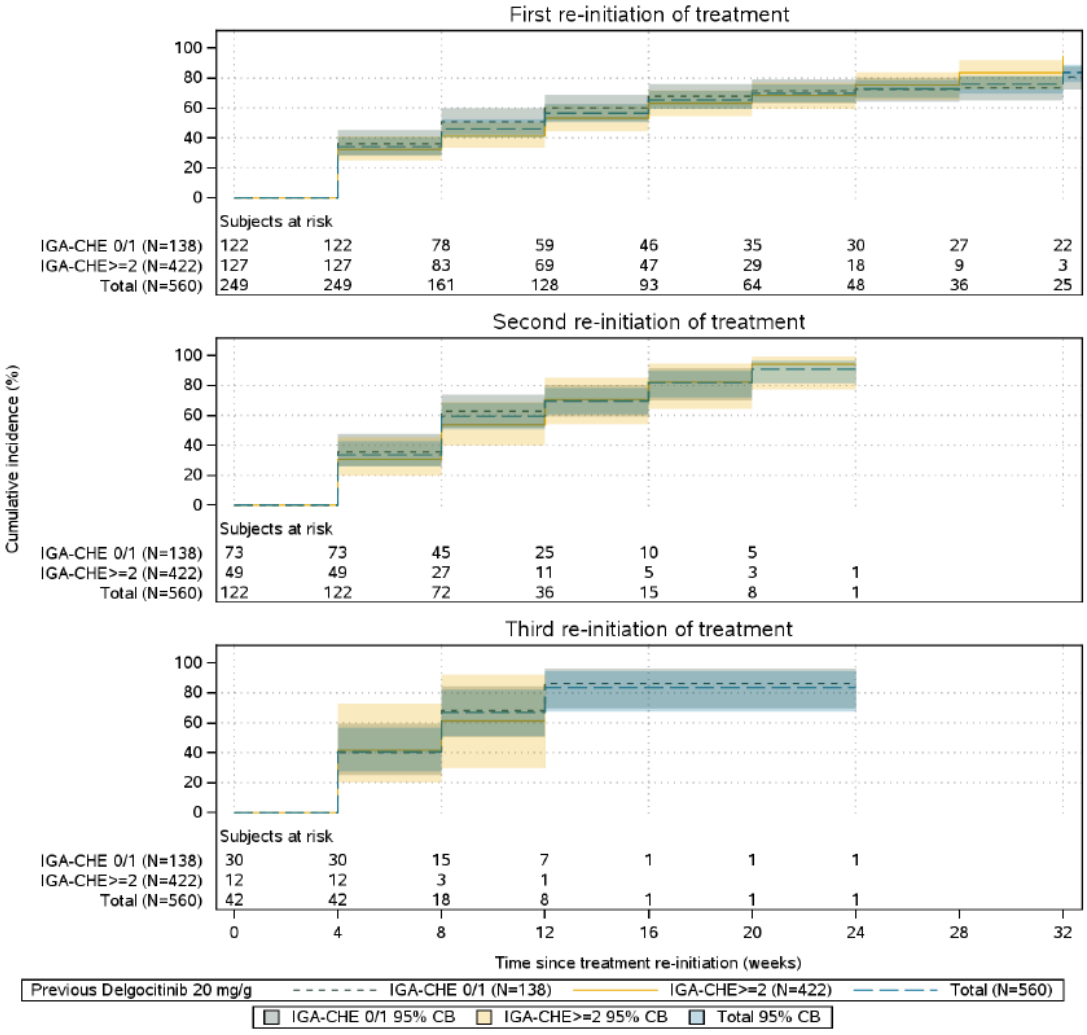
Time to regain IGA-CHE score of 0 or 1

Of the subjects who were treated with delgocitinib cream 20 mg/g in the parent trial and who achieved IGA-CHE TS at Week 16, 122 subjects re-initiated delgocitinib cream 20 mg/g treatment at least once, 73 subjects re initiated treatment at least twice, and 30 subjects re-initiated treatment at least 3 times. Of the subjects who were treated with delgocitinib cream 20 mg/g in the parent trial and who had not achieved IGA-CHE TS at Week 16, 127 subjects re-initiated delgocitinib cream 20 mg/g treatment at least once, 49 subjects re initiated treatment at least twice, and 12 subjects re-initiated treatment at least 3 times. Few subjects re-initiated treatment more than 3 times.

Overall, for the majority of subjects (>70%) who re-initiated treatment, the re-initiation was triggered by an IGA CHE score of 2 (mild). Less than one third of subjects for whom re-initiation was triggered had an IGA CHE score of 3 or 4 again.

The time to regain IGA-CHE score of 0 or 1 following re-initiation of treatment is shown in Figure 12.

Figure 12 - Time to regain IGA-CHE score of 0 or 1 following re-initiation of treatment by baseline IGA-CHE TS - Trial 1403 - subjects in SAF previously treated with delgocitinib cream 20 mg/g in parent trial



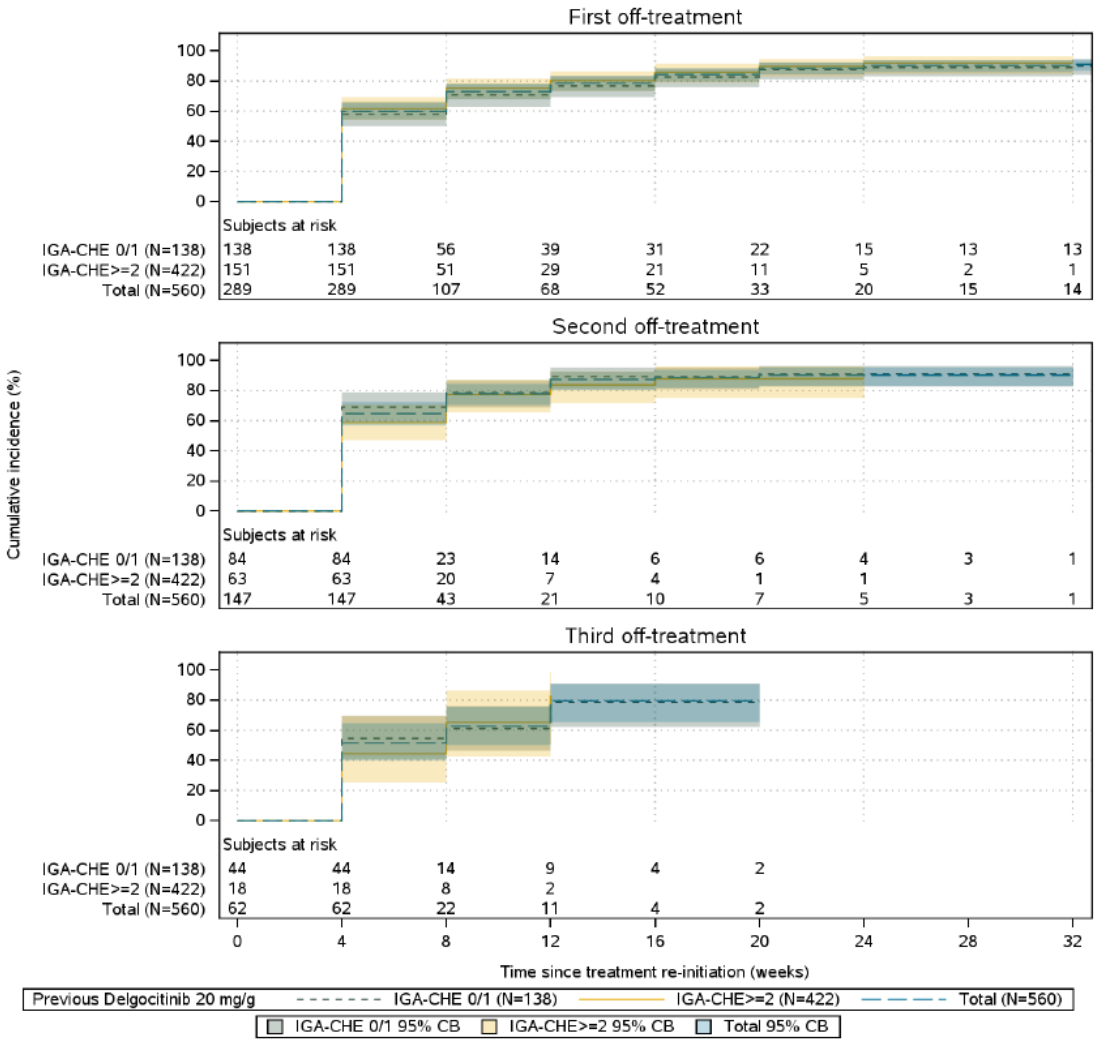
Abbreviations: CB = confidence band. IGA-CHE = Investigator's Global Assessment for chronic hand eczema. IGA-CHE TS = IGA-CHE treatment success i.e. an IGA-CHE score of 0 (clear) or 1 (almost clear) with a >= 2-step improvement from baseline. IMP = investigational medicinal product. N = number of subjects. SAF = safety analysis set.
Notes: Cumulative incidence (%) = 1 minus the Kaplan Meier estimate of having event at Week X expressed as a percentage. An event is defined as first time achieving response (IGA-CHE 0/1). Subjects completing treatment period, discontinuing IMP or initiating rescue treatment are censored at the day of the event, whichever occur first.

Time to lose IGA-CHE score of 0 or 1 (IGA-CHE score of ≥2)

All 138 subjects who were treated with delgocitinib cream 20 mg/g in the parent trial and who achieved IGA-CHE TS at Week 16 had at least 1 off-treatment period, 84 subjects had at least 2 off treatment periods, and

44 subjects had at least 3 off-treatment periods. Of the subjects who were treated with delgocitinib cream 20 mg/g in the parent trial and who had not achieved IGA-CHE TS at Week 16, 151 subjects had at least 1 off-treatment period, 63 subjects had at least 2 off treatment periods, and 18 subjects had at least 3 off-treatment periods. Few subjects had more than 3 off-treatment periods. The time to lose IGA-CHE score of 0 or 1 during the off-treatment periods is shown in Figure 13.

Figure 13 - Time to lose IGA-CHE score of 0 or 1 during first, second, and third off treatment period by baseline IGA-CHE TS - Trial 1403 - subjects in SAF previously treated with delgocitinib cream 20 mg/g in parent trial

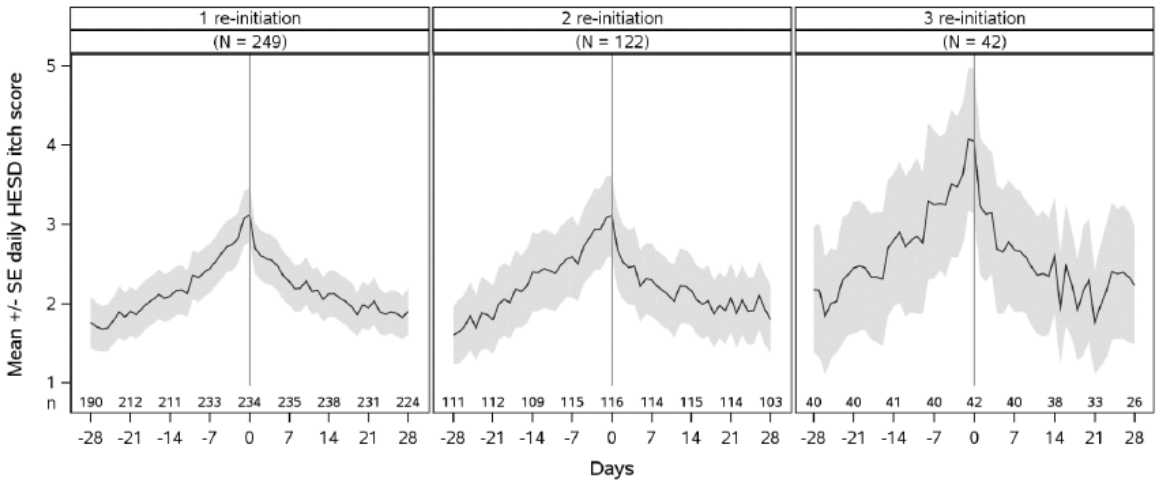


Abbreviations: CB = confidence band. IGA-CHE = Investigator's Global Assessment for chronic hand eczema. IGA-CHE TS = IGA-CHE treatment success i.e. an IGA-CHE score of 0 (clear) or 1 (almost clear) with a >= 2-step improvement from baseline. IMP = investigational medicinal product. N = number of subjects. SAF = safety analysis set.
Notes: Cumulative incidence (%) = 1 minus the Kaplan Meier estimate of having event at Week X expressed as a percentage. An event is defined as first time having an IGA-CHE score >= 2, initiation of rescue treatment, or permanent discontinuation of IMP, whichever occurs first. Subjects completing the treatment period are censored at the day of end of treatment.

HESD itch and pain scores

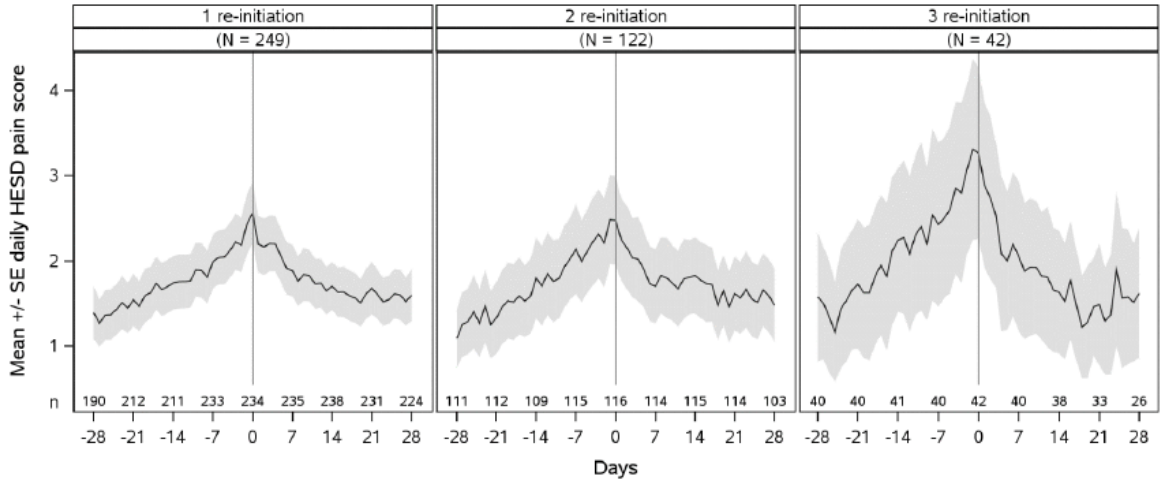
HESD itch and pain scores after re-initiation of delgocitinib cream 20 mg/g treatment is shown in Figure 14 and Figure 15.

Figure 14 - Daily HESD itch score up to and after re-initiation of treatment, observed cases – Trial 1403 – subjects in SAF previously treated with delgocitinib cream 20 mg/g



Abbreviations: HESD = Hand Eczema Symptom Diary. N = number of subjects re-initiating treatment. n = number of subjects with observation.
SAF = safety analysis set. SE = standard error.
Notes: Day 0 indicates first day of treatment re-initiation. Time between re-initiation may be shorter than 28 days. Thus, some subjects can have overlapping periods between the different re-initation periods.

Figure 15 - Daily HESD pain score up to and after re-initiation of treatment, observed cases – Trial 1403 – subjects in SAF previously treated with delgocitinib cream 20 mg/g



Abbreviations: HESD = Hand Eczema Symptom Diary. N = number of subjects re-initiating treatment. n = number of subjects with observation.
SAF = safety analysis set. SE = standard error.
Notes: Day 0 indicates first day of treatment re-initiation. Time between re-initiation may be shorter than 28 days. Thus, some subjects can have overlapping periods between the different re-initation periods.

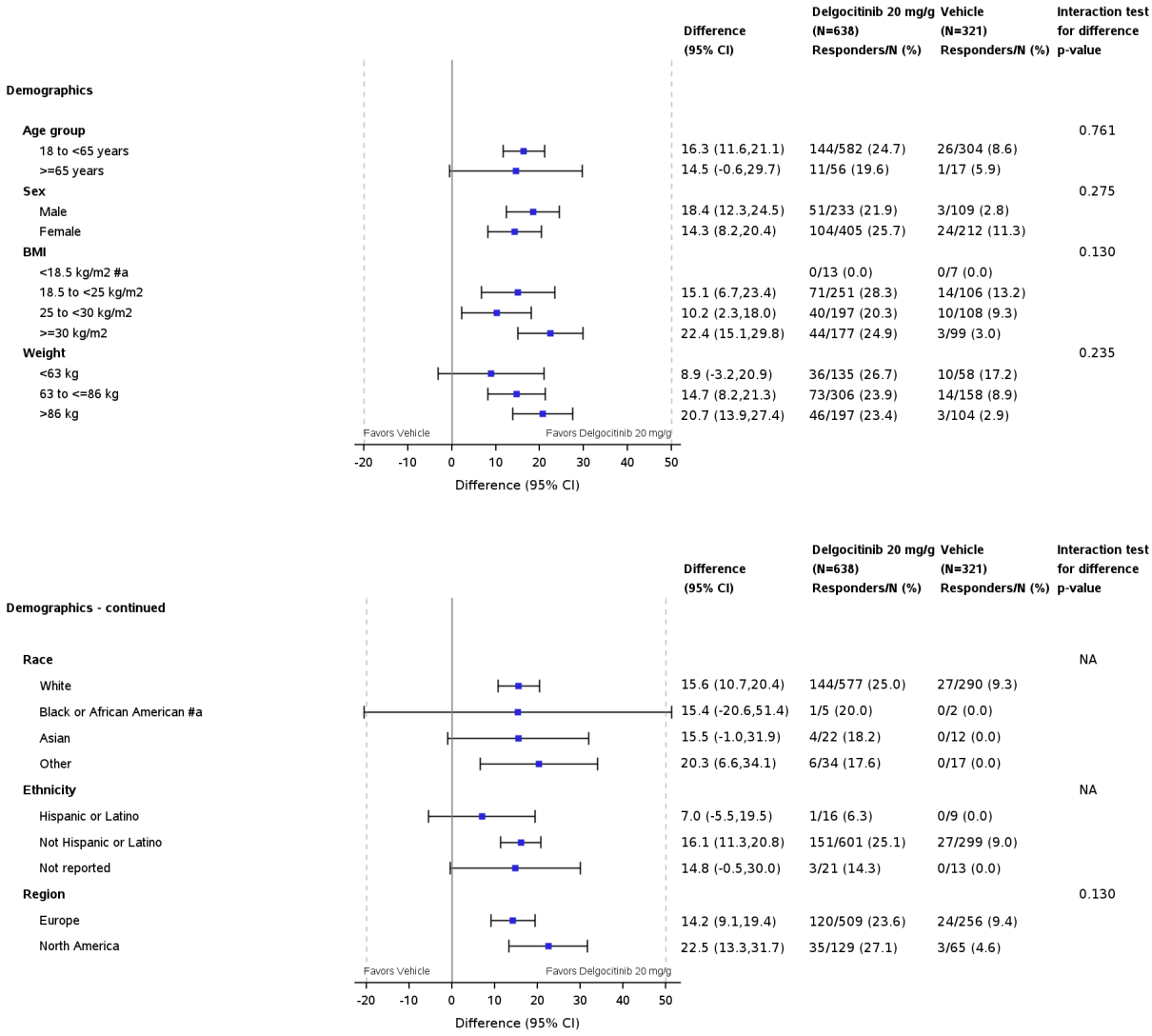
- **Ancillary analyses**

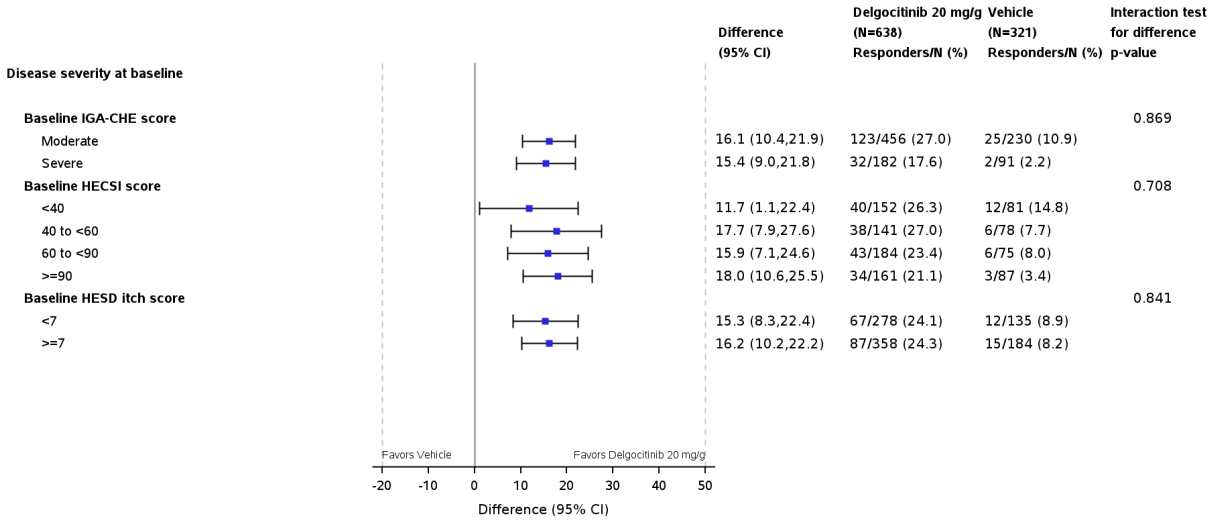
Subgroup Analysis

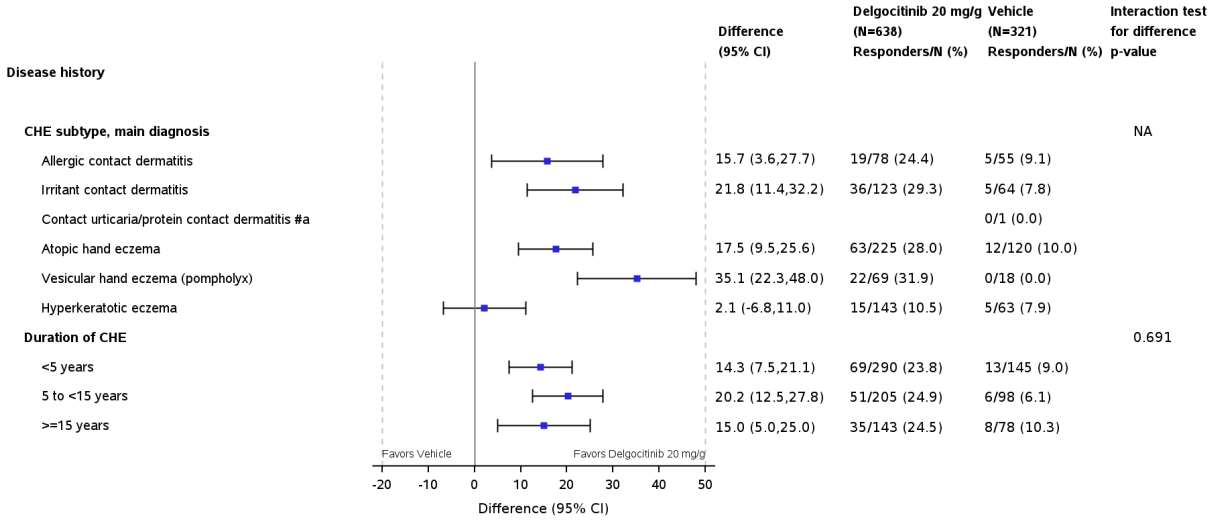
A predefined subgroup analysis for the pooled data from studies 1401 and 1402 for the primary endpoint is shown in Figure 16.

The interaction test for responder odds ratios (delgocitinib cream 20 mg/g relative to cream vehicle) across subgroups indicated a treatment-by-subgroup interaction for sex, weight and BMI. However, a post-hoc interaction test performed for differences in response rates (delgocitinib cream 20 mg/g minus cream vehicle) showed no observed treatment-by-subgroup interactions (Figure 16).

Figure 16 - IGA-CHE TS at Week 16 by subgroups (Trials 1401 and 1402 pooled) – FAS







- **Summary of main efficacy results**

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 28 - Summary of efficacy for study 1401 (DELTA 1)

Title: A phase 3 clinical study to confirm efficacy and evaluate safety of twice-daily delgocitinib cream 20 mg/g compared with cream vehicle for a 16-week treatment period in adult subjects with moderate to severe chronic hand eczema (DELTA 1)	
Study identifier	Protocol number: LP0133-1401 EudraCT/EU CT number: 2020-002960-30

Title: A phase 3 clinical study to confirm efficacy and evaluate safety of twice-daily delgocitinib cream 20 mg/g compared with cream vehicle for a 16-week treatment period in adult subjects with moderate to severe chronic hand eczema (DELTA 1)			
Design	A randomised (2:1), double-blind, vehicle-controlled, parallel-group, multi-site trial in adult subjects with moderate to severe CHE. The trial was conducted in 6 countries (Canada, France, Germany, Italy, Poland, and United Kingdom). The trial consisted of a screening period, a treatment period, and an off-treatment safety follow-up period. Subjects who transferred to the long-term extension trial (Trial 1403) were not required to complete the off-treatment safety follow-up period.		
	Duration of screening phase:		1-4 weeks.
	Duration of main phase:		16 weeks.
	Duration of run-in phase:		Not applicable.
	Duration of extension phase:		Not applicable. Subjects were invited to participate in the long-term extension trial (Trial 1403).
	Duration of safety follow-up phase:		2 weeks (only subjects not continuing in the long-term extension trial [Trial 1403]).
Hypothesis	Confirmatory superiority hypotheses were tested for delgocitinib cream 20 mg/g vs. cream vehicle based on the primary analysis of the primary estimand (composite).		
Treatments groups	Delgocitinib cream 20 mg/g		Delgocitinib cream 20 mg/g twice daily for 16 weeks. - Randomised: 325 subjects. - Exposed: 325 subjects.
	Cream vehicle		Cream vehicle twice daily for 16 weeks. - Randomised: 162 subjects. - Exposed: 162 subjects.
Endpoints and definitions	Primary endpoint	IGA-CHE TS at Week 16	An IGA-CHE score of 0 (clear) or 1 (almost clear) with a ≥2-step improvement from baseline to Week 16.
	Key secondary endpoints (binary endpoints; not presented in the order of the testing hierarchy)	IGA-CHE TS at Week 8	An IGA-CHE score of 0 (clear) or 1 (almost clear) with a ⩾2-step improvement from baseline to Week 8.
		IGA-CHE TS at Week 4	An IGA-CHE score of 0 (clear) or 1 (almost clear) with a ⩾2-step improvement from baseline to Week 4.
		HECSI-75 at Week 16	At least 75% improvement in HECSI score from baseline to Week 16.
		HECSI-75 at Week 8	At least 75% improvement in HECSI score from baseline to Week 8.

Title: A phase 3 clinical study to confirm efficacy and evaluate safety of twice-daily delgocitinib cream 20 mg/g compared with cream vehicle for a 16-week treatment period in adult subjects with moderate to severe chronic hand eczema (DELTA 1)			
		HECSI-90 at Week 16	At least 90% improvement in HECSI score from baseline to Week 16.
		Reduction of HESD itch score (weekly average) of ⩾4 points from baseline at Week 16	Reduction of HESD itch score (weekly average) of ⩾4 points from baseline at Week 16 among subjects with a baseline HESD itch score (weekly average) ⩾4 points.
		Reduction of HESD itch score (weekly average) of ⩾4 points from baseline at Week 8	Reduction of HESD itch score (weekly average) of ⩾4 points from baseline at Week 8 among subjects with a baseline HESD itch score (weekly average) ⩾4 points.
		Reduction of HESD itch score (weekly average) of ⩾4 points from baseline at Week 4	Reduction of HESD itch score (weekly average) of ⩾4 points from baseline at Week 4 among subjects with a baseline HESD itch score (weekly average) ⩾4 points.
		Reduction of HESD itch score (weekly average) of ⩾4 points from baseline at Week 2	Reduction of HESD itch score (weekly average) of ⩾4 points from baseline at Week 2 among subjects with a baseline HESD itch score (weekly average) ⩾4 points.
		Reduction of HESD score (weekly average) of ≥4 points from baseline at Week 16	Reduction of HESD score (weekly average) of ⩾4 points from baseline at Week 16 among subjects with a baseline HESD score (weekly average) ⩾4 points.

Title: A phase 3 clinical study to confirm efficacy and evaluate safety of twice-daily delgocitinib cream 20 mg/g compared with cream vehicle for a 16-week treatment period in adult subjects with moderate to severe chronic hand eczema (DELTA 1)			
		Reduction of HESD score (weekly average) of ≥4 points from baseline at Week 8	Reduction of HESD score (weekly average) of ⩾4 points from baseline at Week 8 among subjects with a baseline HESD score (weekly average) ⩾4 points.
		Reduction of HESD score (weekly average) of ≥4 points from baseline at Week 4	Reduction of HESD score (weekly average) of ⩾4 points from baseline at Week 4 among subjects with a baseline HESD score (weekly average) ⩾4 points.
		Reduction of HESD pain score (weekly average) of ⩾4 points from baseline at Week 16	Reduction of HESD pain score (weekly average) of ⩾4 points from baseline at Week 16 among subjects with a baseline HESD pain score (weekly average) ⩾4 points.
		Reduction of HESD pain score (weekly average) of ⩾4 points from baseline at Week 8	Reduction of HESD pain score (weekly average) of ⩾4 points from baseline at Week 8 among subjects with a baseline HESD pain score (weekly average) ⩾4 points.
		Reduction of HESD pain score (weekly average) of ⩾4 points from baseline at Week 4	Reduction of HESD pain score (weekly average) of ⩾4 points from baseline at Week 4 among subjects with a baseline HESD score (weekly average) ⩾4 points.
		Reduction of DLQI score of ⩾4 points from baseline at Week 16	Reduction of DLQI score of ⩾4 points from baseline at Week 16 among subjects with a baseline DLQI score ⩾4 points.

Title: A phase 3 clinical study to confirm efficacy and evaluate safety of twice-daily delgocitinib cream 20 mg/g compared with cream vehicle for a 16-week treatment period in adult subjects with moderate to severe chronic hand eczema (DELTA 1)			
	Key secondary endpoints (continuous endpoints; not presented in the order of the testing hierarchy)	Percentage change in HECSI score from baseline to Week 16	Percentage change in HECSI score from baseline to Week 16.
		Change in HESD itch score (weekly average) from baseline to Week 16	Change in HESD itch score (weekly average) from baseline to Week 16.
		Change in HESD score (weekly average) from baseline to Week 16	Change in HESD score (weekly average) from baseline to Week 16.
		Change in HESD pain score (weekly average) from baseline to Week 16	Change in HESD pain score (weekly average) from baseline to Week 16.
		Change in DLQI score from baseline to Week 16	Change in DLQI score from baseline to Week 16.
		Change in HEIS score from baseline to Week 16	Change in HEIS score from baseline to Week 16.
		Change in HEIS PDAL score from baseline to Week 16	Change in HEIS PDAL score from baseline to Week 16.
Database lock	17 November2022		
Results and Analysis			
Analysis description	**Primary Analysis**		

Title: A phase 3 clinical study to confirm efficacy and evaluate safety of twice-daily delgocitinib cream 20 mg/g compared with cream vehicle for a 16-week treatment period in adult subjects with moderate to severe chronic hand eczema (DELTA 1)			
Analysis population and time point description	The primary analysis was based on FAS. FAS included subjects randomised and exposed to IMP. The primary endpoint was assessed at Week 16. The key secondary binary endpoints were assessed at Weeks 2, 4, 8, or 16, and the key continuous endpoints were assessed at Week 16. For the binary endpoints, the primary estimand (composite) assessed the treatment difference in response rate after 2, 4, 8, or 16 weeks achieved without initiation of rescue treatment or permanent discontinuation of IMP. For the continuous endpoints, the primary estimand (composite) assessed the treatment difference in change from baseline to Week 16 achieved without initiation of rescue treatment or permanent discontinuation of IMP.		
Descriptive statistics and estimate variability	Treatment group	Delgocitinib cream 20 mg/g	Cream vehicle
	Number of subjects (FAS)	325	162
	Primary endpoint[1]		
	n (subjects with data at baseline)	325	162
	IGA-CHE TS at Week 16 Responders (%)	64 (19.7)	16 (9.9)
	Key secondary endpoints (binary endpoints)[1, 2]		
	n (subjects with data at baseline)	325	162
	IGA-CHE TS at Week 8 Responders (%)	74 (22.8)	17 (10.5)
	IGA-CHE TS at Week 4 Responders (%)	50 (15.4)	8 (4.9)
	n (subjects with data at baseline)	325	162
	HECSI-75 at Week 16 Responders (%)	160 (49.2)	38 (23.5)
	HECSI-75 at Week 8 Responders (%)	163 (50.2)	42 (25.9)
	HECSI-90 at Week 16 Responders (%)	96 (29.5)	20 (12.3)
	n (subjects with data at baseline)	323	161
	Reduction of HESD itch score (weekly average) of $\geqslant$4 points from baseline at Week 16[3] Responders (%)	152 (47.1)	37 (23.0)

Title: A phase 3 clinical study to confirm efficacy and evaluate safety of twice-daily delgocitinib cream 20 mg/g compared with cream vehicle for a 16-week treatment period in adult subjects with moderate to severe chronic hand eczema (DELTA 1)			
	Reduction of HESD itch score (weekly average) of ⩾4 points from baseline at Week 8[3] Responders (%)	138 (42.7)	35 (21.7)
	Reduction of HESD itch score (weekly average) of ⩾4 points from baseline at Week 4[3] Responders (%)	99 (30.7)	18 (11.2)
	Reduction of HESD itch score (weekly average) of ⩾4 points from baseline at Week 2[3] Responders (%)	50 (15.5)	10 (6.2)
	n (subjects with data at baseline)	309	156
	Reduction of HESD score (weekly average) of ≥4 points from baseline at Week 16[4] Responders (%)	146 (47.2)	38 (24.4)
	Reduction of HESD score (weekly average) of ≥4 points from baseline at Week 8[4] Responders (%)	123 (39.8)	27 (17.3)
	Reduction of HESD score (weekly average) of ≥4 points from baseline at Week 4[4] Responders (%)	92 (29.8)	16 (10.3)
	n (subjects with data at baseline)	291	149
	Reduction of HESD pain score (weekly average) of ⩾4 points from baseline at Week 16[5] Responders (%)	143 (49.1)	41 (27.5)
	Reduction of HESD pain score (weekly average) of ⩾4 points from baseline at Week 8[5] Responders (%)	134 (46.0)	33 (22.1)
	Reduction of HESD pain score (weekly average) of ⩾4 points from baseline at Week 4[5] Responders (%)	100 (34.4)	22 (14.8)
	n (subjects with data at baseline)	305	148

Title: A phase 3 clinical study to confirm efficacy and evaluate safety of twice-daily delgocitinib cream 20 mg/g compared with cream vehicle for a 16-week treatment period in adult subjects with moderate to severe chronic hand eczema (DELTA 1)			
	Reduction of DLQI score of ⩾4 points from baseline at Week 16[6] Responders (%)	227 (74.4)	74 (50.0)
	Key secondary endpoints (continuous endpoints)[1, 2]		
	n (subjects with data at baseline)	325	162
	Percentage change in HECSI score from baseline to Week 16 LSMean (SE)	-56.5 (3.4)	-21.2 (4.8)
	n (subjects with data at baseline)	324	162
	Change in HESD itch score (weekly average) from baseline to Week 16 LSMean (SE)	-3.6 (0.2)	-1.9 (0.2)
	Change in HESD score (weekly average) from baseline to Week 16 LSMean (SE)	-3.4 (0.1)	-1.7 (0.2)
	Change in HESD pain score (weekly average) from baseline to Week 16 LSMean (SE)	-3.4 (0.2)	-1.8 (0.2)
	n (subjects with data at baseline)	321	158
	Change in DLQI score from baseline to Week 16 LSMean (SE)	-7.6 (0.3)	-3.9 (0.4)
	n (subjects with data at baseline)	321	158
	Change in HEIS score from baseline to Week 16 LSMean (SE)	-1.46 (0.05)	-0.82 (0.08)
	Change in HEIS PDAL score from baseline to Week 16 LSMean (SE)	-1.46 (0.06)	-0.86 (0.08)
Effect estimate per comparison		Comparison groups	Delgocitinib cream 20 mg/g vs cream vehicle
	Primary endpoint[1]		
	IGA-CHE TS at Week 16	Treatment diff.	9.8
		95% CI	3.6; 16.1
		P-value[7]	0.006
	Key secondary endpoints (binary endpoints)[1, 2]		
	IGA-CHE TS at Week 8	Treatment diff.	12.3

Title: A phase 3 clinical study to confirm efficacy and evaluate safety of twice-daily delgocitinib cream 20 mg/g compared with cream vehicle for a 16-week treatment period in adult subjects with moderate to severe chronic hand eczema (DELTA 1)			
		95% CI	5.7; 18.9
		P-value[7]	0.001
	IGA-CHE TS at Week 4	Treatment diff.	10.4
		95% CI	5.3; 15.6
		P-value[7]	<0.001
	HECSI-75 at Week 16	Treatment diff.	25.7
		95% CI	17.2; 34.3
		P-value[7]	<0.001
	HECSI-75 at Week 8	Treatment diff.	24.2
		95% CI	15.5; 33.0
		P-value[7]	<0.001
	HECSI-90 at Week 16	Treatment diff.	17.2
		95% CI	10.1; 24.3
		P-value[7]	<0.001
	Reduction of HESD itch score (weekly average) of ⩾4 points from baseline at Week 16[3]	Treatment diff.	24.1
		95% CI	15.5; 32.6
		P-value[7]	<0.001
	Reduction of HESD itch score (weekly average) of ⩾4 points from baseline at Week 8[3]	Treatment diff.	21.0
		95% CI	12.6; 29.4
		P-value[7]	<0.001
	Reduction of HESD itch score (weekly average) of ⩾4 points from baseline at Week 4[3]	Treatment diff.	19.5
		95% CI	12.5; 26.5
		P-value[7]	<0.001
	Reduction of HESD itch score (weekly average) of ⩾4 points from baseline at Week 2[3]	Treatment diff.	9.3
		95% CI	3.8; 14.7
		P-value[7]	0.004
	Reduction of HESD score (weekly average) of ≥4 points from baseline at Week 16[4]	Treatment diff.	22.8
		95% CI	14.0; 31.7
		P-value[7]	<0.001
	Reduction of HESD score (weekly average) of ≥4 points from baseline at Week 8[4]	Treatment diff.	22.5
		95% CI	14.4; 30.6
		P-value[7]	<0.001
	Reduction of HESD score (weekly average) of ≥4 points from baseline at Week 4[4]	Treatment diff.	19.5
		95% CI	12.5; 26.5
		P-value[7]	<0.001

Title: A phase 3 clinical study to confirm efficacy and evaluate safety of twice-daily delgocitinib cream 20 mg/g compared with cream vehicle for a 16-week treatment period in adult subjects with moderate to severe chronic hand eczema (DELTA 1)			
	Reduction of HESD pain score (weekly average) of ⩾4 points from baseline at Week 16[5]	Treatment diff.	21.7
		95% CI	12.4; 30.9
		P-value[7]	<0.001
	Reduction of HESD pain score (weekly average) of ⩾4 points from baseline at Week 8[5]	Treatment diff.	23.9
		95% CI	15.2; 32.7
		P-value[7]	<0.001
	Reduction of HESD pain score (weekly average) of ⩾4 points from baseline at Week 4[5]	Treatment diff.	19.6
		95% CI	11.8; 27.5
		P-value[7]	<0.001
	Reduction of DLQI score of ⩾4 points from baseline at Week 16[6]	Treatment diff.	24.5
		95% CI	15.0; 33.9
		P-value[7]	<0.001
	Key secondary endpoints (continuous endpoints)[1, 2]		
	Percentage change in HECSI score from baseline to Week 16 LSMean (SE)	Treatment diff.	-35.2
		95% CI	-46.7; -23.8
		P-value[8]	<0.001
	Change in HESD itch score (weekly average) from baseline to Week 16 LSMean (SE)	Treatment diff.	-1.7
		95% CI	-2.3; -1.2
		P-value[8]	<0.001
	Change in HESD score (weekly average) from baseline to Week 16 LSMean (SE)	Treatment diff.	-1.7
		95% CI	-2.2; -1.2
		P-value[8]	<0.001
	Change in HESD pain score (weekly average) from baseline to Week 16 LSMean (SE)	Treatment diff.	-1.6
		95% CI	-2.1; -1.0
		P-value[8]	<0.001
	Change in DLQI score from baseline to Week 16 LSMean (SE)	Treatment diff.	-3.6
		95% CI	-4.7; -2.6
		P-value[8]	<0.001
	Change in HEIS score from baseline to Week 16 LSMean (SE)	Treatment diff.	-0.64
		95% CI	-0.83; -0.45
		P-value[8]	<0.001
	Change in HEIS PDAL score from baseline to Week 16 LSMean (SE)	Treatment diff.	-0.60
		95% CI	-0.79; -0.40
		P-value[8]	<0.001

Title: A phase 3 clinical study to confirm efficacy and evaluate safety of twice-daily delgocitinib cream 20 mg/g compared with cream vehicle for a 16-week treatment period in adult subjects with moderate to severe chronic hand eczema (DELTA 1)	
	[1] Primary analysis of the primary estimand (composite). [2] Endpoints are not presented in the order of the testing hierarchy. [3] Among subjects with a baseline HESD itch score (weekly average) ≥4 points. [4] Among subjects with a baseline HESD score (weekly average) ≥4 points. [5] Among subjects with a baseline HESD pain score (weekly average) ≥4 points. [6] Among subjects with a baseline DLQI score ≥4 points. [7] The primary analysis for the primary estimand (composite) for the binary endpoints was the Cochran-Mantel-Haenszel test stratified by region and baseline IGA-CHE score. [8] The primary analysis for the primary estimand (composite) for the continuous endpoints was an ANCOVA model with effects of treatment group, region, baseline IGA-CHE score, and baseline value (endpoint of interest).
Notes	The trial included several exploratory endpoints. The results of the majority of the exploratory endpoints supported the findings of the primary and key secondary endpoints. Early onset of action was observed from Week 1 or Week 2 for the exploratory endpoints IGA-CHE TS, HECSI, HESD, DLQI, HEIS, and EQ-5D-5L scores in the delgocitinib cream 20 mg/g group.
Analysis description	For the primary and key secondary endpoints, confirmatory one-sided (superiority) hypotheses were tested for delgocitinib cream 20 mg/g vs. cream vehicle based on the primary analysis for the primary estimand (composite). A closed testing procedure with hierarchical tests, alpha splitting, and alpha recycling was used to control the overall type I error at a nominal one-sided 2.5% level. The statistical testing strategy was built on the principle that the IGA-CHE TS superiority at Week 16 had to be established before testing for additional benefits (key secondary endpoints) related to efficacy and health related quality of life.

Table 29 - Summary of efficacy for study 1402 (DELTA 2)

Title: A phase 3 clinical study to confirm efficacy and evaluate safety of twice-daily delgocitinib cream 20 mg/g compared with cream vehicle for a 16-week treatment period in adult subjects with moderate to severe chronic hand eczema (DELTA 2)	
Study identifier	Protocol number: LP0133-1402 EudraCT/EU CT number: 2020-002961-32
Design	A randomized (2:1), double-blind, vehicle-controlled, parallel-group, multi-site trial in adult subjects with moderate to severe CHE. The trial was conducted in 7 countries (Belgium, Canada, Denmark, Germany, the Netherlands, Poland, and Spain). The trial consisted of a screening period, a treatment period, and an off-treatment safety follow-up period. Subjects who transferred to the long-term extension trial (Trial 1403) were not required to complete the off-treatment safety follow-up period.

Title: A phase 3 clinical study to confirm efficacy and evaluate safety of twice-daily delgocitinib cream 20 mg/g compared with cream vehicle for a 16-week treatment period in adult subjects with moderate to severe chronic hand eczema (DELTA 2)			
	Duration of screening phase:		1-4 weeks.
	Duration of main phase:		16 weeks.
	Duration of run-in phase:		Not applicable.
	Duration of extension phase:		Not applicable. Subjects were invited to participate in the long-term extension trial (Trial 1403).
	Duration of safety follow-up phase:		2 weeks (only subjects not continuing in the long-term extension trial [Trial 1403]).
Hypothesis	Confirmatory superiority hypotheses were tested for delgocitinib cream 20 mg/g vs. cream vehicle based on the primary analysis of the primary estimand (composite).		
Treatments groups	Delgocitinib cream 20 mg/g		Delgocitinib cream 20 mg/g twice daily for 16 weeks. - Randomized: 314 subjects. - Exposed: 313 subjects.
	Cream vehicle		Cream vehicle twice daily for 16 weeks. - Randomized: 159 subjects. - Exposed: 159 subjects.
Endpoints and definitions	Primary endpoint	IGA-CHE TS at Week 16	An IGA-CHE score of 0 (clear) or 1 (almost clear) with a ≥2-step improvement from baseline to Week 16.
	Key secondary endpoints (binary endpoints; not presented in the order of the testing hierarchy)	IGA-CHE TS at Week 8	An IGA-CHE score of 0 (clear) or 1 (almost clear) with a ⩾2-step improvement from baseline to Week 8.
		IGA-CHE TS at Week 4	An IGA-CHE score of 0 (clear) or 1 (almost clear) with a ⩾2-step improvement from baseline to Week 4.
		HECSI-75 at Week 16	At least 75% improvement in HECSI score from baseline to Week 16.
		HECSI-75 at Week 8	At least 75% improvement in HECSI score from baseline to Week 8.
		HECSI-90 at Week 16	At least 90% improvement in HECSI score from baseline to Week 16.

Title: A phase 3 clinical study to confirm efficacy and evaluate safety of twice-daily delgocitinib cream 20 mg/g compared with cream vehicle for a 16-week treatment period in adult subjects with moderate to severe chronic hand eczema (DELTA 2)			
		Reduction of HESD itch score (weekly average) of ⩾4 points from baseline at Week 16	Reduction of HESD itch score (weekly average) of ⩾4 points from baseline at Week 16 among subjects with a baseline HESD itch score (weekly average) ⩾4 points.
		Reduction of HESD itch score (weekly average) of ⩾4 points from baseline at Week 8	Reduction of HESD itch score (weekly average) of ⩾4 points from baseline at Week 8 among subjects with a baseline HESD itch score (weekly average) ⩾4 points.
		Reduction of HESD itch score (weekly average) of ⩾4 points from baseline at Week 4	Reduction of HESD itch score (weekly average) of ⩾4 points from baseline at Week 4 among subjects with a baseline HESD itch score (weekly average) ⩾4 points.
		Reduction of HESD itch score (weekly average) of ⩾4 points from baseline at Week 2	Reduction of HESD itch score (weekly average) of ⩾4 points from baseline at Week 2 among subjects with a baseline HESD itch score (weekly average) ⩾4 points.
		Reduction of HESD score (weekly average) of ≥4 points from baseline at Week 16	Reduction of HESD score (weekly average) of ⩾4 points from baseline at Week 16 among subjects with a baseline HESD score (weekly average) ⩾4 points.
		Reduction of HESD score (weekly average) of ≥4 points from baseline at Week 8	Reduction of HESD score (weekly average) of ⩾4 points from baseline at Week 8 among subjects with a baseline HESD score (weekly average) ⩾4 points.

Title: A phase 3 clinical study to confirm efficacy and evaluate safety of twice-daily delgocitinib cream 20 mg/g compared with cream vehicle for a 16-week treatment period in adult subjects with moderate to severe chronic hand eczema (DELTA 2)			
		Reduction of HESD score (weekly average) of ≥4 points from baseline at Week 4	Reduction of HESD score (weekly average) of ⩾4 points from baseline at Week 4 among subjects with a baseline HESD score (weekly average) ⩾4 points.
		Reduction of HESD pain score (weekly average) of ⩾4 points from baseline at Week 16	Reduction of HESD pain score (weekly average) of ⩾4 points from baseline at Week 16 among subjects with a baseline HESD pain score (weekly average) ⩾4 points.
		Reduction of HESD pain score (weekly average) of ⩾4 points from baseline at Week 8	Reduction of HESD pain score (weekly average) of ⩾4 points from baseline at Week 8 among subjects with a baseline HESD pain score (weekly average) ⩾4 points.
		Reduction of HESD pain score (weekly average) of ⩾4 points from baseline at Week 4	Reduction of HESD pain score (weekly average) of ⩾4 points from baseline at Week 4 among subjects with a baseline HESD score (weekly average) ⩾4 points.
		Reduction of DLQI score of ⩾4 points from baseline at Week 16	Reduction of DLQI score of ⩾4 points from baseline at Week 16 among subjects with a baseline DLQI score ⩾4 points.
	Key secondary endpoints (continuous endpoints; not presented in the order of the testing hierarchy)	Percentage change in HECSI score from baseline to Week 16	Percentage change in HECSI score from baseline to Week 16.

Title: A phase 3 clinical study to confirm efficacy and evaluate safety of twice-daily delgocitinib cream 20 mg/g compared with cream vehicle for a 16-week treatment period in adult subjects with moderate to severe chronic hand eczema (DELTA 2)			
		Change in HESD itch score (weekly average) from baseline to Week 16	Change in HESD itch score (weekly average) from baseline to Week 16.
		Change in HESD score (weekly average) from baseline to Week 16	Change in HESD score (weekly average) from baseline to Week 16.
		Change in HESD pain score (weekly average) from baseline to Week 16	Change in HESD pain score (weekly average) from baseline to Week 16.
		Change in DLQI score from baseline to Week 16	Change in DLQI score from baseline to Week 16.
		Change in HEIS score from baseline to Week 16	Change in HEIS score from baseline to Week 16.
		Change in HEIS PDAL score from baseline to Week 16	Change in HEIS PDAL score from baseline to Week 16.
Database lock	25-Jan-2023		
Results and Analysis			
Analysis description	**Primary Analysis**		

Title: A phase 3 clinical study to confirm efficacy and evaluate safety of twice-daily delgocitinib cream 20 mg/g compared with cream vehicle for a 16-week treatment period in adult subjects with moderate to severe chronic hand eczema (DELTA 2)			
Analysis population and time point description	The primary analysis was based on FAS. FAS included subjects randomised and exposed to IMP. The primary endpoint was assessed at Week 16. The key secondary binary endpoints were assessed at Weeks 2, 4, 8, or 16, and the key continuous endpoints were assessed at Week 16. For the binary endpoints, the primary estimand (composite) assessed the treatment difference in response rate after 2, 4, 8, or 16 weeks achieved without initiation of rescue treatment or permanent discontinuation of IMP. For the continuous endpoints, the primary estimand (composite) assessed the treatment difference in change from baseline to Week 16 achieved without initiation of rescue treatment or permanent discontinuation of IMP.		
Descriptive statistics and estimate variability	Treatment group	Delgocitinib cream 20 mg/g	Cream vehicle
	Number of subjects (FAS)	313	159
	Primary endpoint[1]		
	n (subjects with data at baseline)	313	159
	IGA-CHE TS at Week 16 Responders (%)	91 (29.1)	11 (6.9)
	Key secondary endpoints (binary endpoints)[1, 2]		
	n (subjects with data at baseline)	313	159
	IGA-CHE TS at Week 8 Responders (%)	101 (32.3)	15 (9.4)
	IGA-CHE TS at Week 4 Responders (%)	46 (14.7)	13 (8.2)
	n (subjects with data at baseline)	313	159
	HECSI-75 at Week 16 Responders (%)	155 (49.5)	29 (18.2)
	HECSI-75 at Week 8 Responders (%)	158 (50.5)	31 (19.5)
	HECSI-90 at Week 16 Responders (%)	97 (31.0)	14 (8.8)
	n (subjects with data at baseline)	309	156
	Reduction of HESD itch score (weekly average) of $\geqslant$4 points from baseline at Week 16[3] Responders (%)	146 (47.2)	31 (19.9)

Title: A phase 3 clinical study to confirm efficacy and evaluate safety of twice-daily delgocitinib cream 20 mg/g compared with cream vehicle for a 16-week treatment period in adult subjects with moderate to severe chronic hand eczema (DELTA 2)			
	Reduction of HESD itch score (weekly average) of ⩾4 points from baseline at Week 8[3] Responders (%)	131 (42.4)	21 (13.5)
	Reduction of HESD itch score (weekly average) of ⩾4 points from baseline at Week 4[3] Responders (%)	94 (30.4)	19 (12.2)
	Reduction of HESD itch score (weekly average) of ⩾4 points from baseline at Week 2[3] Responders (%)	40 (12.9)	10 (6.4)
	n (subjects with data at baseline)	308	153
	Reduction of HESD score (weekly average) of ≥4 points from baseline at Week 16[4] Responders (%)	137 (44.5)	32 (20.9)
	Reduction of HESD score (weekly average) of ≥4 points from baseline at Week 8[4] Responders (%)	115 (37.3)	19 (12.4)
	Reduction of HESD score (weekly average) of ≥4 points from baseline at Week 4[4] Responders (%)	80 (26.0)	14 (9.2)
	n (subjects with data at baseline)	294	141
	Reduction of HESD pain score (weekly average) of ⩾4 points from baseline at Week 16[5] Responders (%)	143 (48.6)	32 (22.7)
	Reduction of HESD pain score (weekly average) of ⩾4 points from baseline at Week 8[5] Responders (%)	124 (42.2)	18 (12.8)
	Reduction of HESD pain score (weekly average) of ⩾4 points from baseline at Week 4[5] Responders (%)	91 (31.0)	15 (10.6)
	n (subjects with data at baseline)	299	153

Title: A phase 3 clinical study to confirm efficacy and evaluate safety of twice-daily delgocitinib cream 20 mg/g compared with cream vehicle for a 16-week treatment period in adult subjects with moderate to severe chronic hand eczema (DELTA 2)			
	Reduction of DLQI score of ⩾4 points from baseline at Week 16[6] Responders (%)	216 (72.2)	70 (45.8)
	Key secondary endpoints (continuous endpoints)[1, 2]		
	n (subjects with data at baseline)	313	159
	Percentage change in HECSI score from baseline to Week 16 LSMean (SE)	-58.9 (3.2)	-13.4 (4.5)
	n (subjects with data at baseline)	312	157
	Change in HESD itch score (weekly average) from baseline to Week 16 LSMean (SE)	-3.4 (0.2)	-1.4 (0.2)
	Change in HESD score (weekly average) from baseline to Week 16 LSMean (SE)	-3.2 (0.1)	-1.4 (0.2)
	Change in HESD pain score (weekly average) from baseline to Week 16 LSMean (SE)	-3.3 (0.2)	-1.3 (0.2)
	n (subjects with data at baseline)	310	159
	Change in DLQI score from baseline to Week 16 LSMean (SE)	-7.0 (0.3)	-3.1 (0.5)
	n (subjects with data at baseline)	310	159
	Change in HEIS score from baseline to Week 16 LSMean (SE)	-1.45 (0.06)	-0.64 (0.08)
	Change in HEIS PDAL score from baseline to Week 16 LSMean (SE)	-1.48 (0.06)	-0.66 (0.08)
Effect estimate per comparison		Comparison groups	Delgocitinib cream 20 mg/g vs cream vehicle
	Primary endpoint[1]		
	IGA-CHE TS at Week 16	Treatment diff.	22.2
		95% CI	15.8; 28.5
		P-value[7]	<0.001
	Key secondary endpoints (binary endpoints)[1, 2]		
	IGA-CHE TS at Week 8	Treatment diff.	22.9

Title: A phase 3 clinical study to confirm efficacy and evaluate safety of twice-daily delgocitinib cream 20 mg/g compared with cream vehicle for a 16-week treatment period in adult subjects with moderate to severe chronic hand eczema (DELTA 2)			
		95% CI	16.0; 29.8
		P-value[7]	<0.001
	IGA-CHE TS at Week 4	Treatment diff.	6.5
		95% CI	0.8; 12.3
		P-value[7]	0.043
	HECSI-75 at Week 16	Treatment diff.	31.3
		95% CI	23.1; 39.5
		P-value[7]	<0.001
	HECSI-75 at Week 8	Treatment diff.	31.0
		95% CI	22.7; 39.3
		P-value[7]	<0.001
	HECSI-90 at Week 16	Treatment diff.	22.2
		95% CI	15.4;29.0
		P-value[7]	<0.001
	Reduction of HESD itch score (weekly average) of ⩾4 points from baseline at Week 16[3]	Treatment diff.	27.4
		95% CI	19.0; 35.8
		P-value[7]	<0.001
	Reduction of HESD itch score (weekly average) of ⩾4 points from baseline at Week 8[3]	Treatment diff.	29.0
		95% CI	21.3; 36.7
		P-value[7]	<0.001
	Reduction of HESD itch score (weekly average) of ⩾4 points from baseline at Week 4[3]	Treatment diff.	18.3
		95% CI	11.0; 25.6
		P-value[7]	<0.001
	Reduction of HESD itch score (weekly average) of ⩾4 points from baseline at Week 2[3]	Treatment diff.	6.6
		95% CI	1.1; 12.0
		P-value[7]	0.031
	Reduction of HESD score (weekly average) of ≥4 points from baseline at Week 16[4]	Treatment diff.	23.7
		95% CI	15.1; 32.2
		P-value[7]	<0.001
	Reduction of HESD score (weekly average) of ≥4 points from baseline at Week 8[4]	Treatment diff.	25.0
		95% CI	17.5; 32.5
		P-value[7]	<0.001
	Reduction of HESD score (weekly average) of ≥4 points from baseline at Week 4[4]	Treatment diff.	16.9
		95% CI	10.2; 23.7
		P-value[7]	<0.001

Title: A phase 3 clinical study to confirm efficacy and evaluate safety of twice-daily delgocitinib cream 20 mg/g compared with cream vehicle for a 16-week treatment period in adult subjects with moderate to severe chronic hand eczema (DELTA 2)			
	Reduction of HESD pain score (weekly average) of ⩾4 points from baseline at Week 16[5]	Treatment diff.	26.0
		95% CI	17.0; 35.1
		P-value[7]	<0.001
	Reduction of HESD pain score (weekly average) of ⩾4 points from baseline at Week 8[5]	Treatment diff.	29.6
		95% CI	21.7; 37.4
		P-value[7]	<0.001
	Reduction of HESD pain score (weekly average) of ⩾4 points from baseline at Week 4[5]	Treatment diff.	20.5
		95% CI	13.1; 27.8
		P-value[7]	<0.001
	Reduction of DLQI score of ⩾4 points from baseline at Week 16[6]	Treatment diff.	26.4
		95% CI	17.0; 35.9
		P-value[7]	<0.001
	Key secondary endpoints (continuous endpoints)[1, 2]		
	Percentage change in HECSI score from baseline to Week 16 LSMean (SE)	Treatment diff.	-45.5
		95% CI	-56.4; -34.6
		P-value[8]	<0.001
	Change in HESD itch score (weekly average) from baseline to Week 16 LSMean (SE)	Treatment diff.	-2.0
		95% CI	-2.5; -1.4
		P-value[8]	<0.001
	Change in HESD score (weekly average) from baseline to Week 16 LSMean (SE)	Treatment diff.	-1.9
		95% CI	-2.4; -1.4
		P-value[8]	<0.001
	Change in HESD pain score (weekly average) from baseline to Week 16 LSMean (SE)	Treatment diff.	-2.0
		95% CI	-2.6; -1.5
		P-value[8]	<0.001
	Change in DLQI score from baseline to Week 16 LSMean (SE)	Treatment diff.	-3.9
		95% CI	-5.0; -2.8
		P-value[8]	<0.001
	Change in HEIS score from baseline to Week 16 LSMean (SE)	Treatment diff.	-0.81
		95% CI	-0.99; -0.62
		P-value[8]	<0.001
	Change in HEIS PDAL score from baseline to Week 16 LSMean (SE)	Treatment diff.	-0.82
		95% CI	-1.01; -0.62
		P-value[8]	<0.001

Title: A phase 3 clinical study to confirm efficacy and evaluate safety of twice-daily delgocitinib cream 20 mg/g compared with cream vehicle for a 16-week treatment period in adult subjects with moderate to severe chronic hand eczema (DELTA 2)	
	[1] Primary analysis of the primary estimand (composite). [2] Endpoints are not presented in the order of the testing hierarchy. [3] Among subjects with a baseline HESD itch score (weekly average) ≥4 points. [4] Among subjects with a baseline HESD score (weekly average) ≥4 points. [5] Among subjects with a baseline HESD pain score (weekly average) ≥4 points. [6] Among subjects with a baseline DLQI score ≥4 points. [7] The primary analysis for the primary estimand (composite) for the binary endpoints was the Cochran-Mantel-Haenszel test stratified by region and baseline IGA-CHE score. [8] The primary analysis for the primary estimand (composite) or the continuous endpoints was an ANCOVA model with effects of treatment group, region, baseline IGA-CHE score, and baseline value (endpoint of interest).
Notes	The trial included several exploratory endpoints. The results of the majority of the exploratory endpoints supported the findings of the primary and key secondary endpoints. Early onset of action was observed from Week 1 or Week 2 for the exploratory endpoints IGA-CHE TS, HECSI, HESD, DLQI, HEIS, and EQ-5D-5L scores in the delgocitinib cream 20 mg/g group.
Analysis description	For the primary and key secondary endpoints, confirmatory one-sided (superiority) hypotheses were tested for delgocitinib cream 20 mg/g vs. cream vehicle based on the primary analysis for the primary estimand (composite). A closed testing procedure with hierarchical tests, alpha splitting, and alpha recycling was used to control the overall type I error at a nominal one-sided 2.5% level. The statistical testing strategy was built on the principle that the IGA-CHE TS superiority at Week 16 had to be established before testing for additional benefits (key secondary endpoints) related to efficacy and health related quality of life.

2.5.5.3. Clinical studies in special populations

	Age 65-74 (Older subjects number /total number)	**Age 75-84 (Older subjects number /total number)**	**Age 85+ (Older subjects number /total number)**
Controlled trials (Trials 1273, 1401 and 1402)	82/1218	14/1218	2/1218
Non-controlled trials (Trial 2285)	1/16	0/16	0/16

Note: To avoid double counting, subjects participating in the non-controlled extension Trial 1403 are included under 'controlled trials' as they started treatment in the controlled Trials 1401 and 1402.

2.5.5.4. Supportive study

Study 1180 was a phase 2a, double-blind, multi-centre, prospective, randomised, 2-arm, vehicle-controlled, parallel-group trial, designed to investigate efficacy and safety of twice-daily topical application of delgocitinib ointment 30 mg/g in subjects with mild to severe CHE.

91 subjects were treated with at least 1 application of delgocitinib ointment 30 mg/g (60 subjects) or ointment vehicle (31 subjects), and 86 subjects completed the study. 5 out of the 91 subjects permanently discontinued IMP prior to Week 8. The discontinuation rate was 1.7 % for delgocitinib ointment and 12.9% for ointment vehicle.

The primary objective was to compare the efficacy of twice-daily applications of delgocitinib ointment 30 mg/g with ointment vehicle for up to 8 weeks in the treatment of subjects with CHE.

The primary endpoint was subjects with PGA TS at Week 8.

The secondary endpoints were:

- HECSI at Week 8.
- Subjects with PaGA TS at Week 8.

PGA TS, i.e. PGA score of 'clear' in subjects classified as 'mild' at baseline, or a PGA score of 'clear or 'almost clear' in subjects classified as 'moderate' or 'severe' at baseline. The odds of achieving PGA TS at Week 8 was statistically significantly higher (p=0.009) in the delgocitinib ointment group compared with the ointment vehicle group.

HECSI: Subjects in the delgocitinib ointment 30 mg/g group had a statistically significantly lower (p=0.003) mean HECSI score, adjusted for predominant CHE subtype and baseline HECSI score, than subjects in the ointment vehicle group at Week 8.

PaGA TS, i.e. PaGA score of 'clear' for subjects classified as 'very mild' or 'mild' at baseline, or a PaGA score of 'clear' or 'very mild' for subjects classified as 'moderate' or 'severe' at baseline: The proportion of subjects achieving PaGA TS at Week 8 was numerically higher in the delgocitinib ointment 30 mg/g group compared with the ointment vehicle group, but the difference was not statistically significant.

2.5.6. Discussion on clinical efficacy

The phase 3 clinical programme of delgocitinib in moderate to severe CHE consisted of 2 pivotal studies 1401 and 1402 evaluating the efficacy of topical delgocitinib cream 20 mg/g twice daily for 16 weeks and a long-term extension study 1403 where delgocitinib was administered as needed up to 36 weeks.

The initially proposed indication was treatment of moderate to severe CHE in adults who have had an inadequate response to, or for whom topical corticosteroids are not advisable. At the CHMP request, the applicant agreed to modify the wording of the indication in line with EU-approved indications as follows: treatment of moderate to severe CHE in adults for whom topical corticosteroids are inadequate or inappropriate. The applicant also added the new IGA-CHE scale to SmPC section 5.1 to clarify e.g. how moderate (IGA-CHE score 3) and severe CHE (IGA-CHE score 4) were defined.

Furthermore, the applicant was requested to discuss, based on all available data (including but not limited to the phase 2 study data and study 1403 data) whether the benefit of delgocitinib could be extrapolated to subjects with mild CHE, but with inadequate response to corticosteroids or when corticosteroids are not advisable/appropriate. The applicant clarified that mild CHE was not included in the phase 3 program and is not part of the target population for delgocitinib cream 20 mg/g. Only 12 subjects with mild CHE were included in the 20 mg/g treatment arm in the phase 2b study 1273. According to the applicant, patients with mild CHE are not considered to have high unmet medical need and are to be well managed by current

treatment strategies and available therapies, such as preventive measures, moisturisers and TCS. This is agreed.

It is noted that several modifications to the phase 3 protocols were made after the SA EMA/H/SA/3854/3/2020/II that focused on the phase 3 programme. In terms of efficacy endpoints, the changes that were made following interaction with the Health Authorities included: the final IGA-CHE scale was slightly modified, PaGA was removed as an efficacy endpoint, the responder threshold for HESD endpoints was changed from 3 to 4, two items were removed from the final 6-item HESD score and some changes were made in the statistical testing hierarchy. In terms of study 1403 specifically, the criteria for on/off treatment were modified as PaGA was removed as an endpoint, and the threshold for stopping treatment was changed from IGA-CHE score 0 to IGA-CHE score 0 or 1. Some further modifications were made that were not fully aligned with the SA, including selection of only one dose regimen 20 mg/g to the phase 3 programme. However, despite these changes, the discrepancies between the SA and the final phase 3 programme are not considered to preclude an adequate assessment of delgocitinib in the treatment of moderate to severe CHE.

Dose selection for the phase 3 studies

Altogether 258 subjects were randomised into the Phase 2b dose-range finding study 1273 in mild-to-severe CHE. Subjects received delgocitinib cream 1, 3, 8, or 20 mg/g or vehicle twice daily for 16 weeks.

The study design and eligibility criteria of the study were appropriate. Although some differences between the study groups were seen at baseline e.g. in the subtypes of CHE main diagnosis (27.5% with hyperkeratotic eczema in delgocitinib 3 mg/g group vs. other groups with range of 11.5–18.0%), the groups were well balanced for the baseline and demographic characteristics. The subjects had a CHE defined as hand eczema that had persisted for more than 3 months or returned twice or more within the last 12 months, and history of inadequate response to TCS or TCS treatment being medically inadvisable, corresponding to the Phase 3 studies population. In contrast to the Phase 3 study, study 1273 included mild CHE, but exploratory analyses were also performed in subjects with moderate to severe CHE (IGA-CHE ≥3). The definition of IGA-CHE was also modified after the Phase 2b study, i.e. the results between Phase 2b and the pivotal Phase 3 studies are not directly comparable in the moderate to severe CHE population (IGA-CHE ≥3).

For the primary endpoint, delgocitinib 8 and 20 mg/g showed a statistically significant treatment effect compared to the vehicle. In the overall population, IGA-CHE TS at Week 16 was achieved by 36.54% of the subjects in the 8 mg/g group and 37.74% in the 20 mg/g group vs. 8.00% in the vehicle group. In the moderate to severe population, IGA-CHE TS was achieved by 41.46% in the 8 mg/g group, 39.02% in the 20 mg/g group vs. 10.53% in the vehicle group. For the secondary endpoints and other predefined efficacy and quality of life endpoints, delgocitinib 8 mg/g and 20 mg/g demonstrated comparable efficacy. In a post-hoc analysis, the proportion of IGA-CHE TS responders in subjects with moderate CHE was numerically highest in the delgocitinib 8 mg/g group, whereas in the subjects with severe CHE, the proportion of IGA-CHE TS responders was numerically highest in the 20 mg/g group. Overall, the efficacy data did not clearly indicate a better efficacy for the 20 mg/g over 8 mg/g. This was already noted in the SA (EMEA/H/SA/3854/3/2020/II), in which the applicant was asked to consider conducting at least one of the proposed pivotal studies with both 8 mg/g and 20 mg/g dose. However, the applicant chose to conduct the pivotal studies with 20 mg/g dose only, as it was considered to provide the best possible treatment effect for the subjects considered the hardest to treat and the choice of 20 mg/g was not viewed to compromise safety.

Design and conduct of clinical studies

Pivotal studies 1401 and 1402

Study design and treatments

The pivotal studies 1401 and 1402 were identical in design and consisted of a screening period of 1 to 4 weeks, a 16-week treatment period where subjects were randomised 2:1 to delgocitinib cream 20 mg/g or cream vehicle to be applied twice daily, and a 2-week off-treatment follow-up period for the assessment of safety. Subjects who transferred to the long-term extension study 1403 were not required to complete the off-treatment follow-up period. Emollients were to be used according to the normal routine and were not recorded as concomitant medications. Use of any rescue treatment led to treatment discontinuation.

The 16-week treatment duration was chosen based on results from the phase 2a study 1180 in adults. The applicant stated that this decision stems from evaluating data based on reaching treatment effect plateau, which was not reached at week 8, so the treatment period was prolonged to 16 weeks for pivotal studies. The 16-week timepoint was further considered adequate by the CHMP based on Phase 2b results discussed during the SA (EMEA/H/SA/3854/3/2020/II).

Study population

The eligibility criteria for the studies 1401 and 1402 were identical. The enrolled subjects were adults with a diagnosis of CHE, defined as hand eczema that has persisted for more than 3 months or returned twice or more within the last 12 months. Disease severity was graded as moderate to severe according to the IGA-CHE score developed and validated by the applicant (i.e. IGA-CHE score of 3 or 4). The definition for a chronic disease (CHE) and the use of a 5-point IGA-CHE for the scoring of CHE severity for inclusion in phase 3 studies was agreed during the SA and is agreed by CHMP. In addition, HESD itch score (weekly average) of at least 4 points at baseline was required for inclusion. The enrolled subjects were to have a documented recent history of inadequate response to treatment with TCS or documentation that TCS are otherwise medically inadvisable. The inclusion criteria used to define the moderate to severe CHE population are considered acceptable. The used exclusion criteria can be also supported, including those related to other skin conditions, previous and current treatments, infections and other diseases/conditions.

The assessments related to CHE history (e.g. previous diagnostic procedures, presence of atopy, previous treatments), exogenous risk factors (e.g. occupational and domestic exposures to potential triggering factors and tobacco smoking) seemed adequate for characterisation of the study population.

While nummular hand eczema and pulpitis were not part of the CHE classification used in the pivotal trials using the 2015 European Society of Contact Dermatitis guideline, they were included in the more recent guideline that divided CHE into etiological and clinical subtypes (2022 guideline). Given the fact that nummular hand eczema and pulpitis are often clinical presentations of the CHE subtypes atopic hand eczema, irritant contact dermatitis and/or allergic contact dermatitis, any restrictions for the use of delgocitinib to the clinical subtypes of nummular hand eczema or pulpitis was not deemed necessary. Further, only 1 subject with contact urticaria/protein contact dermatitis as main CHE subtype was enrolled in the vehicle group and 14 subjects had contact urticaria/protein contact dermatitis as additional diagnosis (7 in delgocitinib group and 7 in vehicle group). Nevertheless, when reaching a stage of chronic inflammation, it would be expected that delgocitinib, a pan-JAK inhibitor targeting key inflammatory pathways where JAK-associated cytokines are involved, would be effective also in contact urticaria/protein contact dermatitis. Therefore, generalisability to all CHE subtypes was ultimately agreed by CHMP.

Although diagnostic patch testing within 3 years prior to screening was mandatory in Europe, it was not part of the inclusion criteria in the phase 3 pivotal studies. Overall, the treatment effect of delgocitinib was favourable regardless of whether the patch test was performed or not. Therefore, in can be concluded that the absence of patch testing did not have key impact on the overall interpretation of the study results. Furthermore, diagnostic patch testing is not considered to be a prior requirement for receiving delgocitinib treatment.

Endpoints

The instruments used in the pivotal studies for the key endpoints included both ClinROs (IGA-CHE, HECSI) and PROs (HESD, HEIS and DLQI). IGA-CHE, HESD and HEIS were developed by the applicant, whereas HECSI and DLQI are validated and well-known instruments that have been used in clinical practice and clinical studies.

IGA-CHE is a single item ClinRO that assesses the severity of the subject's global disease on a 5-point scale ranging from 0 (clear) to 4 (severe). IGA-CHE plays a key role in the overall assessment of delgocitinib, as it defines the wording of the indication and key inclusion criteria (moderate to severe CHE), but also the primary efficacy endpoint used in phase 3 studies 1401 and 1402, i.e. IGA-TS, defined as IGA-CHE score of 0 or 1 (clear or almost clear) with at least a 2-step improvement from baseline at Week 16.

Following interaction with the Health Authorities, the scale used in the phase 3 studies was slightly modified. To verify the measurement properties of the final IGA-CHE scale, blinded data from study 1401, pooled across treatment groups, was used in the psychometric evaluation. These analyses conducted, including assessment of reliability (test-retest reliability), validity (convergent validity and known-groups comparisons) and ability to detect change, confirmed the IGA-CHE scale as a sufficiently valid instrument for the use in the phase 3 studies, as intended. Furthermore, the 2-point improvement as a conservative responder definition for the phase 3 studies was supported by the psychometric analyses conducted.

HECSI is a validated ClinRO measure to assess the severity and extent of CHE. In addition to the use of percentage change from baseline in HECSI, 75% and 90% improvements in HECSI score, i.e. HECSI-75 and HECSI-90 were used as key secondary endpoints. The analyses conducted by the applicant using data from the phase 2b study 1273 provided support for the use of HECSI-75 and particularly HECSI-90 as clinically relevant response thresholds to treatment.

HESD is a PRO instrument used to assess the worst severity of subject's itch, pain, cracking, redness, dryness, and flaking over the past 24 hours. The HESD scale discussed during the SA (EMA/H/SA/3854/3/2020/II) consisted of 8 items and its use as one of the secondary endpoints in phase 3 studies was generally supported. However, following interaction with the Health Authorities, 2 items (skin thickening and swelling) were removed from the final HESD. The analyses assessing the psychometric properties of the final 6-item HESD scale using the data from the phase 3 study 1401 confirmed the reliability and validity of HESD. The analysis for a meaningful change supported the ≥4 reductions (weekly average) in HESD score, HESD itch score, and HESD pain score as clinically relevant improvements.

HEIS is a 9-item PRO instrument in which subjects assess how much their CHE impacts their daily activities, i.e. Proximal Daily Activities Limitation (PDAL) (3 items), embarrassment with appearance of their hands (two items), frustration with CHE, sleep, work, and physical functioning over the past 7 days. HEIS was first used in the phase 2b study 1273 and the data from the study was used to support the use HEIS in the context of use in adults with moderate to severe CHE. The data was discussed during the SA (EMA/H/SA/3854/3/2020/II), where it was concluded that the findings provide support for good measurement properties and an adequate content validity of the HEIS instrument. Only one change was

made to the final scale used in the phase 3 studies (item assessing difficulty holding/gripping objects was removed from the HEIS PDAL domain and moved to be a single item in a 'physical functioning' domain based on the structural validity findings). The used endpoints in the pivotal phase 3 studies, i.e. change in HEIS score from baseline to Week 16 and change in HEIS PDAL score from baseline to Week 16 as key secondary endpoints in the study can be supported.

DLQI is a validated questionnaire and consists of 10 items addressing the subject's perception of the impact of their skin disease on different aspects of quality of life over the last week. A change of at least 4 points has been considered a clinically relevant change. The chosen key secondary endpoints, i.e. reduction of DLQI score of ≥4 points from baseline at week 16 and change in DLQI score from baseline to week 16 can be endorsed.

In summary, the development and validation of the new instruments used for the efficacy evaluation in phase 3 studies was thoroughly documented by the applicant and the IGA-CHE, HESD and HEIS scales can be considered fit for purpose. Overall, the selection of the chosen primary and key secondary endpoints that assess both the clinician's and patient's view on CHE are supported.

Statistical methods

A closed testing procedure for primary and key secondary endpoints with hierarchical tests, alpha splitting, and alpha recycling was used to control the overall type I error at a nominal one-sided 2.5% level. The statistical testing strategy was designed to test superiority for primary outcome measure IGA-CHE TS at Week 16 in comparison to vehicle cream. Then (if tested superior), equal strategy testing for key secondary endpoints was done. The primary estimand 'composite' strategy evaluated the treatment effect in adult subjects with moderate to severe CHE, without initiation of rescue treatment or permanent discontinuation of IMP. For binary endpoints, the difference in response rates between the two treatment groups were analysed using the Cochran-Mantel-Haenszel test stratified by region and baseline IGA-CHE score. For continuous endpoints, the change (or percentage change) from baseline to the endpoint of interest was analysed using an ANCOVA model with effects of treatment group, region, baseline IGA-CHE score, and baseline value (endpoint of interest). The closed testing procedure with hierarchical tests, alpha splitting and alpha recycling is considered acceptable. The FAS was defined as all subjects randomised and exposed to IMP.

Several estimands were pre-defined, one primary estimand and two supplementary estimands, together with two sensitivity analyses. The primary estimand is not conservative if IEs are not truly indicative of non-response for the clinical endpoint and if more IEs occur in the cream vehicle arm. This would lead to overestimation of the treatment effect. The same is true for continuous endpoints for which non-response assumption was implemented by imputing subject's worst value (including the baseline value). The two supplementary estimands are considered to reflect relevant questions, respectively, about treatment effects in absence of a disruptive effect of a pandemic to the treatment and 'de facto' outcomes depending on whether treatment is prescribed. The imputation and analysis models used to estimate the respective estimands are considered appropriate.

The pooled analysis of studies 1401 and 1402 was not controlled for multiplicity. The pooled analyses provided overall estimates based on both trials and were used to support the analyses on subgroups of interest. The estimands and the testing hierarchy was the same as in the individual studies. For the pooled efficacy analyses, an additional stratification variable study ID was used, besides the stratification variables region and baseline IGA-CHE score used in studies 1401 and 1402. The pooled analysis was appropriate, as the individual studies were basically identical. The extension study 1403 was descriptive in nature.

Protocol amendments/deviations

One substantial protocol amendment was made in the early phase of studies 1401 and 1402 to comply with request from health authorities, to accommodate for the conduct of the trial in Russia, and to proceed with administrative and editorial changes. However, due to operational challenges, Russian sites were not initiated.

Altogether 118 and 115 important protocol deviations were reported in studies 1401 and 1402, respectively. Few subjects were randomised with a baseline HESD itch score (weekly average) of <4 points and excluded from the analyses of ≥4 points reduction of HESD itch score but not from the analysis of the primary endpoint. Only one subject in study 1402 that was randomised in error and not treated, was excluded from the FAS. In addition, 13 subjects in study 1401 and 8 subjects in study 1402 had protocol violation related to missing/late primary endpoint assessment. The protocol deviations were not considered to impact on the validity of the studies or overall interpretation of the efficacy results.

Efficacy data and additional analyses

Pivotal studies 1401 and 1402

Participant flow

Altogether 487 and 473 subjects were randomised, and 446 and 413 completed the studies 1401 and 1402, respectively. The percentage on subjects completing the treatment without rescue treatment was higher in delgocitinib groups vs. vehicle group in both studies (93.8% vs. 87.0% in study 1401, and 92.7% vs. 75.5% in study 1402). Lack of efficacy was more common reason for discontinuation in vehicle group than in the delgocitinib group, i.e. 4.3% vs. 1.5% in study 1401 and 8.8% vs. 1.9% in study 1402.

Demographic and other baseline characteristics

The baseline demographics and disease characteristics between the study groups were generally well balanced in both studies. In studies 1401 and 1402, respectively, the mean age was 43.8 and 44.4 years, 62.8% and 66.0% were women and 91.8% and 93.2% were white. In terms of the disease characteristics, all subjects in both studies had a moderate to severe disease (IGA-CHE ≥3), but somewhat more subjects had severe CHE in study 1401 (32.9%) vs. study 1402 (23.9%) and the HECSI score was higher in study 1401 (77.5%) vs. study 1402 (65.5%) indicating a slight difference in the populations between the studies. This slight difference was not considered to impact the overall interpretation of the study results.

In terms of CHE history, the study groups were well balanced in terms of duration of CHE and age at onset of CHE in both studies. Atopic HE was the most common main CHE subtype. 44.0% and 45.7% in study 1401, and 26.1% and 28.9% in study 1402 in delgocitinib and vehicle groups, respectively, had atopic HE as the main diagnosis. Some differences were seen in the distribution of the main CHE subtypes between the groups, but not to the extent that would influence the overall interpretation of the efficacy. Only 1 subject in vehicle group in study 1402 had contact urticaria/protein contact dermatitis as the main diagnosis of CHE.

There were no relevant imbalances between the study groups in terms of previous CHE treatments. Almost all (>99%) were reported to have inadequate response to TCS during the last 12 months.

Efficacy results

Primary endpoint

A significantly greater percentage of subjects achieved the IGA-CHE TS at week 16 in the delgocitinib groups compared to the vehicle group in both pivotal studies. Based on the primary analysis of the primary estimand

(composite), 19.7% and 29.1% of subjects treated with delgocitinib 20 mg/g cream twice daily vs. 9.9% and 6.9% of subjects treated with the vehicle achieved IGA-CHE TS in studies 1401 and 1402, respectively. This translated into a 9.8% (95% CI 3.6, 16.1, p=0.006) and 22.2% (95% CI 15.8, 28.5, p<0.001) estimated treatment difference from placebo in studies 1401 and 1402.

The robustness of the primary outcome was demonstrated by the supplementary estimands considering the potential impact of COVID-19 on the result (pandemic-modified composite) and by evaluating the treatment effect regardless of rescue treatment or permanent discontinuation (treatment policy), as well as several sensitivity analyses, which all led to similar results as the primary analysis. It was noted, however, that the number of IE were higher in the vehicle group in both pivotal studies and therefore the primary estimand (composite) could have slightly overestimated the treatment effect in the hypothetical scenario where all randomised subjects completed 16 weeks of randomised treatment through Week 16 without resorting to rescue medication. Therefore, the applicant was requested to discuss how appropriately non-response/worst observation imputation reflected a hypothetical scenario where the IEs did not occur (for the primary endpoint and in general), and how the imbalance of number of IEs and the missing data, between delgocitinib cream 20 mg/g and cream vehicle, influenced the results of the primary 'composite' estimand. Specifically, that proportionally more subjects in the control arm were imputed as non-response. Further, the applicant was requested to discuss the reasons for the higher number of permanent discontinuations of IMP/missing data in the vehicle group in study 1402 compared to study 1401. The applicant provided results of the primary and secondary endpoints using hypothetical estimand, i.e. imputing missing data and data after initiation of rescue treatment or after permanent discontinuation of IMP under the MAR assumption. Small increases in response rates and slightly larger least squares mean changes were seen in both treatment groups when applying the hypothetical strategy. Overall, however, the results did not differ much from the results of the composite estimand. This further confirmed the robustness of the results in the pivotal studies. In terms of the observed difference in vehicle group discontinuation rates between the pivotal studies, no clear explanation was identified, and the imbalance was concluded to likely be due to random variation.

Key secondary endpoints

The results for IGA-CHE TS were favourable for delgocitinib also at week 4 and 8 timepoints, which were included in the multiplicity adjusted testing hierarchy. In terms of other objective signs of CHE, the proportion of subjects achieving HECSI-75 (weeks 8 and 16) and HECSI-90 (week 16), as well as the percentage change in HECSI from baseline (week 16) were significantly higher in the delgocitinib group vs. vehicle. In the assessment of subjective signs and symptoms of CHE, significantly greater proportion of subjects had ≥4 point reduction from baseline in the weekly average HESD itch score (weeks 2, 4, 8 and 16), HESD pain score (weeks 4, 8 and 16) and HESD score (weeks 4, 8 and 16). The results for the change from baseline at week 16 in HESD itch score, HESD pain score and HESD score were also in favour of delgocitinib over vehicle. With regards to subjective assessment of quality of life, delgocitinib demonstrated superiority over vehicle in reduction of DLQI score ≥4 points from baseline to week 16, as well as change from baseline to week 16 in DLQI score, HEIS score and HEIS PDAL score. Overall, for all key secondary endpoints included in the multiplicity adjusted testing hierarchy, delgocitinib demonstrated a statistically significant improvement over vehicle.

Overall, the results demonstrate that delgocitinib has a clinically relevant benefit on moderate to severe CHE, as evaluated by ClinROs (investigator-rated severity and extent of CHE) and PROs (subject-rated signs and symptom and CHE-related quality of life).

Onset of efficacy

The treatment response to delgocitinib was observed early on, particularly for the PROs, i.e. subject-rated assessments of signs and symptoms, and CHE-related QoL. Nevertheless, using the pooled data, a favourable effect of delgocitinib in the IGA-CHE TS was observed already at week 1, demonstrating an early onset of benefit also when using an objective and strict investigator-rated measure of CHE severity.

Observed data for the primary outcome showed a treatment plateau after Week 8 and possibly a slight steady decline so it appeared this is the time of reaching full treatment effect. The applicant was therefore requested to discuss whether the treatment should be stopped earlier than the initially proposed week 16 if no improvement is observed. The applicant performed an early predictor analysis to inform on how well early improvements can predict clinical responses for IGA-CHE TS or HECSI-75 at Week 16. To evaluate the accuracy of the early improvement predictors (≥1 step improvement in IGA-CHE or ≥HECSI-25), sensitivity and negative predictive values were assessed at Weeks 4, 8 and 12. High values for both sensitivity and negative predictive value were observed at Week 12. Based on this analysis, SmPC section 4.2 was updated to reflect that treatment should be discontinued if no improvement is seen after 12 weeks of continuous treatment.

Subgroup analysis

A predefined subgroups was performed based on the pooled data from studies 1401 and 1402, including various demographic factors, disease severity and disease history. In general, the results in the subgroups were consistent with the overall population. In subjects with moderate and severe disease, 27.0% and 17.6% of subjects treated with delgocitinib achieved IGA-CHE TS.

In terms of main CHE subtypes, the 95% CI for the primary endpoint IGA-CHE TS was in favour of delgocitinib for all subtypes, except for hyperkeratotic eczema. In a post-hoc analysis for hyperkeratotic eczema, however, the point estimates for all endpoints were in favour of delgocitinib and the 95% CI was in favour of delgocitinib for reduction of HESD itch, HESD pain, and HESD scores (weekly average) of ≥4 points from baseline. Overall, although some variability in treatment effect for the key endpoints were observed depending on the main CHE diagnosis, delgocitinib demonstrated a meaningful benefit in all main CHE subtypes included in the study. As discussed above, a generalisability to the entire CHE is supported although there was no data in subjects with contact urticaria/protein contact dermatitis as the main CHE subtype.

<u>Study 1403</u>

For all subjects treated with delgocitinib in the pivotal studies, the mean number of on-treatment periods in study 1403 was 1.5 (range 0-6), mean treatment period duration was 123 days, and mean number of days in response (IGA-CHE score of 0 or 1) was 46 days.

Subjects that received delgocitinib in the pivotal studies and were IGA-CHE TS responders

The mean cumulative number of days in response was 111 days (median 110, range 7-259) and mean proportion of days in response was 46% (median 44, range 4-100), i.e. there were individual(s) that retained IGA-CHE score of 0 or 1 for the entire 36-week off-treatment period. Approximately 60% and 72% of the IGA-CHE TS responders lost the response at week 4 and week 8, respectively, which is not unexpected considering the population that is difficult to treat. When interpreting the loss of response, the strict criteria of IGA-CHE score of 0 or 1 needs to be noted, as it allowed signs of 'barely perceptible erythema' only, with no other signs of CHE. The median time to first IGA-CHE score of ≥2 was 4 weeks.

Subjects that received delgocitinib in the pivotal study and were IGA-CHE TS non-responders

The mean cumulative number of days in response was 25 days (median 0, range 0-217) and the mean proportion of days in response was 10% (median 0, range 0-88). The estimated cumulative proportion of subjects with IGA-CHE score of 0 or 1 in this group was 48.1% at the end of the treatment period.

In terms of efficacy endpoints, for subjects that were treated with delgocitinib in the pivotal studie, the proportions of subjects with IGA-CHE score of 0 or 1, HECSI-90, HECSI-75, ≥4-point reductions in HESD itch, HESD pain and HESD scores were maintained approximately at the same level through the 1403 study with as needed treatment, while improvement in all secondary endpoints were seen in subjects that were treated with vehicle in the pivotal study.

As the data in both pivotal studies supported treatment duration of 16 weeks, the applicant was requested to address whether long term data from exposure to delgocitinib cream 20 mg/g from the study 1403 will be sufficient to elaborate on efficacy for chronic use. The applicant clarified that continuous chronic use beyond initial treatment period with delgocitinib is not an intended use, rather as-needed treatment is proposed. Among IGA-CHE TS responders treated with delgocitinib in the pivotal studies and who re-initiated delgocitinib treatment after first off-treatment period, 80.7% regained an IGA-CHE score of 0 or 1 at the end of the treatment period. Among IGA-CHE TS non-responders treated with delgocitinib in the pivotal studies and who re-initiated delgocitinib treatment after first off-treatment period, 94.5% gained an IGA-CHE score of 0 or 1 at the end of the treatment period.

To better understand a) which subjects retained vs. rapidly lost the treatment response (IGA-CHE score of 0 or 1) while off-treatment in study 1403 among IGA-CHE TS responders treated with delgocitinib in pivotal studies, and b) which subjects achieved IGA-CHE 0 or 1 on continued delgocitinib treatment in study 1403 among IGA-CHE TS non-responders treated with delgocitinib in pivotal studies, the applicant provided more detailed analysis of these subjects, considering the main CHE subtypes, CHE severity (moderate or severe) and CHE duration at baseline. Depending on the main CHE subtype, 30.8-57.9% and 20.4-52.6% of subjects who achieved IGA-TS at week 16, retained the IGA-CHE score of 0 or 1 at week 4 and week 8, respectively. The proportion of subjects who retained the response at weeks 4 and 8 was highest in subjects with allergic contact dermatitis (57.9% and 52.9%. respectively), followed by subjects with vesicular hand eczema (50.0% and 35.0%, respectively). The IGA-TS was lost at week 4 in 44.0% of subjects with severe CHE and in 27.6% of subjects with moderate CHE at baseline. Also, the duration of CHE had impact, with less subjects losing the IGA-CHE TS if the duration of CHE at baseline was <5 years vs. ≥5 years. In subjects treated with delgocitinib cream 20 mg/g who did not achieve IGA CHE TS at Week 16 in parent trials, the cumulative proportion of subjects achieving IGA CHE score of 0 or 1 continuously increased over time in all subgroups. At the end of the treatment IGA CHE score of 0 or 1 was achieved in the CHE subgroups as follows; vesicular hand eczema (63.4%), irritant contact dermatitis (60.3%), allergic contact dermatitis (58.1%), atopic hand eczema (44.3%), hyperkeratotic eczema (32.3%), moderate CHE at baseline (52.3%), severe CHE at baseline (39.6%). No apparent differences between the subgroups based on CHE duration at baseline was seen. Based on the analyses provided, it can be concluded that in case of incomplete response at week 16 (i.e. subjects not reaching IGA-CHE TS), further improvement was seen in all subgroups independent of CHE subtype, severity or CHE duration. Therefore, continuation of treatment twice daily beyond 16 weeks until the skin is clear or almost clear is justifiable.

Time to losing and time to regaining IGA-CHE treatment response

At the CHMP request, the applicant provided more detailed data on the time to losing and time to regaining IGA-CHE treatment response (after first and subsequent re-initiations) for responders and non-responders. Supportive data on HESD pain and itch scores were also provided.

In the Study 1403, 122 responders from the parent study re-initiated delgocitinib cream 20 mg/g treatment at least once, 73 re-initiated treatment at least twice, and 30 re-initiated treatment at least 3 times. 127 non-responders from the parent study re-initiated delgocitinib cream 20 mg/g treatment at least once, 49 re-initiated treatment at least twice, and 12 re-initiated treatment at least 3 times. Re-initiation of treatment was triggered by an IGA-CHE score of 2 for over 70% of patients, and for less than one third by an IGA-CHE score of 3 or 4. Time to regain IGA-CHE score of 0 or 1 is described for up to 3 treatment re-initiations.

For the responders from the parent studies the estimated median time to regain IGA-CHE score of 0 or 1 was the same (8 weeks) following the first, second, and third treatment re-initiation. After 4 weeks, more than one third of the subjects had regained an IGA-CHE score of 0 or 1, with the cumulative incidence estimated as 36.1% after the first re-initiation, 35.6% after the second re-initiation, and 40.0% after the third re-initiation. The cumulative incidence estimated values continued to raise and by the end of the treatment period, the cumulative proportion of subjects who had regained an IGA-CHE score of 0 or 1 was estimated as 80.7% after the first treatment re-initiation, 89.3% after the second treatment re-initiation, and 86.3% after the third treatment re-initiation. There were similar treatment responses observed for responders and non-responders from the parent trial.

Analyses of HESD pain and itch scores after re-initiation of treatment are supportive of results for IGA-CHE score, with improvement within 2 weeks after re-initiation.

138 responders from the parent studies had at least 1 off-treatment period, 84 subjects had at least 2 off-treatment periods, and 44 subjects had at least 3 off-treatment periods. 151 non-responders had at least 1 off-treatment period, 63 subjects had at least 2 off-treatment periods, and 18 subjects had at least 3 off-treatment periods. Time to lose IGA-CHE score of 0 or 1 is described for up to 3 off-treatment periods.

For responders from the parent studies, the estimated median time to lose IGA-CHE score of 0 or 1 was the same (4 weeks) in the first, second, and third off-treatment period.

In conclusion, the results show that treatment responses (IGA-CHE score of 0 or 1) can be regained after re-initiation of the delgocitinib treatment in approximately the same time as for the initial treatment. Median time to regain IGA-CHE score of 0 or 1 was 8 weeks. Clinically relevant improvement (week 2) in mean daily HESD pain and itch scores were also observed. Presented clinical data on the time to losing and time to regaining IGA-CHE treatment response (after first and subsequent re-initiations) supports as-needed use of delgocitinib.

Withdrawal and potential rebound effect

The SA (EMEA/H/SA/3854/3/2020/II) on the long-term extension study was not followed and data on delgocitinib withdrawal and potential rebound effect was missing. At CHMP's request, the applicant provided a post-hoc analysis of potential rebound effect defined as a HECSI score >25% higher than at baseline in the parent studies and of subjects off-treatment with worsening in IGA-CHE score in study 1403 from baseline in the parent studies. Evaluation of potential withdrawal effect based on full 1403 AE data was also provided by the applicant. Although the design of studies in delgocitinib clinical development programme did not include

evaluation of delgocitinib withdrawal and potential rebound effect, it is concluded that the available data suggest low potential for withdrawal and rebound effects of delgocitinib treatment.

2.5.7. Conclusions on the clinical efficacy

Overall, the clinical development programme for delgocitinib cream in CHE in adults was robust.

In two pivotal phase 3 studies conducted in subjects with moderate to severe CHE, delgocitinib cream demonstrated efficacy vs. cream vehicle on the primary endpoint of IGA-CHE score of 0 or 1 (clear or almost clear) with at least a 2-step improvement from baseline at Week 16; consistently greater effects vs. vehicle group were also seen on key secondary endpoints.

The CHMP concluded that the efficacy data available supports the following indication:

Anzupgo is indicated for the treatment of moderate to severe chronic hand eczema (CHE) in adults for whom topical corticosteroids are inadequate or inappropriate (see section 5.1).

Results obtained from the clinical efficacy analyses are adequately reflected in the SmPC.

2.5.8. Clinical safety

Evaluation of safety is mainly based on the vehicle-controlled Phase 3 studies 1401 (N* = 487) and 1402 (N = 472), their open-label extension 1403 (N = 769) as well as the vehicle-controlled Phase 2b study 1273 (N = 258); whereas the Phase 3 studies were conducted in adult subjects with moderate to severe CHE, study 1273 also included subjects with mild CHE. Data on the following additional studies, with most of them addressing specific safety aspects, are also included:

- 2285, Phase 1 PK study in adult subjects with moderate to severe CHE (N = 16)
- 1180, vehicle-controlled Phase 2a proof-of-concept study with delgocitinib ointment in adult subjects with at least mild CHE (N = 91)
- 1181, maximal usage study in paediatric and adult subjects with moderate to severe atopic dermatitis (AD) (N = 46)
- 1275, vehicle-controlled Phase 2b study in adult subjects with mild to severe AD (N = 250)
- 1408, investigating phototoxic potential in healthy subjects (N = 35)
- 1411, investigating photoallergic potential in healthy subjects (N = 60)
- 1409, a cardiovascular safety / QTc study with systemically administered delgocitinib in healthy subjects (conducted primarily to support development in AD) (N = 40)
- 1426, an ongoing vehicle-controlled Phase 3 study in adolescent subjects 12-17 years of age with moderate to severe CHE (planned N = 92)
- 1528, an ongoing active-controlled Phase 3 study comparing topical delgocitinib to alitretinoin capsules in adult subjects with severe CHE (planned N = 510)

* All N's herein refer to number of subjects exposed to IMP (delgocitinib or vehicle) in the corresponding study.

For the long-term extension study 1403, all data collected up to a cut off of 30 December 2022 were included in the initial submission. The expression '1403p' is used for this study when data collected until this data lock-point is referred to. Full data were provided at the CHMP request.

For safety evaluation, data were integrated into 4 pools:

- **Primary pool:** Safety data from studies 1273, 1401 and 1402. Used for the primary evaluation of safety data as these studies provide 16-week controlled trial design for the comparison of delgocitinib cream 20 mg/g vs cream vehicle.
- **Long-term safety pool:** Safety data from studies 1401, 1402, and 1403. Used as the main source of the evaluation of long-term safety of delgocitinib cream (up to 52 weeks). Data are presented according to actual treatment at time of reporting.
- **Intermittent-use pool:** Safety data from studies 1401, 1402, and 1403. Used to supplement the evaluation of long-term safety of as-needed treatment with delgocitinib cream after 16 weeks of continuous treatment. Data are presented according to treatment in the corresponding feeder trials 1401 and 1402.
- **Exposure pool:** Safety data from all clinical trials with delgocitinib cream 1, 3, 8, or 20 mg/g in AD and CHE, i.e. studies 1181, 1273, 1275, 1401, 1402, 1403, and 2285. Used for the evaluation of less frequent safety findings including SAEs and deaths. Data are presented according to actual treatment at time of reporting.

The following safety focus areas were identified: 'dermal safety, 'allergic reactions', 'serious or severe infections, 'herpes viral infections, 'low blood cell count, 'elevated lipid parameters, 'vaccination side effects, including COVID-19 vaccine', 'hepatic and renal safety', 'cardiovascular safety, 'malignancies' and 'rare events'.

Descriptive statistics were used in the analysis of safety parameters. All AEs described are treatment-emergent i.e. AEs starting after the first application of IMP or AEs that started before the first application of IMP and worsened in intensity after first application of IMP. AEs are presented by Medical Dictionary for Regulatory Activities (MedDRA) preferred term (PT) and primary system organ class (SOC) and are summarised in terms of the number and percentage of subjects with AEs, the number of AEs, and the rate of AEs (number of AEs per 100 patient years of exposure/observation time).

2.5.8.1. Patient exposure

In the Primary pool, AE rates were calculated as events per 100 patient-years of observation (PYO), where PYO includes the 2 weeks safety follow-up period.

For exposure calculations and corresponding AE rates, the applicant has accounted for the intermittent exposure in study 1403 in several distinct ways:

In the Long-term safety pool, the data from the extension study 1403 is included based on the current treatment at the time of the assessment or AE reporting (exposure time during on-treatment periods were included in the delgocitinib column, and exposure time during off-treatment periods were included in the vehicle/off-treatment column); as such, the time in study of one subject in 1403 can be distributed across more than one treatment group. AE rates were calculated as events per 100 PYO, where PYO for delgocitinib 20 mg/g includes the PYO from the parent trials in subjects randomised to delgocitinib 20 mg/g, as well as the on-treatment periods in 1403. Likewise, PYO for vehicle/off-treatment includes the PYO from the parent

trials in subjects randomised to vehicle, as well as the off-treatment and safety follow-up periods in study 1403.

In the Intermittent-use pool, the data from the extension study 1403 is included based on parent trial treatment. Exposure in the Intermittent-use pool was calculated in 2 ways. With both ways, exposure follows the subjects based on their randomisation to parent trial treatment of either delgocitinib cream 20 mg/g or cream vehicle:

- Exposure calculated as PYO includes the 2-week safety follow-up period, for both treatment groups. This approach is used for the AE data presentations, as it is in alignment with the approach used in the other pools and thus facilitates comparisons.
- Delgocitinib and/or delgocitinib as needed exposure includes only exposure time on delgocitinib cream 20 mg/g (parent trial) and/or the as needed treatment phase of study 1403.

The Exposure pool comprises the 5 CHE studies (1273, 1401, 1402, 1403, and 2285) and the 2 AD studies (1181 and 1275). In this pool, observation time in 1403 is assigned according to current treatment and subjects' exposure can thus contribute to more than one treatment group.

Exposures based on these accounting principles are summarised in Table 30.

Table 30 - Exposure by trial and by pools – SAF

	Delgocitinib (All doses) (N=1343 PYO=729.13)		Vehicle or off-treatment (N=963 PYO=248.09)		Total (N=1529 PYO=977.22)	
	n (%)	PYO	n (%)	PYO	n (%)	PYO
CHE trials #a	1097 (81.7)	672.96	913 (94.8)	237.01	1233 (80.6)	909.97
1273	208 (15.5)	68.92	50 (5.2)	16.01	258 (16.9)	84.92
1401	325 (24.2)	100.85	162 (16.8)	48.55	487 (31.9)	149.40
1402	313 (23.3)	95.87	159 (16.5)	45.36	472 (30.9)	141.22
1403 #a	779 (58.0)	407.52	770 (80.0)	128.14	801 (52.4)	535.66
1403 #b	560 (41.7)	378.03	241 (25.0)	157.62	801 (52.4)	535.66
2285	16 (1.2)	0.96			16 (1.0)	0.96
AD trials	246 (18.3)	56.18	50 (5.2)	11.08	296 (19.4)	67.25
1181	46 (3.4)	9.75			46 (3.0)	9.75
1275	200 (14.9)	46.43	50 (5.2)	11.08	250 (16.4)	57.51
Pools						
Primary pool	691 (51.5)	214.72	371 (38.5)	109.91	1062 (69.5)	324.63
Long-term safety pool #a	873 (65.0)	603.08	863 (89.6)	221.01	959 (62.7)	824.08
Intermittent-use pool #b	638 (47.5)	573.21	321 (33.3)	250.87	959 (62.7)	824.08
Exposure pool #a	1343 (100.0)	729.13	963 (100.0)	248.09	1529 (100.0)	977.22

Abbreviations: AD = atopic dermatitis. CHE = chronic hand eczema. N = number of subjects within a treatment group. PYO = patient years of observation. SAF = safety analysis set. % = percentage of subjects.
Notes: Off-treatment applies to Trial 1403 only. Primary pool: Trials 1273(20 mg and vehicle), 1401, 1402. Long-term safety pool: Trials 1401, 1402, 1403. Intermittent-use pool: Trials 1401, 1402, 1403. Exposure pool: all AD and CHE trials with delgocitinib cream. a: subjects were allocated to treatment columns according to actual time on or off treatment during Trial 1403. Subjects may contribute with exposure to more than one treatment group for Trial 1403. b: subjects were allocated to treatment columns
according to parent trial treatment during Trial 1403.

Exposure in the Primary pool

Table 31 - Summary of exposure – Primary pool – SAF

	Delgocitinib 20 mg/g (N=691)	Vehicle (N=371)
Patient years of observation (PYO)		
n	691	371
Sum	214.72	109.91
Mean (SD)	0.311 (0.045)	0.296 (0.071)
Median (Q1;Q3)	0.309 (0.309;0.318)	0.309 (0.307;0.320)
Min;max	0.01;0.56	0.02;0.39
Patient weeks of exposure (PWE)		
n	691	371
Sum	10733.96	5276.11
Mean (SD)	15.534 (2.863)	14.221 (4.472)
Median (Q1;Q3)	16.132 (15.989;16.275)	16.132 (15.704;16.275)
Min;max	0.29;24.13	0.43;20.27
Patient years of exposure (PYE)		
n	691	371
Sum	205.86	101.19
Mean (SD)	0.298 (0.055)	0.273 (0.086)
Median (Q1;Q3)	0.309 (0.307;0.312)	0.309 (0.301;0.312)
Min;max	0.01;0.46	0.01;0.39
Exposure time, n (%)		
n	691 (100.0)	371 (100.0)
>= 8 weeks	664 (96.1)	325 (87.6)
>= 16 weeks	642 (92.9)	297 (80.1)
>= 26 weeks		

Abbreviations: N = number of subjects within a treatment group. n = number of subjects with observation. PWE = patient weeks of exposure. PYE = patient years of exposure. PYF = patient years of follow-up. PYO = patient years of observation. Q1 = first quartile. Q3 = third quartile. SAF = safety analysis set. SD = standard deviation. % = percentage of subjects.
Notes: Exposure end is defined as last day with IMP application. Weeks rounded to next whole number of weeks.

Exposures in the Long-term and Intermittent pools

Table 32 - Summary of exposure – Long-term safety pool – SAF

	Delgocitinib 20 mg/g (N=873)	Vehicle or off-treatment (N=863)
Patient years of observation (PYO)		
n	873	863
Sum	603.08	221.01
Mean (SD)	0.691 (0.268)	0.256 (0.210)
Median (Q1;Q3)	0.693 (0.485;0.964)	0.257 (0.044;0.375)
Min;max	0.00;1.07	0.00;1.16
Patient weeks of observation (PWO)		
n	873	863
Sum	31446.26	11523.99
Mean (SD)	36.021 (13.988)	13.353 (10.940)
Median (Q1;Q3)	36.118 (25.268;50.251)	13.419 (2.284;19.558)
Min;max	0.14;55.82	0.14;60.39
Observation time, n (%)		
n	873 (100.0)	863 (100.0)
>= 8 weeks	850 (97.4)	504 (58.4)
>= 16 weeks	812 (93.0)	403 (46.7)
>= 26 weeks	659 (75.5)	120 (13.9)
>= 36 weeks	502 (57.5)	33 (3.8)
>= 46 weeks	302 (34.6)	8 (0.9)
>= 52 weeks	206 (23.6)	5 (0.6)

Abbreviations: N = number of subjects within a treatment group. n = number of subjects with observation. PWO = patient weeks of observation. PYO = patient years of observation. Q1 = firstquartile. Q3 = third quartile. SAF = safety analysis set. SD = standard deviation. % = percentage of subjects with observation.
Notes: Delgocitinib 20 mg/g PYO = PYO from delgocitinib group in Trials 1401 and 1402 + Trial 1403 on-treatment periods. Vehicle or off-treatment PYO = PYO from vehicle group in Trials 1401 and 1402 + Trial 1403 off-treatment periods + Trial 1403 safety follow-up period. Weeks rounded to next whole number of weeks. A subject can contribute to both treatment groups.

Table 33 - Summary of exposure – Intermittent-use pool – SAF

	Delgocitinib 20 mg/g to on/off delgocitinib 20 mg/g (N=638)	Vehicle to on/off delgocitinib 20 mg/g (N=321)
Patient years of delgocitinib and or delgocitinib as needed exposure		
n	638	321
Sum	545.59	148.45
Mean (SD)	0.855 (0.284)	0.462 (0.308)
Median (Q1;Q3)	0.999 (0.942;1.002)	0.690 (0.003;0.693)
Min;max	0.01;1.11	0.00;0.75
Delgocitinib and or delgocitinib as needed exposure time, n (%)		
n	638 (100.0)	321 (100.0)
>= 8 weeks	616 (96.6)	233 (72.6)
>= 16 weeks	597 (93.6)	218 (67.9)
>= 26 weeks	533 (83.5)	203 (63.2)
>= 36 weeks	508 (79.6)	188 (58.6)
>= 46 weeks	484 (75.9)	
>= 52 weeks	466 (73.0)	
Patient years of observation (PYO)		
n	638	321
Sum	573.21	250.87
Mean (SD)	0.898 (0.276)	0.782 (0.357)
Median (Q1;Q3)	1.038 (0.964;1.043)	1.035 (0.389;1.040)
Min;max	0.02;1.17	0.02;1.16
Observation time, n (%)		
n	638 (100.0)	321 (100.0)
>= 8 weeks	627 (98.3)	299 (93.1)
>= 16 weeks	612 (95.9)	284 (88.5)
>= 26 weeks	544 (85.3)	231 (72.0)
>= 36 weeks	511 (80.1)	212 (66.0)
>= 46 weeks	486 (76.2)	199 (62.0)
>= 52 weeks	476 (74.6)	195 (60.7)

Abbreviations: N = number of subjects within a treatment group. n = number of subjects with observation. PWE = patient weeks of exposure. PYF = patient years of follow-up. PYO = patient years of observation. Q1 = first quartile. Q3 = third quartile. SAF = safety analysis set. SD = standard deviation. % = percentage of subjects.
Notes: PYO is calculated as number of days from first IMP application in parent trial to end of trial divided by 365.25. Weeks rounded to next whole number of weeks. Patient years of delgocitinib as needed exposure: delgocitinib: from date of first IMP application to end of treatment period in Trial 1403. For subjects not continuing in Trial 1403 patient years of delgocitinib as needed exposure is parent trial PYE. Vehicle: from date of baseline visit in 1403 to end of treatment period in Trial 1403.

Exposure in the Exposure pool

Table 34 - Summary of exposure – Exposure pool – SAF

	Delgocitinib (All doses) (N=1343)	Vehicle or off-treatment (N=963)
Patient years of observation (PYO)		
n	1343	963
Sum	729.13	248.09
Mean (SD)	0.543 (0.305)	0.258 (0.203)
Median (Q1;Q3)	0.476 (0.309;0.830)	0.257 (0.047;0.359)
Min;max	0.00;1.16	0.00;1.16
Patient weeks of observation (PWO)		
n	1343	963
Sum	38019.20	12936.17
Mean (SD)	28.309 (15.921)	13.433 (10.583)
Median (Q1;Q3)	24.840 (16.132;43.256)	13.419 (2.427;18.702)
Min;max	0.14;60.39	0.14;60.39
Observation time, n (%)		
n	1343 (100.0)	963 (100.0)
>= 8 weeks	1284 (95.6)	596 (61.9)
>= 16 weeks	1026 (76.4)	452 (46.9)
>= 26 weeks	670 (49.9)	123 (12.8)
>= 36 weeks	508 (37.8)	34 (3.5)
>= 46 weeks	307 (22.9)	9 (0.9)
>= 52 weeks	210 (15.6)	6 (0.6)

Abbreviations: N = number of subjects within a treatment group. n = number of subjects with observation. PWO = patient weeks of observation. PYO = patient years of observation. Q1 = first quartile. Q3 = third quartile. SAF = safety analysis set. SD = standard deviation. % = percentage of subjects with observation.
Notes: Weeks rounded to next whole number of weeks. Delgocitinib (all doses) PYO = PYO from delgocitinib group(s) in Trials 1181,1273,1275,1401,1402,2285 + Trial 1403 on-treatment periods. Vehicle or off-treatment PYO = PYO from vehicle group in Trials 1273,1275,1401,1402 + Trial 1403 off-treatment periods + Trial 1403 safety follow-up period. A subject can contribute to both treatment groups.

Demographic characteristics in the Primary pool are summarised in Table 35.

Table 35 - Demographic characteristics – Primary pool - SAF

	Delgocitinib 20 mg/g (N=691)	Vehicle (N=371)	Total (N=1062)
Age (years)			
n	691	371	1062
Mean (SD)	44.7 (14.5)	43.4 (14.6)	44.3 (14.5)
Median (Q1;Q3)	45.0 (33.0;56.0)	43.0 (31.0;55.0)	44.0 (32.0;56.0)
Min;max	18;87	18;86	18;87
Age group, n (%)			
n	691 (100.0)	371 (100.0)	1062 (100.0)
< 65 years	632 (91.5)	348 (93.8)	980 (92.3)
>= 65 years	59 (8.5)	23 (6.2)	82 (7.7)
Sex, n (%)			
n	691 (100.0)	371 (100.0)	1062 (100.0)
Male	252 (36.5)	132 (35.6)	384 (36.2)
Female	439 (63.5)	239 (64.4)	678 (63.8)
Race, n (%)			
n	691 (100.0)	371 (100.0)	1062 (100.0)
White	629 (91.0)	340 (91.6)	969 (91.2)
Black or African American	5 (0.7)	2 (0.5)	7 (0.7)
Asian Chinese	1 (0.1)	1 (0.3)	2 (0.2)
Asian other	22 (3.2)	11 (3.0)	33 (3.1)
American Indian or Alaska Native	1 (0.1)		1 (0.1)
Native Hawaiian or Other Pacific Islander	1 (0.1)		1 (0.1)
Other	7 (1.0)	1 (0.3)	8 (0.8)
Multiple	3 (0.4)	4 (1.1)	7 (0.7)
Not reported	22 (3.2)	12 (3.2)	34 (3.2)
Ethnicity, n (%)			
n	691 (100.0)	371 (100.0)	1062 (100.0)
Hispanic or Latino	17 (2.5)	12 (3.2)	29 (2.7)
Not Hispanic or Latino	653 (94.5)	346 (93.3)	999 (94.1)
Not reported	21 (3.0)	13 (3.5)	34 (3.2)
Region, n (%)			
n	691 (100.0)	371 (100.0)	1062 (100.0)
Europe	557 (80.6)	302 (81.4)	859 (80.9)
North America	134 (19.4)	69 (18.6)	203 (19.1)

Abbreviations: N = number of subjects within a treatment group. n = number of subjects with observation. Q1 = first quartile. Q3 = third quartile. SAF = safety analysis set. SD = standard deviation. % = percentage of subjects with observation.

In the Primary pool, mean duration of CHE was approximately 10 years. The most common CHE subtypes were atopic hand eczema (37%), hyperkeratotic eczema (21%) and irritant contact dermatitis (21%).

2.5.8.2. Adverse events

2.5.8.2.1. Common adverse events

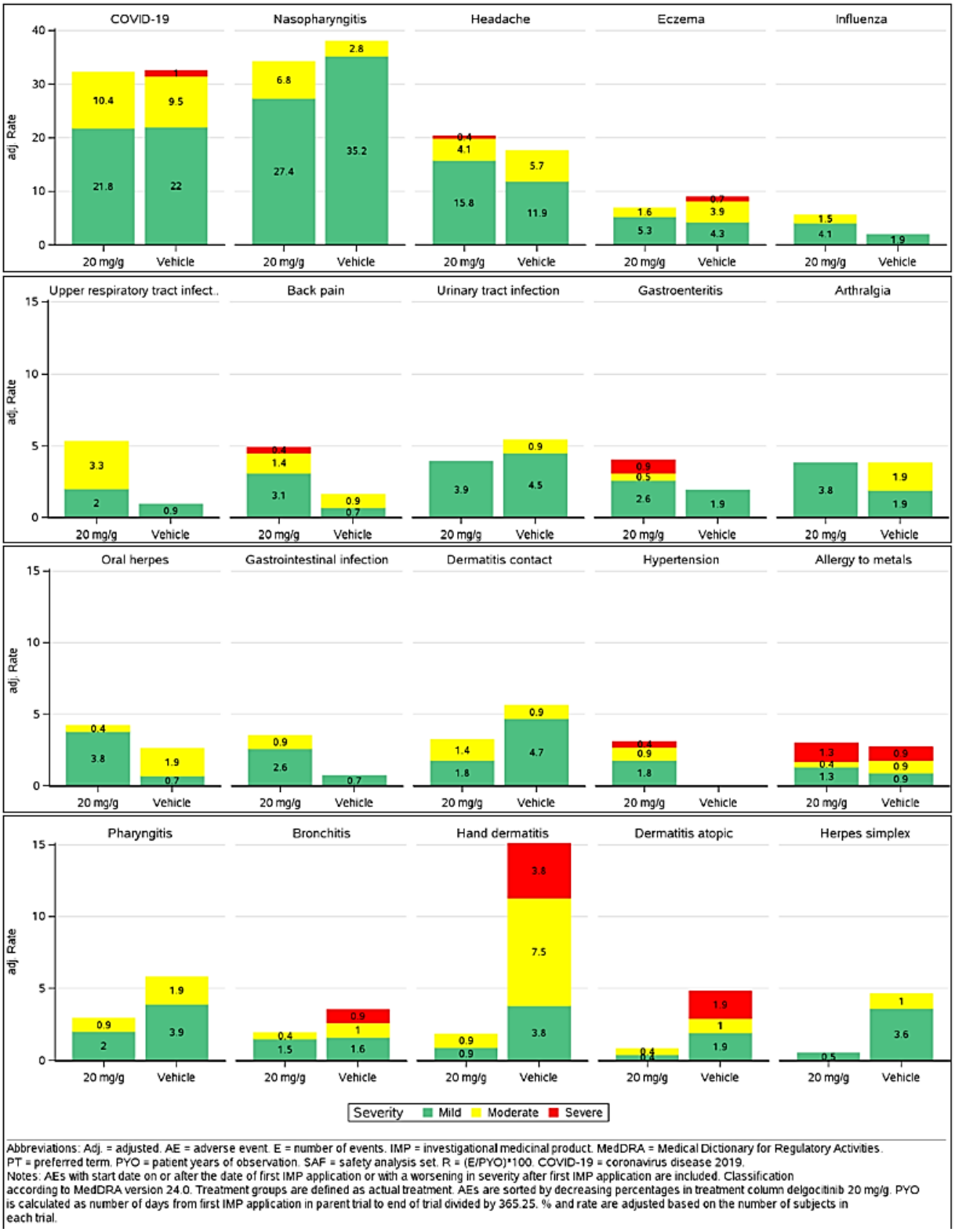
The overall proportion of subjects with AEs and event rates of these were similar for delgocitinib cream 20 mg/g and cream vehicle (48.2% and 49.0% of subjects, 314.5 and 334.7 E/PYO×100, respectively). Severe AEs (2.1% and 2.7% of subjects, 9.5 and 15.8 E/PYO×100, respectively) and serious AEs (1.5% and 1.7% of

subjects, 5.4 and 7.6 E/PYO×100, respectively) also occurred at similar proportions and rates for delgocitinib and vehicle. The majority of the AEs were non-serious, mild or moderate in intensity, and had resolved by the end of the trials. AEs leading to withdrawal from trial or permanent discontinuation of IMP occurred at low rates.

In the Intermittent use pool, the adjusted event rates in the delgocitinib to on/off delgocitinib group were 248.1 E/PYO×100 for all AEs, 6.6 E/PYO×100 for all SAEs, and 8.72 E/PYO×100 for all severe AEs. Any AEs were reported for 69%, any SAE for 4.7% and any severe AE for 5.2% of subjects.

In the Primary pool, the 2 SOCs with highest incidence of AEs were Infections and infestations, primarily driven by PTs COVID-19 and nasopharyngitis, and Skin and subcutaneous tissue disorders, primarily driven by PTs hand dermatitis and eczema. The overall proportion of subjects reporting AEs and the rate of AEs reported within these SOCs were similar or lower with delgocitinib than vehicle. A summary of AEs by individual PT and intensity is displayed in Figure 17.

Figure 17 - Histogram of most frequent AEs (⩾1%) by intensity - Primary pool – SAF



Abbreviations: Adj. = adjusted. AE = adverse event. E = number of events. IMP = investigational medicinal product. MedDRA = Medical Dictionary for Regulatory Activities. PT = preferred term. PYO = patient years of observation. SAF = safety analysis set. R = (E/PYO)*100. COVID-19 = coronavirus disease 2019.
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. Classification according to MedDRA version 24.0. Treatment groups are defined as actual treatment. AEs are sorted by decreasing percentages in treatment column delgocitinib 20 mg/g. PYO is calculated as number of days from first IMP application in parent trial to end of trial divided by 365.25. % and rate are adjusted based on the number of subjects in each trial.

Note: The 'Y' axis scale is different for the 1st of the 4 plots in the panel. It should be noted that CHE flares are coded to LLT chronic hand eczema/PT hand dermatitis events, while events coded to PT eczema refer to involvement outside of or in addition to the hands.

Within the SOC Infections and infestations, several PTs were used for reporting of respiratory tract infections, and the applicant therefore carried out a MedDRA search for all commonly reported PTs concerning respiratory tract infections. Overall, the proportions and rates of 'common respiratory tract infection' (group term) AEs were similar for delgocitinib and vehicle (21.3% and 21.5% of subjects, 80.1 and 79.2 E/PYO×100, respectively). In both groups, all events were non-serious, mild to moderate in intensity; in most cases, the event was deemed unrelated to IMP, and no action was taken with IMP.

Back pain and hypertension were reported more frequently with delgocitinib than with vehicle. Back pain was reported by 10 subjects (1.6%; 4.9 E/PYO×100) with delgocitinib vs 2 subjects (0.5%; 1.6 E/PYO×100) with vehicle. Hypertension was reported for 7 subjects (1.0%; 3.1 E/PYO×100) with delgocitinib vs 0% of subjects with vehicle.

According to the applicant, none of the events for either PT were considered related to IMP, and no clustering with respect to time to onset was seen. Based on a dedicated evaluation of these PTs, the Applicant considered these imbalances to be random and of no clinical relevance.

Common adverse events by causal relationship

In the Primary pool, AEs that were considered possibly or probably related to IMP by the investigator ('related AEs') occurred at lower proportion and rate with delgocitinib than vehicle (6.0% vs 8.2% of subjects; 25.0 vs 36.4 E/PYO×100). All related AEs were non-serious, and most related AEs were mild in intensity. A total of 3 severe related AEs were reported (1 event of PT streptococcal infection in the delgocitinib group and 2 events of PT hand dermatitis in 2 subjects in the vehicle group). Most related events were single occurrences.

Common adverse events by intensity

In the Primary pool, most AEs for both delgocitinib cream 20 mg/g and cream vehicle were mild or moderate in intensity (mild: 38.1% and 38.9% of subjects; 221.67 and 227.03 E/PYO×100, moderate: 18.5% and 18.0% of subjects; 83.4 and 91.8 E/PYO×100). Severe AEs occurred at similar proportion but lower rate with delgocitinib than with vehicle (2.1% and 2.7% of subjects, 9.5 and 15.8 E/PYO×100). According to the applicant, no pattern or clustering of severe events were observed for delgocitinib at the SOC or PT level.

In the Long-term pool, there were 14 subjects (1.6%) in the delgocitinib group with a severe AE in SOC Infections and infestations, corresponding to an adjusted event rate of 2.7 E/PYO×100. In the vehicle/off-treatment group, there were 5 such subjects (0.6%), corresponding to an adjusted event rate of 2.3 E/PYO×100.

ADRs for labelling

For purposes of populating the table of adverse drug reactions (ADR) in the SmPC, the applicant evaluated AEs for a plausible causal relationship to IMP. This included an evaluation of AEs related to drug class effects, drug metabolism, route of administration, and common AEs observed in the clinical trials with delgocitinib cream. The main assessment for ADRs was conducted on the Primary pool as this represents the safety dataset in the clinical development program with vehicle-controlled trials to evaluate relationship to delgocitinib cream against the background data with cream vehicle. The long-term safety data was used to further evaluate the rate of AEs and the AE changes over time.

Screening for possible ADRs reported was performed using a systematic approach:

- Evaluation of AEs that occurred in ≥1% of subjects and with a higher proportion or rate for delgocitinib cream vs cream vehicle.
- Evaluation of AEs identified during the assessment of the pre-specified AESIs and other safety focus areas based on clinical relevance, treatment differences in the proportion or rate of events, onset time, and investigator-judged relation to IMP. The second condition was applied independent of the first condition, i.e., without regard to reporting frequency.

All treatment-emergent AEs that met the above criteria for a potential ADR were further characterised for a potential causal relationship to the drug using the following considerations:

- Whether the difference in incidence between delgocitinib cream 20 mg/g and cream vehicle was observed consistently across safety populations (CHE Primary pool [up to 16 weeks], Long-term safety pool [including data up to 52 weeks as needed treatment]) and among the individual CHE studies.
- Whether the potential ADRs were consistent with the pharmacology of the drug or route of administration.
- Whether there was a pattern in the timing and or in the Investigator judged relation to IMP.
- Whether the potential ADRs could be better explained by alternative aetiologies or other considerations (e.g. hypersensitivity to concomitant medication or allergens used in diagnostic patch test).

Based on the assessment, the applicant has identified one AE to be listed as an ADR in the SmPC (Table 36). The ADR 'Application site reactions' was based on the PTs that were reported with delgocitinib cream 20 mg/g within the HLT 'application and instillation site reactions' (i.e. PTs application site pain, application site paraesthesia, application site pruritus, and application site erythema). According to the applicant, these events had an early onset (most within a week of first dose), were considered related to IMP by the investigator, and had a median duration in the delgocitinib cream 20 mg/g group of 3 days. Application site reactions were reported at a lower proportion and rate with delgocitinib (1.0%, 4.1 E/PYO×100) than vehicle (2.5%, 10.4 E/PYO×100) indicating that it was the cream rather than the API that caused the reactions. There was no indication of an allergic component to the ‘application site reactions’.

Table 36 - ADRs in subjects with CHE treated with delgocitinib cream 20 mg/g – by SOC and frequency – Primary pool

System organ class ADR	Frequency[a]	Primary pool (up to 16 weeks)					
		Delgocitinib cream 20 mg/g (N=691; PYO=215)			Cream vehicle (N=371; PYO=110)		
		n	(adj.%)	Adj. R	n	(adj.%)	Adj. R
General disorders and administration site conditions							
Application site reactions[b]	Common	7	(1.0)	4.11	9	(2.5)	10.4

Abbreviations: adj = adjusted; ADR = adverse drug reaction; HLT = high level term; N = number of subjects; n = number of subjects with events; PYO = patient years of observation; R = event rate (events per 100 PYO); SOC = system organ class. % = proportion of subjects.

Notes: Proportion and rate are adjusted based on the number of subjects in each trial. **a** = frequencies for ADRs are listed using the following categories: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1000 to <1/100); rare (≥1/10000 to <1/1000); very rare (<1/10000); **b** = Search for events using the HLT 'application and instillation site reactions'.

Safety focus areas

The primary safety evaluation was based on the Primary pool, but for the safety focus areas that are less frequent in the general population or the trial population, the search for events was done on the Exposure pool to increase the likelihood of identifying potential signals.

Overall summaries of results based on analyses of the safety focus areas are displayed in Table 37 for the Primary pool, and in Table 38 for the Exposure pool.

Table 37 - Summary of safety focus areas – Primary pool – SAF

	Delgocitinib 20 mg/g (N=691, PYO=214.72)			Vehicle (N=371, PYO=109.91)		
	n (adj. %)	E	adj. R	n (adj. %)	E	adj. R
Dermal safety						
Application site reactions	7 (1.0)	9	4.11	9 (2.5)	11	10.40
Acnes	2 (0.3)	2	0.92			
Local skin infection	5 (0.7)	5	2.26	4 (1.0)	4	3.50
Skin atrophy						
Allergic reactions	35 (5.4)	41	20.05	38 (10.0)	51	45.05
Serious and severe infections	7 (1.0)	8	3.62	2 (0.6)	2	1.90
Herpes viral infection	9 (1.3)	10	4.69	8 (2.1)	9	8.10
Eczema Herpeticum (AESI)						
Abnormal blood cell count	8 (1.1)	14	6.32	1 (0.3)	2	1.94
Lymphocytopenia	3 (0.4)	3	1.36			
Abnormal lipid parameters	15 (2.1)	18	8.12	5 (1.4)	7	6.51
Vaccination side effects, including COVID-19 vaccination	5 (0.7)	5	2.26	1 (0.3)	4	3.89

Abbreviations: Adj. = adjusted. AE = adverse event. AESI = adverse event of special interest. E = number of events. N = number of subjects within a treatment group. n = number of subjects with events. PYO = patient years of observation. R = (E/PYO)×100. SAF = safety analysis set. % = percentage of subjects with events.
Notes: The safety focus areas are captured by MedDRA searches. Some searches overlap, AEs may therefore appear in more than one search. The AESIs are captured by CRF form. 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. Treatment groups are defined as actual treatment. % and rate are adjusted based on the number of subjects in each trial. (a) The search abnormal blood cell count includes increases and decreases in blood cell counts, while the safety focus area focuses on low blood cell count. (b) The search for abnormal lipid parameters includes increases and decreases in lipids, however all AEs reported were associated with increases or high levels of lipids.

Table 38 - Summary of safety focus areas – Exposure pool – SAF

	Delgocitinib (All doses) (N=1343, PYO=729.13)			Vehicle or off-treatment (N=963, PYO=248.09)		
	n (%)	E	R	n (%)	E	R
Embolic and thrombotic events	1 (0.1)	1	0.14	2 (0.2)	2	0.81
Deep vein thrombosis (AESI)						
Pulmonary embolism (AESI)						
Cardiovascular events of interest				1 (0.1)	1	0.40
All-cause mortality	1 (0.1)	1	0.14	2 (0.2)	2	0.81
Torsades de pointes/QT prolongation				1 (0.1)	1	0.40
Malignancy	4 (0.3)	4	0.55	1 (0.1)	1	0.40
Non-melanoma skin cancer (NMSC)	1 (0.1)	1	0.14			
Rare events	6 (0.4)	6	0.82			

Abbreviations: Adj. = adjusted. AE = adverse event. AESI = adverse event of special interest. E = number of events. N = number of subjects within a treatment group. n = number of subjects with events. PYO = patient years of observation. R = (E/PYO)×100. SAF = safety analysis set. % = percentage of subjects with events. Delgocitinib PYO = parent trial delgocitinib exposure + Trial 1403 delgocitinib 20 mg/g exposure. Vehicle or off-treatment PYO = parent trial vehicle exposure + Trial 1403 off-treatment exposure + Trial 1403 safety follow-up period.
Notes: The safety focus areas are captured by MedDRA searches. Some searches overlap, AEs may therefore appear in more than one search. The AESIs are captured by CRF form. 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. Treatment groups are defined as actual treatment. % and rate are adjusted based on the number of subjects in each trial.
AEs are allocated to the specific treatment when the AE occurs. A subject can contribute with AEs to multiple treatments groups. DVT and PE were only identified as an AESI for Trials 1401, 1402, 1403 and 2285.

Dermal safety

The applicant assessed dermal safety in terms of 'application site reactions', 'acnes', 'local skin infections', 'skin atrophy' and 'local tolerability' (assessed by both subject and investigator). Dedicated studies were undertaken to evaluate phototoxic and photoallergic potential.

In the Primary pool, the reporting rate of 'local skin infections' was similar with delgocitinib and vehicle. All events were non-serious and of mild or moderate intensity. All events had resolved by the end of the trial, and approximately half of the events in both treatment groups were judged to be possibly or probably related to IMP by the investigator. The median duration of 'local skin infections' was 15 days with delgocitinib and 12.5 days with vehicle. One event of PT skin bacterial infection, with onset the first day of delgocitinib treatment, led to permanent discontinuation of IMP.

'Local skin infections' were reported at a similar rate with delgocitinib in the Long-term safety pool and the Primary pool. None of the events reported in study 1403 were serious or severe, none were considered related to IMP nor led to treatment intervention.

In the Primary pool, 'Application site reactions' were reported by a lower proportion of subjects and at a lower rate with delgocitinib (1.0% of subjects, 4.1 E/PYO×100) than with vehicle (2.5% of subjects, 10.4 E/PYO×100), suggesting that the 'application site reactions' were caused by the excipients in the cream formulations rather than the delgocitinib API. No lesional/perilesional events of LLT allergic contact dermatitis

were reported with delgocitinib cream in the Primary pool or the Exposure pool, indicating that the application site reactions were not due to allergic reactions.

The majority of 'application site reactions' (>75%) reported with delgocitinib had an early onset (within the first week of treatment). The median duration of the events was 3 days for delgocitinib and 8 days for vehicle. All events were non-serious, of mild or moderate intensity, and judged to be possibly or probably related to IMP by the investigator, except for one event in the vehicle group.

Considering the common occurrence of 'application site reactions' (reported in 1% of subjects treated with delgocitinib cream 20 mg/g), the timing of the events, the expectedness of the events, and that all but one of the events were judged related to IMP, 'application site reactions' is considered a common ADR by the applicant.

'Acnes' were reported in 2 subjects (0.3%) on delgocitinib (0.92 E/PYO×100) vs 0 subjects on vehicle. Both events were non-serious and of mild intensity and were not localised to the application site.

Local tolerability was assessed in terms of the subjects' perception of stinging/burning in connection with IMP application. The proportion of subjects sensing no or only mild stinging/burning increased over time in both treatment groups, but the increase appeared to be faster in the delgocitinib group. In an analysis of severe stinging/burning by CHE subtype, no substantial differences were found between subtypes; consistent with the main analysis, the adjusted rate of severe stinging/burning was higher in the vehicle group across subtypes.

The investigators suspected local skin reactions related to IMP application for 3 subjects on delgocitinib and 13 subjects on vehicle. Of the 21 events of local skin reactions that the investigators suspected to be related to IMP application, 11 subjects had an IMP patch test evaluation performed during studies 1401 and 1402. One vehicle-treated subject in study 1402 had a 'weak positive reaction' at the first reading and a 'doubtful reaction' at the second reading and had an AE of RT allergic contact dermatitis assessed as related to IMP. The 10 other subjects with IMP patch tests had negative test results, i.e. no events of allergic contact dermatitis were reported with delgocitinib. Ten AEs originated from the IMP patch tests: 3 events in 3 subjects with delgocitinib (0.4% of subjects) and 7 events in 7 subjects with cream vehicle (1.9% of subjects). Half of the events were reported as PT dermatitis contact and the remaining as different eczema events and application site reactions.

Phototoxic potential (study 1408)

Positive reactions were seen in between 4 and 10 subjects (11% to 29%) across the 5 treatments (delgocitinib cream 1, 3, 8, and 20 mg/g and cream vehicle) at 24 or 48 hours after irradiation. All subjects experiencing a positive skin reaction on active treatment also experienced a positive skin reaction on cream vehicle. No skin reactions rated higher than score 1 (erythema) were seen in any of the test fields at any post-irradiation assessment time point (24 and 48 hours). The Investigator concluded that there was no indication of any clinically relevant difference between active treatments and cream vehicle at 24 or 48 hours after irradiation.

All 4 strengths of delgocitinib cream and the cream vehicle were well tolerated with no treatment-emergent AEs reported.

Photoallergic potential (study 1411)

No positive skin reaction (score = 2) was seen in any of the subjects at 72 hours after irradiation in the challenge phase.

Allergic reactions

The 'allergic reactions' search was based on the SMQ Hypersensitivity (narrow) which includes the PTs dermatitis contact, hand dermatitis, dermatitis atopic, and dermatitis allergic. Thus, the 'allergic reactions' search, particularly within the SOC Skin and subcutaneous tissue disorders, may capture events reflecting a worsening of underlying illness (atopy, CHE, and AD) rather than actual allergic reactions.

In the Primary pool, 'allergic reactions' were reported in 5.4% of subjects on delgocitinib (20.0 E/PYO×100) compared to 10.0% of subjects on vehicle (45.0 E/PYO×100). No AEs captured by the 'allergic reactions' search appeared to reflect genuine allergic reactions to delgocitinib cream.

A serious 'allergic reaction' was reported in 1 subject in the delgocitinib group and 2 subjects in the vehicle group; other events were non-serious. A severe 'allergic reaction' was reported in 6 subjects in the vehicle group; all other events were of mild or moderate intensity. 'Allergic reactions' led to withdrawal from trial/permanent discontinuation of IMP in 2 subjects on delgocitinib and 15 subjects on vehicle. Out of the 41 events in the delgocitinib group, 3 were considered probably or possibly related to IMP, as compared to 17/51 events in the vehicle group.

Of the 92 'allergic reactions', 86 were from the SOC Skin and subcutaneous tissue disorders. A few 'allergic reactions' were reported in the SOC Immune system disorders. All of these were allergic reactions to concomitant medication or diagnostic patch test allergens and none were considered related to IMP.

There was no pattern in the time of onset of 'allergic reactions' across the 16-week treatment period.

In the Long-term safety pool, 'allergic reactions' with delgocitinib were reported at a lower rate compared to the Primary pool (16.2 E/PYO×100 vs. 20.0 E/PYO×100), and the rate was also lower in the delgocitinib group than the vehicle/off treatment group (16.2 E/PYO×100 vs. 27.6 E/PYO×100). None of the 'allergic reactions' reported appeared to reflect genuine allergic reactions to delgocitinib cream.

Serious or severe infections

Events of 'serious or severe infections' were captured as serious or severe AEs within the SOC Infections and infestations. There were 7 subjects (1.0%) with such events in the delgocitinib group vs 2 subjects (0.6%) in the vehicle group; the corresponding adjusted event rates were 3.6 E/PYO×100 for delgocitinib vs 1.9 E/PYO×100 for vehicle.

Of the reported events captured by this search, 1 was a skin infection: a severe event of PT streptococcal infection, judged to be possibly or probably related to IMP (delgocitinib cream 20 mg/g) and led to withdrawal from the trial; other events in this category were considered unrelated to IMP. None of the 'serious or severe infections' were lesional/perilesional.

In the long-term pool, there were 20 subjects (2.3%) in the delgocitinib group with a 'Serious or severe infection', corresponding to an adjusted event rate of 3.6 E/PYO×100. In the vehicle/off-treatment group, there were 7 such subjects (0.8%), corresponding to an adjusted event rate of 3.2 E/PYO×100.

Due to the numerical imbalance in the rate of serious or severe infections in the Primary pool, both when looking at serious and severe infections together and when looking at serious events alone, the applicant further analysed serious and severe infections in context of the long-term safety pool. Based on the analysis, the applicant made the following conclusions:

- None of the events were local skin infections.

- In the Long-term safety pool, the rate of serious or severe infections was similar between events reported while on-treatment (R=3.65) or vehicle/off-treatment (R=3.17). Moreover, the rate of serious infections was also similar between on-treatment (R=1.99) or vehicle/off-treatment (R=1.36).
- There was no increase in the rate of serious or severe infections for subjects treated with delgocitinib cream 20 mg/g as needed beyond 16 weeks (Primary pool: R=3.62; Long-term safety pool: R=3.65).
- No causal relationship between delgocitinib cream 20 mg/g and 'serious or severe infections' was identified based on the low number and rate of events with no pattern or clustering of individual event types, and the similar proportion of subjects with events across treatment groups.
- Lastly, in the full dataset for study 1403, all serious infections were non-cutaneous. Spreading of serious or severe infections to become systemic or disseminated, which could be suspected of a systemic immunosuppressant, was not observed.

Herpes viral infections

The reporting of 'herpes viral infection' was similar between delgocitinib and vehicle (1.3% of subjects, 4.7 E/PYO×100 vs 2.1% of subjects, 8.1 E/PYO×100). All events were non-serious and of mild or moderate intensity. All 10 events in the delgocitinib group and 7 of 9 events in the vehicle group were considered unrelated to IMP by the investigator. No events of eczema herpeticum or herpes zoster were reported in the Primary pool.

In the long-term safety pool, 18 subjects (2.1%) had a herpes viral infection event in the delgocitinib group, compared to 11 subjects (1.3%) in the vehicle/off-treatment group; corresponding event rates were 3.5 E/PYOx100 for delgocitinib and 5.9 E/PYOx100 for vehicle/off treatment. The rate of 'herpes viral infections' was similar for subjects treated with delgocitinib compared to the rate with delgocitinib in the Primary pool. Three events of PT herpes zoster were reported in study 1403 (on back, chest, and lips); 2 of the events were reported while on treatment, and the third occurred while off treatment (16 days since latest treatment). All 3 events were mild or moderate, non-serious, and judged not related to IMP.

In the long-term safety pool, 1 subject with a medical history of AD reported eczema herpeticum 2 weeks after an AE of mild oral herpes (judged not related to IMP). The eczema herpeticum event was non-serious, of moderate intensity, and judged by the investigator as possibly related to IMP. The event was polymorphic with papules, vesicles, crusts, and eroded pits and was present in an area with visible eczema. Herpes simplex virus was not confirmed. Delgocitinib was temporarily discontinued for 4 days, and the event resolved after antiviral treatment.

According to the applicant, considering the low number and rate of events, and the similar proportion of subjects with events across treatment groups, no causal relationship between delgocitinib cream 20 mg/g and 'herpes viral infections' or eczema herpeticum was identified.

Low blood cell count

A summary of AEs associated with a decrease in blood cells or low blood cell counts is shown in Table 39.

Table 39 - Low blood cell counts reported as AEs by SOC and PT – Primary pool – SAF

System organ class/ Preferred term	Delgocitinib 20 mg/g (N=691, PYO=214.72) n (adj. %)	E	adj. R	Vehicle (N=371, PYO=109.91) n (adj. %)	E	adj. R
Blood and lymphatic system disorders	4 (0.6)	4	1.83	1 (0.3)	2	1.94
Anaemia	1 (0.1)	1	0.46			
Leukopenia	1 (0.1)	1	0.46			
Lymphopenia	1 (0.1)	1	0.46			
Normocytic anaemia	1 (0.1)	1	0.45			
Thrombocytopenia				1 (0.3)	2	1.94
Investigations						
Lymphocyte count decreased	2 (0.3)	2	0.90			
White blood cell count decreased	1 (0.1)	1	0.45			

Abbreviations: Adj. = adjusted. AE = adverse event. E = number of events. MedDRA = Medical Dictionary for Regulatory Activities. n = number of subjects with events. PT = preferred term. PYO = patient years of observation. R = (E/PYO)×100. SAF = safety analysis set. SOC = system organ class. % = percentage of subjects.
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. Classification according to MedDRA version 24.0. PYO is calculated as number of days from first IMP application in parent trial to end of trial divided by 365.25. % and rate are adjusted based on the number of subjects in each trial.

An AE associated with a low blood cell count was reported in 7 subjects on delgocitinib vs 1 subject on vehicle. Nevertheless, all events were non-serious, mild or moderate in intensity and transient in nature, with none leading to discontinuation of IMP. Of the subjects with events, 3 (all in the delgocitinib group) had low levels of lymphocytes or lymphopenia reported as AEs (PTs lymphopenia [1 subject] and lymphocyte count decreased [2 subjects]), although their lymphocyte counts were within normal range (>1.0×10^9 cells/L). There was no pattern in onset of these events, and all were considered not related to IMP by investigators.

In the Long-term safety pool, 7 additional events of 'lymphocytopenia' were reported by 5 subjects (4 additional subjects and 1 subject for whom an event was already reported in the Primary pool). 5 events were reported by 4 subjects while on delgocitinib cream 20 mg/g treatment, and 2 events were reported by 2 subjects while off-treatment. Of these 7 additional reports captured by the 'lymphocytopenia' search in study 1403, only 2 subjects had lymphocyte counts <1.0 x10e9 cells/L (1 subject on Day 256 while on-treatment [0.7 x10^9 cells/L]; and 1 subject on Day 238 while off-treatment [0.9 x10^9 cells/L].

The applicant assessed the changes or differences between treatment groups in any of the haematology parameters (including lymphocytes) to be of no clinical relevance, based on the evaluation of mean laboratory values over time, shifts from baseline to end of treatment, and individual subject abnormalities across treatment groups, and no causal relationship between delgocitinib cream 20 mg/g and 'low blood cell count' was identified.

AEs associated with any change in haematology parameters are summarised in Table 40.

Table 40 - AEs related to haematology parameter abnormalities – Primary pool – SAF

System organ class/ Preferred term	Delgocitinib 20 mg/g (N=691, PYO=214.72) n (adj. %)	E	adj. R	Vehicle (N=371, PYO=109.91) n (adj. %)	E	adj. R
Investigations						
Lymphocyte count decreased	2 (0.3)	2	0.90			
Neutrophil count increased	2 (0.3)	3	1.34			
Eosinophil count increased	1 (0.1)	1	0.46			
Monocyte count increased	1 (0.1)	1	0.45			
Platelet count increased	1 (0.1)	1	0.45			
White blood cell count decreased	1 (0.1)	1	0.45			
White blood cell count increased	1 (0.1)	1	0.45			
Full blood count abnormal				1 (0.3)	1	0.97
Blood and lymphatic system disorders	4 (0.6)	4	1.83	3 (0.8)	4	3.85
Anaemia	1 (0.1)	1	0.46			
Leukopenia	1 (0.1)	1	0.46			
Lymphopenia	1 (0.1)	1	0.46			
Normocytic anaemia	1 (0.1)	1	0.45			
Lymphadenopathy				2 (0.6)	2	1.90
Thrombocytopenia				1 (0.3)	2	1.94

Abbreviations: Adj. = adjusted. E = number of events. N = = number of subjects. n = number of subjects with events. PT = preferred term. PYO = patient years of observation. R = (E/PYO)×100. SAF = safety analysis set. SOC = system organ class. % = percentage of subjects.
Notes: AEs related to hematology parameter abnormalities within the SOC Investigations and the SOC Blood and lymphatic system disorders are included.

Elevated lipid parameters

In the Primary pool, the number and proportion of subjects reporting AEs of 'elevated lipid parameters' was 15 subjects (2.1%, 8.1 E/PYO×100) for delgocitinib vs 5 subjects (1.4%, 6.5 E/PYO×100) for vehicle. None of the events were serious, severe, or led to discontinuation of IMP or withdrawal from trial.

In the Long-term safety pool, there was no increase in the reporting of elevated lipids over time in terms of AEs or in lipid laboratory measurements as compared to the Primary pool.

No clinically relevant changes or differences between treatment groups were observed for any of the lipid parameters based on evaluation of mean laboratory values over time, shifts from baseline to end of treatment, and individual subject abnormalities across treatment groups.

According to the applicant, based on the low number of subjects with elevated lipid AEs reported and the balanced distribution of individual subjects with lipid elevations between treatment groups, no causal relationship between delgocitinib cream 20 mg/g and 'elevated lipid parameters' was identified.

Vaccination side effects, including COVID-19

Overall, few events of 'vaccine side effects, including COVID-19' were reported in either treatment group. Events were typically local reactions associated with vaccination; none were serious, severe, judged related to IMP, or led to treatment intervention.

Hepatic safety

No cases (neither based on AE reports nor laboratory measurements) of drug-induced liver injury (Hy's law) or hepatic failure were reported in the clinical trials with delgocitinib cream 20 mg/g. Hepatic AEs were overall reported by few subjects in either treatment group, with no clustering observed.

In the Long-term pool, individual AEs in the SOC Hepatobiliary disorders and hepatic AEs in the SOC Investigations were reported at low (<1%) frequencies, with no clustering noted.

Renal safety

Few subjects reported events within the SOC Renal and urinary disorders or the SOC Investigations (delgocitinib: 9 subjects with 9 events; vehicle: 3 subjects with 3 events). All AEs were non-serious, mild and all PTs were reported by ≤ 2 subjects. Half of the events in each treatment group were urinary abnormalities. No increase was seen in the Long-term safety pool.

Cardiovascular safety

For assessment of cardiovascular safety, searches were done for 'embolic and thrombotic events' (including the AESIs 'deep vein thrombosis' and 'pulmonary embolism'), 'cardiovascular events of interest', 'all-cause mortality', and 'Torsades de pointes/QT prolongation'.

No events of 'deep vein thrombosis', 'pulmonary embolism', 'cardiovascular events of interest' or 'Torsades de pointes/QT prolongation' were reported with delgocitinib cream in the Exposure pool.

In total, 6 subjects had events captured by one of the 4 safety focus area searches: 2 subjects while on delgocitinib cream 20 mg/g and 4 subjects while on cream vehicle/off-treatment or during safety follow-up. 1 of these events, a fatal myocardial infarction (MI) [off-treatment, safety follow-up] was captured by the 'cardiovascular events of special interest' search, the 'all-cause mortality' search and the 'embolic and thrombotic events' search.

QTc study (study 1409)

A separate Phase 1 clinical study was carried out to evaluate QTcF prolongation and proarrhythmic potential of orally administered delgocitinib. Study 1409 was a randomised, double-blind, placebo-controlled, parallel-group, single-dose, single-centre clinical study in healthy subjects. The trial was performed in 2 parts, each containing 2 dose cohorts. Each cohort consisted of 8 subjects receiving a single dose of delgocitinib and 2 subjects receiving placebo. The 2 dose levels evaluated in Part 1 were 6 mg (Cohort A) and 12 mg (Cohort B). The 2 dose levels evaluated in Part 2 were 3 mg (Cohort C) and 1.5 mg (Cohort D). 40 subjects were allocated to treatment (8 subjects receiving each of the 4 dose levels of delgocitinib and 8 subjects receiving placebo). All 40 subjects who received IMP (delgocitinib or placebo) were included in the safety analysis set and in the QT/QTc analysis set.

The primary analysis was based on concentration-QTc modelling of the relationship between the delgocitinib plasma concentrations and change from baseline in QTcF (ΔQTcF) with the intent to exclude an effect of placebo-corrected change from baseline in QTcF (ΔΔQTcF) >10 msec at clinically relevant plasma concentrations. The effect of delgocitinib on ΔΔQTcF, ΔΔHR, ΔΔPR, and ΔΔQRS was also evaluated at each post-dose time point ('by-time point' analysis). In addition, an analysis of categorical outliers was performed for changes in HR, PR, QRS, QTcF, T-wave morphology, and U-wave presence.

LS mean placebo-corrected ΔQTcF (ΔΔQTcF) ranged from -6.1 ms (at 6 hours post-dose in the 1.5 mg dose group) to 7.0 ms (at 12 hours post-dose in the 3 mg dose group), without an indication of dose-dependency. In the highest dose group (12 mg), the largest LS mean ΔΔQTcF was 5.2 ms, observed 4 hours post-dose.

The estimated population slope of the concentration-QTc relationship was 0.016 msec per ng/mL (90% confidence interval [CI]: -0.0124–0.0442) with a treatment effect-specific intercept of 1.26 msec (90% CI: -0.971–3.482). Neither the treatment effect-specific intercept (p-value of 0.3444) nor the slope (p-value of 0.3405) was statistically significant at the 10% level.

The predicted ΔΔQTcF at the geometric mean peak delgocitinib concentration is shown in Table 41. An effect on ΔΔQTcF exceeding 10 msec can be excluded within the full observed range of plasma concentrations up to approximately 125 ng/mL.

Table 41 - Predicted ΔΔQTcF interval at geometric mean peak delgocitinib plasma concentration: Study 1409, PK/QTc analysis set

Treatment	Geometric mean C_{max} of delgocitinib (ng/mL)	ΔΔQTcF estimate (msec) (90% CI)
1.5 mg delgocitinib	7.2	1.37 (-0.82, 3.56)
3 mg delgocitinib	18.4	1.55 (-0.61, 3.70)
6 mg delgocitinib	51.0	2.07 (-0.23, 4.36)
12 mg delgocitinib	96.4	2.79 (-0.20, 5.78)

Based on a linear mixed-effects model with ΔQTcF as the dependent variable, time-matched delgocitinib plasma concentration as an explanatory variate, centred baseline QTcF as an additional covariate, treatment (active = 1 or placebo = 0) and time as fixed effects, and a random intercept per subject.

Abbreviations: CI = confidence interval; C_{max} = maximum observed plasma concentration; Δ = change from baseline; ΔΔ = placebo-corrected change from baseline; PK = pharmacokinetic(s); QTc = QT corrected for heart rate; QTcF = QT interval corrected using Fridericia's formula.

According to the applicant, delgocitinib did not have a clinically relevant effect on ECG parameters as assessed in the dedicated QTc study. Likewise, no clinically relevant differences in vital sign measurements (blood pressure and pulse) or ECGs were observed in any of the treatment groups from baseline to end of treatment in the Primary pool. There were no clinically relevant changes observed in vital signs and ECGs over time with delgocitinib cream 20 mg/g in study 1403. The applicant thereby concluded that, based on the sum of findings, safety data do not indicate cardiovascular effects or cardiovascular safety concerns for delgocitinib cream 20 mg/g.

Malignancies

In the Exposure pool, 'malignancies' were reported with a similar rate of events with delgocitinib cream 20 mg/g (0.55 events/PYO*100) and vehicle/off-treatment (0.40 events/PYO*100). Each malignancy PT was only reported once. Of the reported 5 malignancies, 4 were with delgocitinib cream 20 mg/g:

- In 1 subject on vehicle, the PT malignant melanoma occurred 3 months after the subject completed the 8-week study 1275 in subjects with AD.
- 2 subjects presented with signs or symptoms of a neoplasm on Day 1 of delgocitinib cream treatment (PT gallbladder adenocarcinoma and PT oesophageal cancer metastatic).

- 1 subject had PT basal cell carcinoma (NMSC) which presented outside the treatment area as a non-infiltrative hyperkeratotic lesion in ear 57 days after first dose of delgocitinib cream 20 mg/g treatment during study 1403. The subject's risk factors included gender, age 70-80 and a history of sun exposure. The subject received cream vehicle during study 1402.
- 1 subject had PT intraductal proliferative breast lesion identified on Day 286 of delgocitinib cream 20 mg/g treatment in study 1403. The first signs of the event were seen during a routine mammogram. Subject's risk factors for the event were the subject's age 55-60, gender (female) and class III obesity , as well as the subject's medical history of a basal cell carcinoma on the cheek. Subject is in menopause with no hormonal therapy reported.

According to the applicant, the time to onset of the 4 malignancies that were reported while on delgocitinib cream, was shorter than the known latency period for these types of malignancies. This supports that the carcinogenesis of these 4 events started prior to delgocitinib cream treatment was initiated. Taken together, the applicant considered that none of the malignancies suggested a causal relationship between delgocitinib cream and malignancy development, due to the brief time from first dose of delgocitinib cream to onset, the subjects' individual risk factors and the lack of a pattern in the type or timing of events.

Rare events

Six 'rare events' (non-serious) were reported in the Exposure pool (3 events of deafness, 2 events of angioedema, and 1 event of rhabdomyolysis); all 6 events were reported in the delgocitinib cream group and judged not to be related to IMP.

2 of the subjects with deafness recovered without change to IMP (duration of events: 5 and 12 days), whereas the outcome of the third is unknown. This subject had a medical history of 'hardness of hearing'.

A moderate event of angioedema was localised on 1 finger and resolved after 3 days without change to IMP. A mild event of face angioedema resolved within 1 day without change to IMP.

The mild event of rhabdomyolysis did not lead to any change in IMP (delgocitinib cream 3 mg/g). The subject had several confounding factors and relevant concomitant medication.

According to the applicant, there was nothing to suggest a causal relationship between delgocitinib treatment and any of the events and no safety concerns were identified based on a review of the 'rare events'.

2.5.8.3. Serious adverse event/deaths/other significant events

Deaths

Three deaths were reported in the delgocitinib cream clinical development program. The fatal events were reported in the extension study 1403 where all subjects received open-label delgocitinib cream 20 mg/g. All events were assessed as not related to treatment with delgocitinib cream 20 mg/g by both the investigator and sponsor.

Other SAEs

In the Primary pool, the reporting frequencies and rates of SAEs were similar for delgocitinib (1.5% of subjects, 5.4 E/PYO×100) and vehicle (1.7% of subjects, 7.6 E/PYO×100). Apart from one SAE of mild intensity in the delgocitinib group, SAEs were of moderate or severe intensity. None of the SAEs were considered related to IMP.

There was a numerical imbalance in the reporting of events within the SOC 'infections and infestations', with 4 subjects reporting 4 events (0.6 E/PYO×100) in the delgocitinib group and none in the vehicle group. There was no pattern in the types of serious infections reported, and none of the events were related to the treatment area. None of the SAEs within the SOC 'infections and infestations' were considered related to the IMP.

The SAE of epilepsy (reported term: epileptic crisis) was reported in a 20-30-year-oldsubject. The subject had a medical history of asthma, no past history of seizures but a family history of epilepsy or seizures . The event occurred 10 days after first dosing of delgocitinib, The SAE was considered of mild intensity and the subject was reported as having recovered from the event, and no action was taken with IMP.

The SAE of generalised tonic-clonic seizure (reported term: generalised tonic-clonic seizure) was reported in a 20-30-year-old subject. The event occurred 6 days after first administration of delgocitinib. No cause of the event could be identified. The SAE was considered of severe intensity, and the subject was reported as having recovered from the event. No immediate action was taken with IMP in relation to the SAE, but the subject decided to withdraw from the trial.

In the Intermittent use pool, 38 SAEs were reported for 30/638 subjects (4.7%) in the delgocitinib to on/off delgocitinib group (adjusted event rate 6.6 E/PYO×100). Similar to the Primary pool, the frequency and rate were highest in the SOC Infections and infestations; in this SOC, 12 SAEs were reported for 11/638 subjects (1.7%) in the delgocitinib to on/off delgocitinib group (adjusted event rate 2.1 E/PYO×100).

In the Exposure pool, the reporting rates of SAEs were similar for delgocitinib (38 subjects (2.8%), 6.0 E/PYO×100) and vehicle (14 subjects (1.5%), 7.3 E/PYO×100). Five events in the delgocitinib group were considered of mild intensity, while other SAEs were of moderate or severe intensity. None of the SAEs in either group were considered related to IMP.

2.5.8.4. Laboratory findings

Overall, changes in haematology and clinical chemistry laboratory parameters were minimal.

2.5.8.5. Safety in special populations

Effect of intrinsic factors on safety profile

The potential effects of various intrinsic factors (gender, age group, body weight and BMI, race and ethnicity, baseline IGA-CHE score, CHE subtype / main diagnosis, baseline renal and hepatic function) on the safety profile of delgocitinib cream 20 mg/g was examined in the Primary pool. According to the applicant, no clinically relevant differences between subgroups based on intrinsic factors related to demography, disease severity at baseline or disease history were observed based on an evaluation of AE summaries (overall proportions, number of events and rates, seriousness, and causality) and the AE distribution by most frequent SOCs and PTs for the Primary pool. The small sample sizes, limited exposures and low numbers of events in some of the subgroups should be noted.

Use during pregnancy and breast-feeding

Delgocitinib cream has not been systematically studied in pregnant women. Up to the safety data cut-off date (08-Feb-2024), 11 pregnancies were reported across the delgocitinib cream clinical development programme. All 11 pregnancies were reported in the CHE trials: 10 in subjects treated with delgocitinib cream 20 mg/g, 1

in a subject treated with alitretinoin, and none in subjects treated with cream vehicle. No pregnancies were reported in the AD trials. Pregnancy outcomes from female subjects who became pregnant during the clinical programme are presented in Table 42.

Table 42 - Birth outcomes for maternal exposure pregnancies to delgocitinib in the clinical development programme as of 08-Feb-2024

	Delgocitinib total	Vehicle total	Alitretinoin total
CHE	10	-	1
Normal new-born	2		
Elective abortion	3[a]		1
Spontaneous abortion	2		
Ongoing	3		

Abbreviations: CHE = chronic hand eczema.
Note: a = 1 elective abortion was due to congenital malformation of Down's syndrome/Trisomy 21.

The spontaneous abortions occurred at gestational week 9 + 6 days in a 30–40-year-old subject whose last exposure to delgocitinib was about 2 months before the spontaneous abortion, and at gestational week 4 in a 20-30 yearsubject whose last exposure to delgocitinib was about 1 month before the spontaneous abortion.

According to the applicant, these limited clinical data are insufficient to draw meaningful safety conclusions about the effects of delgocitinib during pregnancy; however, none of the individual pregnancy outcomes raised any safety concerns. Nevertheless, as a precautionary measure, the applicant considers it preferable to avoid the use of delgocitinib cream 20 mg/g during pregnancy.

Considering the minimal systemic exposure after topical application of delgocitinib cream in CHE subjects, no effects on breastfed newborns/infants are anticipated and the applicant thereby considers no restrictions warranted.

2.5.8.6. Safety related to drug-drug interactions and other interactions

No clinical interaction studies have been performed. According to the applicant, the potential for interaction with systemic medications is low due to the limited metabolism of delgocitinib, application to a limited body surface area (hands and wrists), and minimal systemic exposure resulting from topical application of delgocitinib.

Delgocitinib has not been evaluated in combination with other topical medications.

2.5.8.7. Discontinuation due to adverse events

In the Primary pool, AEs leading to withdrawal from trial and/or permanent discontinuation of IMP were reported at low frequencies; the frequency was higher in the vehicle group (4.5% of subjects, 16.2 E/PYO×100) than in the delgocitinib group (1.0% of subjects, 3.0 E/PYO×100). In the vehicle group, most discontinuations occurred due to skin problems, particularly hand dermatitis.

2.5.8.8. Post marketing experience

The applicant included a summary of the post-marketing experience with delgocitinib ointment. The data lock point (DLP) was 30-Dec-2022. The cumulative patient exposure from initial launch of delgocitinib ointment in Japan (June 2020) to DLP is shown in Table 43.

Table 43 - Estimated cumulative patient exposure to CORECTIM ointment from marketing experience

By strength	Number of patients
0.25%	150,640
0.5%	1,264,367
By age range (years)	
0-11	173,334
12-17	102,538
18-64	951,919
≥65	167,011

Cumulatively, 2,050 case reports containing 2,473 events have been received. The SOCs for which events were most frequently reported were General disorders and administration site conditions: 1,042 events (42.1%); Skin and subcutaneous tissue disorders: 625 events (25.3%); Injury, poisoning and procedural complications: 486 events (19.6%); Infections and infestations: 249 events (10.1%).

Table 44 - Summarises the PTs representing ⩾1% of all events reported for delgocitinib ointment

SOC	PT	Cumulatively through 30-Dec-2022 Number of events (% of all events) Total number of events: 2,473
General disorders and administration site conditions[a]	Application site erythema	298 (12.05)
	Application site irritation	167 (6.75)
	Application site acne	136 (5.50)
	Application site pruritus	102 (4.12)
	Therapeutic product effect incomplete	74 (2.99)
	Application site swelling	34 (1.37)
	Drug ineffective	26 (1.05)
Skin and subcutaneous tissue disorders	Dermatitis contact	183 (7.40)
	Erythema	91 (3.68)
	Dermatitis atopic	81 (3.27)
	Acne	54 (2.18)
	Skin irritation	53 (2.14)
	Pruritus	46 (1.86)
	Rosacea	26 (1.05)
Injury, poisoning and procedural complications	Off-label use	438 (17.70)
Infections and infestations	Eczema herpeticum	62 (2.51)
	Application site folliculitis	50 (2.02)
	Herpes simplex	40 (1.62)

[a] Including 65 reports (2.63%) of No adverse event.

According to the applicant, reports in SOC General disorders and administration site conditions were predominantly application site reactions (erythema, irritation, acne, pruritus, and swelling). Application site reactions such as erythema, irritation, acne, and pruritus are listed events in the Japanese label for delgocitinib ointment.

Events in SOC Skin and subcutaneous tissue disorders were primarily dermatitis related (dermatitis atopic (reported as flare or aggravation), dermatitis contact, rosacea (reported as rosacea-like dermatitis)) or symptoms associated with dermatitis (erythema, pruritus). In addition to dermatitis-related events, acne and skin irritation were frequently reported. Application site acne is listed in the Japanese label for delgocitinib ointment.

The most frequently reported event in SOC Injury, poisoning and procedural complications was off-label use. In 385 out of 438 cases, the off-label use was reported with no AE; the AEs reported with off-label use in the remaining 53 cases were all non-serious and the majority of the events related to listed reactions for delgocitinib ointment (application site reactions incl. erythema, irritation, folliculitis, and acne, and herpes infections incl. eczema herpeticum).

The most frequently reported events in SOC Infections and infestations were eczema herpeticum, application site folliculitis, and herpes simplex. Limited information, incl. medical and atopic history and course and timing of events, was available. Application site folliculitis, herpes simplex and eczema herpeticum are listed events in the Japanese label for delgocitinib ointment. The database also includes 1 serious and 10 non-serious cases of herpes zoster.

A cumulative summary tabulation of SAEs from post-marketing data sources and from non-interventional studies and other solicited sources, presented by SOC and PT, is displayed in Table 45. A total of 18 SAEs were reported in 16 case reports. Of these, 7 SAEs belonged to the SOC Infections and infestations, 5 SAEs to the SOC Skin and subcutaneous tissue disorders, 2 SAEs related to exposure during pregnancy, and 1 SAE belonged to the SOC Neoplasms benign, malignant, and unspecified. The 3 remaining SAEs were single PTs distributed across 3 different SOCs. 8 of the 18 SAEs were assessed by reporter as not related to delgocitinib. No fatal cases were reported.

Table 45 - Cumulative summary tabulation of SAEs for delgocitinib ointment from post-marketing data sources

Event SOC	Event PT	Spontaneous
Eye disorders	Glaucoma	1
Eye disorders Total		1
Infections and infestations	Eczema herpeticum	4
	Herpes ophthalmic	1
	Herpes zoster	1
	Impetigo	1
Infections and infestations Total		7
Injury, poisoning and procedural complications	Joint injury	1
Injury, poisoning and procedural complications Total		1
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Metastases to lymph nodes	1
Neoplasms benign, malignant and unspecified (incl cysts and polyps) Total		1
Pregnancy, puerperium and perinatal conditions	Abortion	1
	Abortion missed	1
Pregnancy, puerperium and perinatal conditions Total		2
Skin and subcutaneous tissue disorders	Dermatitis atopic	1
	Dermatitis contact	2
	Dermatitis exfoliative generalised	1
	Pemphigoid	1
Skin and subcutaneous tissue disorders Total		5
Surgical and medical procedures	Hospitalisation	1
Surgical and medical procedures Total		1
Grand Total		**18**

A separate search was conducted in the database to identify cases of special interest based on safety concerns associated with systemic JAK inhibition.

For malignancies, one post-marketing case report of malignancy was identified. A female of unknown age treated with delgocitinib ointment for AD reported development of metastases from breast carcinoma to lymph nodes (PT metastases to lymph nodes). The temporal relationship with administration of delgocitinib ointment and outcome of event was not reported, but the event led to discontinuation of CORECTIM treatment. The patient had a relevant medical history of breast adenocarcinoma; however, no details of the diagnosis incl. date, histological and molecular classification, and treatment management were reported.

No post-marketing case reports of non-melanoma skin cancer have been identified for delgocitinib ointment.

As regards serious infections:

- The 4 events of eczema herpeticum occurred in patients with AD aged 14 years to 37 years. Times to onset in the 3 case reports where this was provided were 8 days after start of delgocitinib ointment, 4.5 months after start of delgocitinib ointment, and 12 days after delgocitinib ointment

discontinuation. Co-suspect medication including corticosteroids and ciclosporin were reported in 2 of the cases.

- The events of herpes ophthalmic and herpes zoster were reported in one patient. The patient developed both events 4 days after discontinuation of delgocitinib ointment, however the reason for discontinuation was not reported. Concomitant medication included topical difluprednate, topical tacrolimus and oral olopatadine hydrochloride. Following the recovery of the events, delgocitinib ointment was re-initiated.
- The event of impetigo developed in a child of unknown age treated with delgocitinib ointment for AD. Treatment was initiated, switching from steroids, to improve periocular itching. Periocular impetigo developed approximately 8 months after start of treatment with delgocitinib ointment, temporally associated with onset of allergic reactions due to pollen season. The patient had a known medical history of allergy and concomitant medication included betamethasone valerate and ketotifen fumarate.

No post-marketing case reports of embolic or thrombotic events, cardiovascular events of interest or fatal case reports were identified.

As of 30-Dec-2022, a total of 24 pregnancies in 23 females treated with delgocitinib ointment have been reported in the post-marketing setting from solicited sources and as spontaneous reports. Very limited information has been provided, and for the majority of reports (22 out of 24 pregnancies), no AE or adverse outcome were reported with the pregnancy.

A total of 24 maternal exposure during breast feeding/exposure via breast milk in females treated with delgocitinib ointment have been reported in the post-marketing setting from solicited sources and as spontaneous reports. Very limited information was available, however, no associated AEs in infants/neonates were reported.

2.5.9. Discussion on clinical safety

Twelve clinical studies are included in the clinical development programme for delgocitinib cream. Six studies in participants with CHE, two studies in patients with AD, three studies in healthy subjects with cream formulation and one study with oral delgocitinib in healthy subjects. Full data for the open-label extension study 1403 were provided at the CHMP request. For evaluation of safety, the applicant has used all data available from the clinical development programme, with the primary focus being placed on data from the largest controlled studies (1273, 1401 and 1402). While it is noted that a minor change in formulation has occurred after study 1273, this is deemed of limited relevance for safety evaluation. A pooled approach was utilised, with distinct data pools created for assessment of different safety aspects. In line with the topical route of administration, special attention was paid to application site safety. In addition, specific safety aspects (such as phototoxicity and photosensitisation) were evaluated in dedicated studies in healthy subjects. Overall, the safety dataset is considered appropriate. However, it should be noted that study 1403 is a single-armed trial, and a true comparator for long-term treatment with delgocitinib cream 20 mg/g is thus not available.

Some Phase 2 studies have been carried out in indications other than AD and CHE, mostly with delgocitinib ointment (in inverse psoriasis; alopecia areata; eyebrow alopecia areata; discoid lupus erythematosus, and frontal fibrosing alopecia). Available data from these small studies did not raise safety concerns.

Overall, there are 1340 subjects exposed to any dose of delgocitinib in the Exposure pool; additional subjects have participated e.g. in the dedicated safety studies. In the Intermittent use pool, which can be considered to reflect the intended clinical use of delgocitinib, there are 612 subjects who were exposed to delgocitinib for 26 weeks or above, and 181 subjects with exposure for 52 weeks or above. As such, while the overall size of the safety database is limited, particularly in terms of longer-term exposures, it can be agreed to meet the general minimum requirements expressed in the ICH E1 Guideline.

With respect to demographic and baseline characteristics, there are no notable imbalances between treatment groups in the pooled dataset. Per the exclusion criteria, there is no data on skin safety in immunocompromised patients who are more prone to skin infections, especially if their skin barrier is compromised, as is the case in CHE. Dissemination of localised skin infection can occur if deficits in secondary host defences (i.e., neutrophil function/number, cell mediated immunity, humoral immunity) exist. Nevertheless, given that delgocitinib cream 20 mg/g has minimal systemic exposure which decreases over time likely due to beneficial effects of the IP on skin barrier; systemic effects, including immunosuppression, are thus unlikely.

Moreover, evaluation of safety data in subjects with local skin infections on the hands and subjects with a neutrophil count below the LLN at baseline or with an AE of neutropenia reported during the trial did not raise additional safety concerns.

Adverse events and determination of ADRs

During the 16-week vehicle-controlled period, the proportion of subjects with TEAEs was similar between delgocitinib cream and cream vehicle group (48% versus 49%). The majority (about 98%) of TEAEs were of mild or moderate intensity. For both groups, a similar proportion of patients reported SAEs (1.5% versus 1.7% for delgocitinib cream versus cream vehicle), with few events and no fatalities in either group. Similar proportions of subjects reported severe AEs (2.1% versus 2.7% for delgocitinib cream versus cream vehicle group), with higher rates of events reported for cream vehicle group (9.47 versus 15.81 for delgocitinib cream versus cream vehicle group). The overall number of AEs leading to withdrawal or permanent discontinuation of study drug was low, without clustering of events at PT level. The proportion of subjects who withdrew from trial or permanently discontinued the IMP was low, albeit higher in cream vehicle group (1% in delgocitinib cream vs 4.5% in cream vehicle group) and mainly driven by PT Hand dermatitis which could indicate worsening of CHE in these subjects. No application site reactions led to withdrawal or permanent discontinuation of IMP which points to a good overall tolerability of the drug.

The most commonly reported AEs were in the SOC's Infections and infestations and Skin and subcutaneous tissue disorders. The most common infectious AEs comprised COVID-19 and nasopharyngitis; as regards skin-related AE's, the most common PTs were hand dermatitis and eczema. The analysis of common AEs supports an overall favourable safety profile. In line with the limited absorption and low systemic exposure, there seems to be overall limited potential for systemically mediated adverse effects, even though some AEs which could be referred to as systemic were assessed as related to the IMP, including headache (7 events), alopecia, hepatic enzymes increased, cough, mood swings, heavy menstrual bleeding, haematuria, among others.

The applicant's approach into determination of ADR's to be included in the SmPC is overall agreed. The applicant is proposing 'Application site disorders' to be tabulated as an ADR in Section 4.8 of the SmPC. It is noted that the reporting rate for these disorders is in fact higher for vehicle than delgocitinib, but in light of the route of administration and the mechanistic plausibility (considering that the cream is an integral component of the drug product), the inclusion of this ADR is endorsed.

AESIs and safety focus areas

Eczema herpeticum (EH), deep vein thrombosis (DVT) and pulmonary embolism (PE) were predefined as 'Adverse Events of Special Interest' (AESI). It is unclear why the applicant did not predefine additional AESIs such as major adverse cardiovascular events (MACE), malignancy, serious infections and all-cause mortality, in line with other products in the class. However, the predefined 'Safety focus areas' include most of these safety events. No AESIs of PT EH were reported in the Primary pool (CHE). In the Long-term safety pool, 1 subject with a medical history of AD, reported PT EH (RT eczema herpeticum right neck and b/c eyelids) judged by the investigator as possibly related to IMP. Delgocitinib was discontinued for 4 days, and the event resolved after 20 days with antiviral treatment. No AESIs of DVT or PE were reported with delgocitinib cream.

Dermal safety was one of the main safety focus areas assessed considering the topical application of the IMP. The rates of 'local skin infections' were higher in the cream vehicle group than delgocitinib cream group in the Primary pool (3.5 E/PYO x100 versus 2.3 E/PYO x100, respectively). Reported PTs included 'skin bacterial infection', 'skin infection' and 'application site infection' which are rather unspecific. All the events were non-serious, of mild or moderate severity with the median duration of a few days longer with delgocitinib cream (15.0 days) than with cream vehicle (12.5 days). 'Application site reactions' were reported by a higher proportion of subjects and at a higher rate with cream vehicle (2.5% of subjects, 10.4 E/PYO×100) than with delgocitinib cream 20 mg/g (1.0% of subjects, 4.1 E/PYO×100) suggesting that the events were caused by the excipients in the cream formulations rather than the delgocitinib API. Two events of 'acnes' (PTs acne and dermatitis acneiform) were reported in delgocitinib cream group, neither of which were lesional/perilesional. No PTs of skin atrophy were reported. Local tolerability, assessed by subjects in terms of 'worst stinging/burning in connection with IMP applications during the last week' as well as the investigators assessment of suspected local skin reactions and IMP patch test evaluation, was acceptable and similar between groups. In addition, no indication of phototoxic or photoallergic potential of delgocitinib cream or cream vehicle were observed in healthy subjects.

The most common 'allergic reactions' in both treatment groups were eczema, dermatitis contact, and hand dermatitis, all of which were reported with higher proportions and rates with cream vehicle than delgocitinib cream. Considering the main diagnosis of the subjects is CHE (16% of them also with AD) and the high proportion of those with a history of atopy (39%), it is not surprising that most of the reported allergic reactions events is from SOC 'skin and subcutaneous disorders'.

The proportion of subjects and rate of events reported for 'serious or severe infections' was higher with delgocitinib cream (1.0% of subjects, 3.6 E/PYO×100) than cream vehicle (0.6% of subjects, 1.9 E/PYO×100). All the events reported were single events except gastroenteritis which was reported in 2 subjects in delgocitinib group (and 0 in cream vehicle group). There was no apparent pattern in the type of events reported and the timing of onset. In the Long-term safety pool, most of the events were single events except 2 events of COVID-19, gastroenteritis and peritonsillar abscess each in delgocitinib group. It can be agreed that the risk with delgocitinib currently seems limited. Nevertheless, the applicant has committed to closely follow the topic of 'serious or severe infections' as part of routine pharmacovigilance activities and report the findings in future PSURs.

Low rates of AEs without clustering at PT level indicate no concerns regarding renal and hepatic safety.

Six AEs related to cardiovascular safety were reported, 2 while on delgocitinib and 4 while on vehicle/off-treatment. No safety concerns are raised. Few AEs were reported across groups in regard to ECG evaluation in the Investigations and Cardiac disorders SOC with similar rates between groups. Study 1409, designed to evaluate the QTcF prolongation and proarrhythmic potential of delgocitinib, did not raise any safety concerns

regarding a clinically relevant effect on ECG parameters, including QTcF, HR, PR interval, and QRS duration, based on either changes from baseline or categorical analyses.

Numerically there was a higher number of malignancies in delgocitinib cream group than vehicle group in the Exposure pool (4 vs 1, respectively), however with similar rates between groups. Reported PTs were Gallbladder adenocarcinoma, Intraductal proliferative breast lesion, Oesophageal cancer metastatic and Basal cell carcinoma in the delgocitinib cream group and Malignant melanoma in cream vehicle group. The only 'non-melanoma skin cancer' (basal cell carcinoma) had a time to onset of 57 days, rendering a causal relationship with delgocitinib unlikely. Overall, no safety risks regarding malignancies have been identified; however, the lengths of exposure limit the strength of the currently available evidence base. Furthermore, non-melanoma skin cancer at long-term use has been identified as an important potential risk for other JAK inhibitors. The applicant has emphasised a prominent role of systemic immunosuppression (as opposed to a local effect) in the pathogenesis of NMSC's, and while the overall size of the database for delgocitinib cream has limitations in terms of overall size and treatment durations, as pointed out above, it is noted that there are currently no reported cases of NMSC plausibly associated with delgocitinib cream, and the same appears to hold true also within the post-marketing data for delgocitinib ointment. However, while the extent of systemic exposure to delgocitinib may indeed be limited, a local cause cannot be ruled out, and currently presented data on long-term exposure is limited while the development of NMSC may have a long latency. Therefore, a general warning regarding a potential risk of NMSC, advising patients on periodic skin examination, was considered warranted in the SmPC by the CHMP and was agreed by the applicant. In addition, the applicant also agreed to further address the important potential risk of NMSC at long-term use post-approval i.e. a category 3 PASS will be conducted, see RMP.

Three 'rare events' of PT deafness were reported, 2 with delgocitinib cream 20 mg/g and one with delgocitinib cream 1 mg/g. Given the low proportion of subjects (0.2%) and rate of events (0,48), and no safety signals from preclinical studies, no safety issues are raised. However, it is noteworthy that all the events occured in subjects on delgocitinib cream with no events in the cream vehicle group. At the CHMP request, the applicant agreed to monitor cases of deafness as part of routine pharmacovigilance activities, and report the findings in future PSURs.

Consistent with the low expected systemic exposure, it can be overall agreed that currently available data does not point to topical delgocitinib being associated with safety concerns previously associated with orally administered JAK inhibitors.

Serious adverse events and deaths

Three fatal adverse events were reported within the development programme. All events were assessed as not related to treatment with delgocitinib cream by both the investigator and sponsor.

The occurrence of SAEs is considered to be overall low, albeit higher in the delgocitinib cream (n=8, 1.8%) compared to the cream vehicle group (n=1, 0.4%) in the 16-week vehicle-controlled period. All SAEs were single events within all SOCs, except for PT dermatitis atopic in the cream vehicle group. In the Exposure pool, there seems to be no clustering of SAEs.

There were two events of seizure disorders among subjects on delgocitinib vs. none in the placebo group. Although it can be agreed with the applicant that they currently do not constitute a safety concern, in light of the low expected systemic exposure and the lack of a plausible mechanistic explanation, the applicant agreed to monitor cases of seizure disorders as part of routine pharmacovigilance activities, and report the findings in future PSURs.

Laboratory parameters and vital signs

Changes in laboratory parameters were overall very limited, supporting the view that the low exposure is unlikely to result in significant systemic effects at the population level.

Special populations

Safety data in elderly are limited, with low number of elderly patients (>65) in vehicle-controlled CHE studies (n=82, 7,7% overall). Application site reactions were more often reported in elderly than in younger age groups. A slightly higher systemic exposure was observed in the elderly. This can be partly explained by the disruption of epidermal barrier function with aging. Overall, no safety concerns specific to elderly patients are evident.

There were 21 subjects (15 in delgocitinib 20 mg/g group and 6 in cream vehicle group) with moderately impaired renal function, in whom a slightly higher systemic exposure to delgocitinib was observed. No subjects with severely impaired renal function/end stage renal disease were enrolled in the studies. In the SmPC section 4.2 it is stated that in hepatic and renal impairment 'Dose adjustment is not recommended due to the minimal systemic exposure of topically applied delgocitinib'. However, given the uncertainties regarding patients with severe hepatic and renal impairment, the applicant agreed to amend the SmPC text to reflect that no studies with delgocitinib cream have been performed in patients with severe hepatic and renal impairment.

Use during pregnancy and breast-feeding

Although there is currently no evidence of harmful effects when delgocitinib is used during pregnancy or breast-feeding, the experience to date is extremely limited. Animal studies have shown that delgocitinib is embryotoxic and foetotoxic at doses high in excess of the human exposure. Up to the safety data cut-off date (08-Feb-2024), 11 pregnancies were reported across the delgocitinib cream clinical development programme. All 11 pregnancies were reported in the CHE studies: 10 in subjects treated with delgocitinib cream, 1 in a subject treated with alitretinoin, and none in subjects treated with cream vehicle. Of the 11 pregnancies, two have resulted in normal live births, three pregnancies ended in elective abortion, 2 in spontaneous abortions and 3 were ongoing at the DBL.

While no safety concerns are raised based on the data provided on reported pregnancy outcomes, the experience is extremely limited. Based on the data presented, it can overall be agreed that the systemic absorption of delgocitinib cream is very low, and that the resulting safety margins are sufficient such that use during pregnancy does not need to be contraindicated and use during breast-feeding does not require restrictions. Nevertheless, as a precautionary measure, the applicant considers it preferable to avoid the use of delgocitinib cream during pregnancy. This is supported by CHMP.

Regarding breast-feeding, delgocitinib was present in the milk of lactating rats. The SmPC states that based on the minimal systemic exposure after topical application of delgocitinib, no effects on the breast-fed newborns/infants are anticipated and delgocitinib can be used during breast-feeding. When a breast-feeding mother is using delgocitinib cream, there seems to be a relevant risk of the infant being accidentally exposed through skin contact during breast-feeding or caring for the baby. The applicant therefore agreed to include in the Product Information instructions on appropriate precautionary measures to avoid such accidental exposure.

Drug-drug interactions

No formal clinical interaction studies have been performed, and in light of the limited systemic exposure, this is considered acceptable. The lack of combination studies with other topical medications is reflected in the SmPC section 4.5.

From the safety database all the adverse reactions reported in clinical trials have been included in the Summary of Product Characteristics.

2.5.10. Conclusions on the clinical safety

The safety profile of delgocitinib cream was assessed using all data available from the clinical development programme. The size of the database is overall relatively limited, particularly when it relates to longer-term exposures but is nevertheless considered to meet the general minimum requirements expressed in ICH E1 Guideline and is agreed to enable a sufficient assessment of the general safety profile. While there are limited data as regards safety in elderly patients, no specific safety concerns have been identified.

Overall, the topical formulation appeared to be well tolerated, and no significant safety concerns were identified. This is consistent with the low systemic exposure and consequent expectation of a limited potential for significant systemically mediated adverse effects.

The risk of NMSC at long-term use cannot presently be ruled out with sufficient certainty due to a possible role of local immunosuppression in its pathophysiology. A general warning in section 4.4 of the SmPC was therefore deemed warranted and a PASS will be conducted to further address this risk post-approval (see RMP).

The relevant safety results from the development programme have been included in the SmPC.

2.6. Risk Management Plan

2.6.1. Safety concerns

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

2.6.2. Pharmacovigilance plan

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

2.6.3. Risk minimisation measures

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

2.6.4. Conclusion

The CHMP considers that the risk management plan version 0.3 is acceptable.

2.7. Pharmacovigilance

2.7.1. Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

2.7.2. Periodic Safety Update Reports submission requirements

The requirements for submission of periodic safety update reports for this medicinal product are set out in the Annex II, Section C of the CHMP Opinion. The applicant did request alignment of the PSUR cycle with the international birth date (IBD). The IBD is 23.01.2020. The new EURD list entry will therefore use the IBD to determine the forthcoming Data Lock Points.

2.8. Product information

2.8.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

2.8.2. Labelling exemptions

A request to omit certain particulars from the labelling as per Art.63.3 of Directive 2001/83/EC has been submitted by the applicant and has been found acceptable by the QRD Group for the following reasons:

Due to space constraints, the QRD Group agreed with the proposed omission of the following particulars on the 15 g tube:

- Full MAH name and address (replaced by MAH logo displaying the company name),
- '1 g of cream contains 20 mg of delgocitinib',
- List of excipients.

The particulars to be omitted as per the QRD Group decision described above will however be included in the Annexes published with the EPAR on EMA website, and translated in all languages but will appear in grey-shaded to show that they do not have to be included on the printed materials.

2.8.3. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Anzupgo (Delgocitinib) is included in the additional monitoring list as it contains a new active substance.

Therefore, the summary of product characteristics and the package leaflet includes a statement that this medicinal product is subject to additional monitoring and that this will allow quick identification of new safety information. The statement is preceded by an inverted equilateral black triangle.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

Hand eczema (HE) is a heterogeneous chronic inflammatory skin disorder located anywhere on the hands and wrists. Chronic HE refers to hand eczema which persists for more than 3 months or returns twice or more often within 12 months. CHE shows variable morphology, typically with more erythema, oedema, vesicles, and oozing in the acute phase, as well as erythema, xerosis, scales, lichenification, hyperkeratosis, and fissures in the chronic phase. CHE patients may report that certain triggers including skin irritants, proteins, and contact allergens elicit or worsen their disease. They typically experience itch, pain, and burning sensation, which can impede the performance of activities of routine daily living, work, and recreation.

The initial indication applied for delgocitinib was:

- treatment of moderate to severe chronic hand eczema (CHE) in adults who have had an inadequate response to, or for whom topical corticosteroids are not advisable.

The indication agreed by the CHMP is:

- treatment of moderate to severe chronic hand eczema (CHE) in adults for whom topical corticosteroids are inadequate or inappropriate.

3.1.2. Available therapies and unmet medical need

Basic management strategies in CHE include education, avoidance of clinically relevant allergens, protection from irritants, and frequent use of emollients. Along with emollients, the first line medical treatment is TCS of at least moderate potency to control acute flares of HE. Long-term intermittent use of TCS may be also considered. Although TCS are very effective in the short term, they inhibit repair of the stratum corneum and may cause skin atrophy and interfere with recovery in the long-term.

Currently, there are no approved products 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. Alitretinoin is teratogenic, and therefore pregnancy prevention measures are required for women of child-bearing potential.

Hence, there is an unmet medical need for new effective and safe therapies for moderate to severe CHE.

3.1.3. Main clinical studies

The efficacy evaluation of delgocitinib in CHE is mainly based on the following studies:

- The pivotal studies 1401 and 1402
- Long-term extension study 1403

The pivotal studies 1401 and 1402 were randomised, double-blind, vehicle-controlled studies in subjects with moderate to severe CHE. The long-term extension study 1403 was a non-controlled, open-label extension study in subjects who completed 16 weeks of treatment in studies 1401 and 1402.

In studies 1401 and 1402, subjects were treated with delgocitinib cream 20 mg/g or cream vehicle twice daily for 16 weeks. In study 1403, subjects were treated with delgocitinib cream 20 mg/g as needed for 36 weeks.

The primary endpoint in the pivotal studies 1401 and 1402 was IGA-CHE TS, defined as IGA-CHE score of 0 (clear) or 1 (almost clear) with at least a 2-step improvement from baseline to Week 16. The key secondary endpoints were HECSI-75, HECSI-90, percentage change in HECSI score from baseline, reduction of HESD itch score, reduction of HESD score, reduction of HESD pain score, reduction of DLQI score, change in HESD itch score from baseline, change in HESD score from baseline, change in HESD pain score from baseline, change in HEIS score from baseline, change in HEIS PDAL score from baseline, and change in DLQI score from baseline.

3.2. Favourable effects

A significantly greater percentage of subjects achieved the primary endpoint IGA-CHE TS at week 16 in the delgocitinib groups compared to the vehicle group in both pivotal studies. Based on the primary analysis of the primary estimand (composite), 19.7% and 29.1% of subjects treated with delgocitinib 20 mg/g cream

twice daily vs. 9.9% and 6.9% of subjects treated with the vehicle achieved IGA-CHE TS in studies 1401 and 1402, respectively. This translated into a 9.8% (95% CI 3.6, 16.1, p=0.006) and 22.2% (95% CI 15.8, 28.5, p<0.001) estimated treatment difference from placebo in studies 1401 and 1402. The robustness of the primary outcome was demonstrated by the supplementary estimands considering the potential impact of COVID-19 on the result (pandemic-modified composite) and by evaluating the treatment effect regardless of rescue treatment or permanent discontinuation (treatment policy), as well as several sensitivity analyses, which all led to similar results as the primary analysis.

The key secondary endpoints supported the effects seen in the primary endpoint. In terms of objective signs of CHE, the proportion of subjects achieving HECSI-75 and HECSI-90, as well as the percentage change in HECSI from baseline at week 16 were significantly higher in the delgocitinib group compared to the vehicle group. In the assessment of subjective signs and symptoms of CHE, significantly greater proportion of subjects had ≥4-point reduction from baseline in the weekly average HESD itch score, HESD pain score and HESD score. The results for the change from baseline at week 16 in HESD itch score, HESD pain score and HESD score were also in favour of delgocitinib over vehicle. With regards to subjective assessment of quality of life, delgocitinib demonstrated superiority over vehicle in reduction of DLQI score ≥4 points from baseline to week 16, as well as change from baseline to week 16 in DLQI score, HEIS score and HEIS PDAL score. Overall, for all key secondary endpoints included in the multiplicity adjusted testing hierarchy, delgocitinib demonstrated a statistically significant improvement over vehicle.

The results demonstrate that delgocitinib has a clinically relevant benefit on moderate to severe CHE, as evaluated by ClinROs (investigator-rated severity and extent of CHE) and PROs (subject-rated signs and symptom and CHE-related quality of life).

In terms of long-term efficacy, in subjects with incomplete response at week 16 (i.e. subjects not reaching IGA-CHE TS, but showing some improvement), further improvement was seen in all subgroups independent of CHE subtype, severity or CHE duration. The results from the extension study further showed that treatment responses (IGA-CHE score of 0 or 1) can be regained after re-initiation of the delgocitinib treatment in approximately the same time as for the initial treatment. Median time to regain IGA-CHE score of 0 or 1 was 8 weeks. Clinically relevant improvement (week 2) in mean daily HESD pain and itch scores were also observed. Presented clinical data on the time to losing and time to regaining IGA-CHE treatment response (after first and subsequent re-initiations) support as-needed use of delgocitinib.

3.3. Uncertainties and limitations about favourable effects

Delgocitinib cream has not been evaluated in combination with other topical medicinal products and co-application on the same skin area is not recommended. Consequently, SmPC section 4.5 was revised to highlight that co-application on the same skin areas is not recommended.

3.4. Unfavourable effects

The main unfavourable effects are local tolerability issues. In the Primary pool, severe stinging/burning upon application at Week 1 was reported by 4.9% of subjects on delgocitinib vs. 11.1% of subjects on vehicle. At Week 4, severe stinging/burning upon application was reported by 2.4% of subjects on delgocitinib vs. 5.0% of subjects on vehicle, and at the end of treatment, severe stinging/burning upon application was reported by 0.3% of subjects on delgocitinib vs. 1.2% of subjects on vehicle.

Serious or severe infections were reported for 7 subjects (1.0%: 3.6 E/PYO×100) with delgocitinib vs. 2 subjects (0.6%: 1.9 E/PYO×100) with vehicle in the Primary pool; and for 20 subjects (2.3%; 3.6 E/PYO×100) in delgocitinib group vs. 7 subjects (0.8%; 3.2 E/PYO×100) in vehicle/off-treatment group in the Long-term pool.

There were no events of herpes zoster in either group in the Primary pool. However, herpes zoster was reported in 2 subjects (0.2%; 0.4 E/PYOx100) on delgocitinib vs. 1 subject (0.1%; 0.6 E/PYOx100) off treatment (16 days since last delgocitinib) in the Long-term pool. In addition, there were 1 serious and 10 non-serious cases in Japanese post-marketing data.

Hypertension was reported for 7 subjects (1.0%; 3.1 E/PYO×100) with delgocitinib vs. 0% of subjects with vehicle in the Primary pool.

Elevated lipid parameters were reported for 15 subjects (2.1%, 8.1 E/PYO×100) with delgocitinib vs 5 subjects (1.4%, 6.5 E/PYO×100) with vehicle in the Primary pool.

Lymphocytopenia was reported for 3 subjects (0.4%; 1.4 E/PYO×100) with delgocitinib vs. 0% of subjects with vehicle in the Primary pool.

Three 'rare events' of PT deafness were reported, 2 with delgocitinib cream 20 mg/g and one with delgocitinib cream 1 mg/g.

There were two events of seizure disorders among subjects on delgocitinib vs. none in the placebo group.

Animal studies have shown that delgocitinib is embryotoxic and foetotoxic at doses high in excess of the human exposure. Regarding breast-feeding, delgocitinib was present in the milk of lactating rats.

3.5. Uncertainties and limitations about unfavourable effects

The main uncertainties are related to the limited size of the safety database, especially as it relates to longer-term effects. While significant outright safety concerns have not been identified, many of the unfavourable effects associated with systemically administered JAK inhibitors are infrequent and some are associated with long latencies. In addition, they are most relevant in frail populations (elderly patients, smokers, patients with a history of malignancy) that appear to have been represented only to a limited extent in the development programme. As such, the power of the database for detection of such effects can be considered quite low. Nevertheless, taking into account the low systemic exposure following topical application of delgocitinib cream, inclusion of specific warnings in the SmPC of delgocitinib cream was not considered needed by the CHMP.

While it can be agreed that the risk with delgocitinib cream currently seems limited, the applicant agreed to closely monitor the following safety topics: 'serious or severe infections' and 'seizure', 'deafness' in future PSURs.

While based on the data presented, it can overall be agreed that the systemic absorption of delgocitinib cream is very low, and that the resulting safety margins are sufficient such that use during pregnancy does not need to be contraindicated and use during breast-feeding does not require restrictions, as a precautionary measure, it is preferable to avoid the use of delgocitinib cream 20 mg/g during pregnancy.

Although based on the minimal systemic exposure after topical application of delgocitinib, no effects on the breast-fed newborns/infants are anticipated and delgocitinib can be used during breast-feeding, when a breast-feeding mother is using delgocitinib cream, there seems to be a relevant risk of the infant being

accidentally exposed through skin contact during breast-feeding or caring for the baby. Therefore, the product information was updated to include instructions on appropriate precautionary measures to avoid such accidental exposure.

Due to a potential role of local immunosuppression in the pathophysiology of NMSC, the limited systemic absorption of delgocitinib may not be sufficient to mitigate the important potential risk of NMSC at long-term use. As such, the limited extent of the safety database, particularly as it related to long-term exposures, is a relevant limitation. Therefore, a general warning regarding a potential risk of NMSC, advising patients on periodic skin examination, was included in the SmPC. In addition, this risk will be followed-up post approval (see RMP).

3.6. Effects Table

Table 46 - Effects Table for delgocitinib for the treatment of moderate to severe CHE in adults for whom topical corticosteroids are inadequate or inappropriate.

Effect	Short Description	Unit	Treatment	Control	Uncertainties/ Strength of evidence	References
Favourable Effects						
IGA-CHETS at week 16	IGA-CHE score of 0 or 1 with ≥2-step improvement from baseline	%	delgocitinib 20 mg/g 1401: 19.7 1402: 29.1	 9.9 6.9	Superiority to vehicle shown in both pivotal studies	Pivotal studies 1401 and 1402
HECSI-90 at week 16	≥90% improvement in HECSI from baseline	%	1401: 29.5 1402: 31.0	12.3 8.8	Superiority to vehicle shown in both pivotal studies	Pivotal studies 1401 and 1402
HESD itch score at week 16	≥4-point improvement from baseline	%	1401: 47.1 1402: 47.2	23.0 19.9	Superiority to vehicle shown in both pivotal studies	Pivotal studies 1401 and 1402
HESD pain score at week 16	≥4-point improvement from baseline	%	1401: 49.1 1402: 48.6	27.5 22.7	Superiority to vehicle shown in both pivotal studies	Pivotal studies 1401 and 1402
Unfavourable Effects						
Local tolerability	Proportion of subjects reporting severe stinging/burning	N (%)	Week 1: 4.9% Week 4: 2.4%	Week 1: 11.1% Week 4: 5.0%		Primary pool
Serious or severe infections	Subjects with serious or severe infection AE	N (%; R)	7/691 (1.0%; 3.6)	2/371 (0.6%; 1.9)		Primary pool

Abbreviations: AE, adverse event; N, number of subjects, R, adjusted event rate (events per 100 patient years of observation); SAE, serious adverse event

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

The current treatment options for subjects with moderate to severe CHE, for whom topical corticosteroids are inadequate or inappropriate, are very limited. Therefore, new therapies that are effective and safe in long term treatment in this difficult-to-treat population are needed. Overall, the clinical development programme for delgocitinib cream in CHE in adults is robust. Delgocitinib has clinically relevant benefits in the treatment of moderate to severe CHE in adults for whom topical corticosteroids are inadequate or inappropriate. Importantly, the favourable effects have been demonstrated both by ClinROs (investigator-rated severity and extent of CHE) and PROs (subject-rated signs and symptom and CHE-related quality of life).

In terms of the size of the treatment effect, approximately 20-30% subjects (vs. 7-10% in vehicle group) achieved IGA-CHE TS, which can be regarded as a strict criterion for a treatment response. Therefore, it should be noted that clinically relevant improvements in the two key symptoms of CHE, i.e. pain and itch (defined by ≥4-point reduction in HESD itch score and HESD pain scores at week 16), was achieved by 47-49% of subjects receiving delgocitinib (vs. 20-28% in vehicle group). In terms of the onset of the efficacy, the treatment response to delgocitinib was observed early on, particularly for the subject-rated signs and symptoms, and QoL. Not all subjects seem to benefit from delgocitinib treatment, but the long-term efficacy data support continuation of treatment twice daily in subjects with incomplete response at week 16 (i.e. subjects not reaching IGA-CHE TS, but showing some improvement) until the skin is clear or almost clear. Further, data on the time to losing and time to regaining IGA-CHE treatment response (after first and subsequent re-initiations) support as-needed use of delgocitinib.

The unfavourable effects appear to be mostly limited to local tolerability issues; some subjects on both delgocitinib and vehicle reported severe stinging/burning upon application of the cream. As the proportion of such subjects is even lower with delgocitinib than vehicle, the effect appears to be linked to the formulation rather than specifically to the active ingredient. Application site reactions is the only ADR for delgocitinib cream.

The indication being applied for implies that patients may use the product for long periods; moreover, although the medical significance of CHE is not disputed, the treatment is not addressing a fatal or life-threatening condition. A relatively benign safety profile is expected, and safety concerns associated with orally administered JAK inhibitors can be excluded given the limited systemic exposure and the safety data currently available. Based on the lack of long-term follow-up and due to a possible contributory role of local immunosuppression, SmPC section 4.4 was updated to add a warning regarding a potential risk of NMSC, advising patients on periodic skin examination. In addition, a PASS will be conducted to further characterise this risk in the post-approval setting.

3.7.2. Balance of benefits and risks

The primary endpoint was met, which was supported by key secondary endpoints. Primary and secondary outcomes support the clinical relevance of the treatment effect. The safety profile of delgocitinib is overall acceptable and considered manageable. The balance of benefits and risks of Anzupgo for the treatment of moderate to severe CHE in adults is positive in the following indication:

- Anzupgo is indicated for the treatment of moderate to severe chronic hand eczema (CHE) in adults for whom topical corticosteroids are inadequate or inappropriate (see section 5.1).

3.7.3. Additional considerations on the benefit-risk balance

Third party intervention

Patient representatives provided patient/carer views on the key symptoms, current treatment options and unmet needs in the CHE. They called for a multidisciplinary approach to treat the disease and reminded that CHE can be hugely debilitating, both physically and emotionally, and should be not only evaluated "in the hands". Impact of CHE on quality of life was underlined.

Healthcare professionals provided their experience on the CHE, emphasising the heterogenous nature of the disease with wide range of etiologies and clinical manifestations. They reviewed the current treatment options and pointed out several unmet needs in the management of CHE, including a standard validated severity scale for the use in the clinic with decision threshold guiding treatment.

The contribution from the patient representatives and healthcare professionals is highly appreciated and was taken into account by the CHMP.

3.8. Conclusions

The overall benefit/risk balance of Anzupgo is positive, subject to the conditions stated in section 'Recommendations'.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of Anzupgo is favourable in the following indication:

Anzupgo is indicated for the treatment of moderate to severe chronic hand eczema (CHE) in adults for whom topical corticosteroids are inadequate or inappropriate (see section 5.1).

The CHMP therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

Other conditions and requirements of the marketing authorisation

- **Periodic Safety Update Reports**

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

- **Risk Management Plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

New Active Substance Status

Based on the CHMP review of the available data, the CHMP considers that delgocitinib is to be qualified as a new active substance in itself as it is not a constituent of a medicinal product previously authorised within the European Union.

Refer to Appendix on new active substance (NAS).

5. Appendix

5.1. CHMP AR on New Active Substance (NAS) dated 25 July 2024