Cover Page

Study title:	A phase 3 clinical trial to evaluate efficacy and safety of twice-daily applications of delgocitinib cream 20 mg/g compared with cream vehicle for a 16-week treatment period in adolescents 12-17 years of age with moderate to severe chronic hand eczema (DELTA TEEN)
LEO Pharma number:	LP0133-1426
NCT number:	NCT05355818
Date:	14-Jan-2025

Statistical analysis plan

LP0133-1426

A phase 3 clinical trial to evaluate efficacy and safety of twice-daily applications of delgocitinib cream 20 mg/g compared with cream vehicle for a 16-week treatment period in adolescents 12-17 years of age with moderate to severe chronic hand eczema (DELTA TEEN)

Phase 3 – efficacy/safety

Design of trial:

A randomised, double-blind, vehicle-controlled, parallel-group, multi-site trial

LEO Pharma A/S	**Trial ID:**	**LP0133-1426**
	Date:	**14-Jan-2025**
	Version:	**1.0**

Statistical analysis plan statement

Approval statement, LEO Pharma A/S

Electronic signatures made within LEO Pharma Clinical Vault are legally binding equivalent of traditional handwritten signatures. The following persons have approved this statistical analysis plan by using electronic signatures as presented on the last page of this document:

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Biostatistics lead, Medical Sciences

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QC Biostatistician, Biostatistics

Guidance documents

This statistical analysis plan is designed to comply with the standards issued by the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) E3 Structure and Content of Clinical Study Reports, E6 Good Clinical Practice, E9 Statistical Principles for Clinical Trials, and E9(R1) Addendum on Estimands and Sensitivity Analysis in Clinical Trials.

Table of contents

List of panels

List of abbreviations

AE	adverse event
AESI	adverse event of special interest
ADRG	analysis data reviewer's guide
CI	confidence interval
CMH	Cochran-Mantel-Haenszel
CTP	clinical trial protocol
CTR	clinical trial report
Define.xml	data definition document
DLQI	Dermatology Life Quality Index
ECG	Electrocardiogram
eCRF	electronic case report form
eDiary	electronic diary
FAS	full analysis set
HECSI	Hand Eczema Severity Index
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IE	intercurrent event
IGA	Investigator's Global Assessment
IGA-CHE	Investigator's Global Assessment scale 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 at least a 2-step improvement from baseline
IMP	investigational medicinal product
LOCF	last observation carried forward
MAP	Meta-Analytic-Predictive
MAR	missing at random
MedDRA	Medical Dictionary for Regulatory Activities
MI	Multiple imputation
PK	pharmacokinetic(s)
PRO	patient-reported outcome
PT	preferred term
SAE	serious adverse event
SAF	safety analysis set
SD	standard deviation

SOC	system organ class
TS	treatment success
WOCF	worst observation carried forward

Version history

The statistical analysis plan (SAP) for trial LP0133-1426 is based on the clinical trial protocol (CTP) version 2.0 dated 11-Dec-2023.

SAP version	Date	Change	Rationale
1.0		Not applicable	Original version

1 Introduction

The statistical analysis will be performed as outlined in the CTP version 2.0. This SAP, prepared before the unblinding of the trial, but after the blind review of the data, supplements the CTP and contains a more technical and detailed elaboration of topics related to the specification and implementation of the statistical analysis described in the CTP. The level of detail should enable the reader to reproduce all statistical analyses described in the SAP and the CTP.

Data handling decisions and derivation rules used in the analysis datasets are specified in the ADRG and Data Definition document (define.xml).

1.1 Trial objectives, estimands, and endpoints

Panel 1 presents the objectives and estimands for the primary, key secondary, and the secondary endpoints related to efficacy. The remaining secondary and exploratory objectives and endpoints are presented in Panel 2. For further details on how observed and missing data will be handled according to the IEs for the estimands and endpoints, see Panel 8.

Panel 1:Objectives and estimands for primary, key secondary, and secondary endpoints related to efficacy

Objectives	**Statistical approach**	**Estimands**				**Endpoints**
	Bayesian/ Frequentist	Estimand type (Primary/ Supplementary)	Interpretation	Intercurrent events and strategy	Population level summary	
Primary objective: To evaluate the efficacy of twice-daily applications of delgocitinib cream 20 mg/g compared with cream vehicle in the treatment of adolescents with moderate to severe CHE.	Bayesian and Frequentist.	Primary.	Response achieved without IEs.	Initiation of rescue treatment, permanent discontinuation of IMP. Composite strategy.	Risk difference.	**Primary endpoint:** • IGA-CHE TS at Week 16. (IGA-CHE TS refers to a score of 0 [clear] or 1 [almost clear] with a ≥2-step improvement from baseline).
	Frequentist.	Supplementary.	Response achieved regardless of IEs.	Initiation of rescue treatment, permanent discontinuation of IMP. Treatment policy strategy.		
	Bayesian and Frequentist.	Primary.	Response achieved without IEs.	Initiation of rescue treatment, permanent discontinuation of IMP. Composite strategy.	Risk difference.	**Key secondary endpoint:** • HECSI-90 at Week 16.
	Frequentist.	Primary.	Response achieved without IEs.	Initiation of rescue treatment, permanent discontinuation of IMP. Composite strategy.	Risk difference.	**Secondary endpoint:** • IGA-CHE TS at Weeks 2, 4, 8, and 12.

Objectives	Statistical approach	Estimands				Endpoints
	Bayesian/ Frequentist	Estimand type (Primary/ Supplementary)	Interpretation	Intercurrent events and strategy	Population level summary	
Secondary objectives: To evaluate the health-related quality of life of twice-daily applications of delgocitinib cream 20 mg/g compared with cream vehicle in the treatment of adolescents with moderate to severe CHE.	Bayesian and Frequentist.	Primary.	Response achieved without IEs.	Initiation of rescue treatment, permanent discontinuation of IMP. Composite strategy.	Risk difference.	**Key secondary endpoints:** • Reduction of HESD itch score (weekly average) of ≥4 points from baseline at Week 16.[1] • Reduction of HESD pain score (weekly average) of ≥4 points from baseline at Week 16.[2] • Reduction of HESD score (weekly average) of ≥4 points from baseline at Week 16.[3]
	Frequentist.	Primary.	Change from baseline to Week 16 without IEs.	Initiation of rescue treatment, permanent discontinuation of IMP. Composite strategy.	Difference in mean change.	**Secondary endpoint:** • Change in cDLQI score from baseline to Week 16.

1) Among subjects with a baseline HESD itch score (weekly average) ≥4 points.
2) Among subjects with a baseline HESD pain score (weekly average) ≥4 points.
3) Among subjects with a baseline HESD score (weekly average) ≥4 points.

Abbreviations: cDLQI = Children's Dermatology Life Quality Index; CHE = chronic hand eczema; HECSI = Hand Eczema Severity Index; HECSI-90 = at least 90% improvement in HECSI score from baseline; HESD = Hand Eczema Symptom Diary©; IE = intercurrent event; 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; TS = treatment success.

Panel 2: Secondary and exploratory objectives and endpoints

Objectives	Statistical approach	Estimand				Endpoints
Secondary objective		**Estimand type**	**Interpretation**	**Intercurrent events and strategy**	**Population level summary**	**Secondary endpoint[1]**
To evaluate the safety of twice-daily applications of delgocitinib cream 20 mg/g in the treatment of adolescents with moderate to severe CHE.	Not applicable	Not applicable	Not applicable	Not applicable	Not applicable	• Number of treatment-emergent[2] AEs from baseline up to Week 18[9].

Objectives	Statistical approach	Estimand				Endpoints
Exploratory objectives		**Estimand type**	**Interpretation**	**Intercurrent events and strategy**	**Population level summary**	**Exploratory endpoints**
To evaluate the health-related quality of life and efficacy of twice-daily applications of delgocitinib cream 20 mg/g compared with cream vehicle in the treatment of adolescents with moderate to severe CHE over time.	Frequentist.	Primary.	Response achieved without IEs.	Composite strategy: Initiation of rescue treatment, permanent discontinuation of IMP.	Risk difference.	**Efficacy** • HECSI-90 at Weeks 4 and 8. • HECSI-75 at Weeks 4, 8, and 16. **Health-related quality of life and efficacy** • Reduction of HESD itch score (weekly average) of ≥4 points from baseline at Weeks 2, 4, and 8.[3] • Reduction of HESD itch score (weekly average) of ≥3 points from baseline at Weeks 2, 4, 8, and 16[4]. • Reduction of HESD pain score (weekly average) of ≥4 points from baseline at Weeks 2, 4, and 8.[5] • Reduction of HESD pain score (weekly average) of ≥3 points from baseline at Weeks 2, 4, 8, and 16.[6] • Reduction of HESD score (weekly average) of ≥4 points from baseline at Weeks 2, 4, and 8.[7] • Reduction of HESD score (weekly average) of ≥3 points from baseline at Weeks 2, 4, 8, and 16.[8]

Objectives	Statistical approach	Estimand				Endpoints
					Difference in mean change (or percentage change)	**Efficacy** • Percentage change in HECSI score from baseline to Weeks 4, 8, and 16. **Health-related quality of life and efficacy** • Change in HESD itch score (weekly average) from baseline to Weeks 2, 4, 8, and 16. • Change in HESD pain score (weekly average) from baseline to Weeks 2, 4, 8, and 16. • Change in HESD score (weekly average) from baseline to Weeks 2, 4, 8, and 16. • Change in cDLQI score from baseline to Week 4.

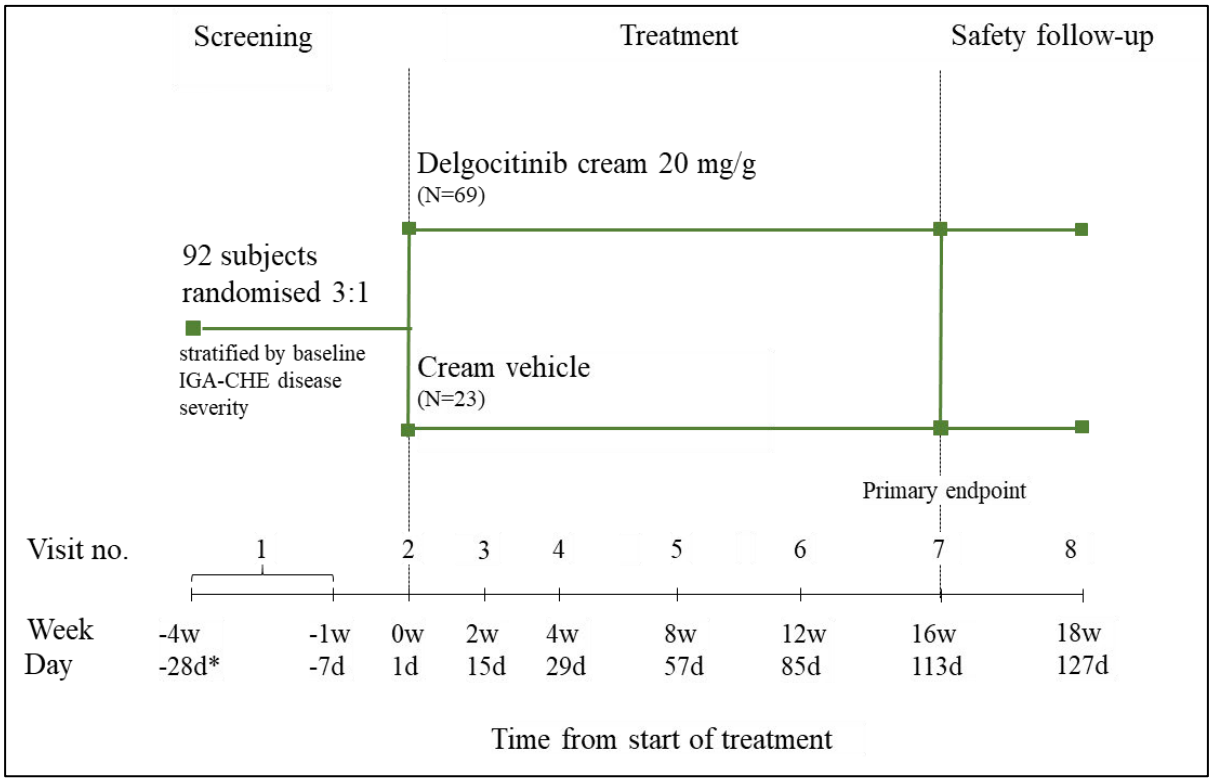
1) In addition to the secondary safety endpoint listed, clinical laboratory tests, vital signs, and physical examination at screening and end of treatment; use of rescue treatment; and subjects' assessment of local tolerability will be evaluated.
2) An event will be considered treatment emergent if started after the first application of IMP or if started before the first application of IMP and worsened in severity after first dose of IMP.
3) Among subjects with a baseline HESD itch score (weekly average) ≥4 points.
4) Among subjects with a baseline HESD itch score (weekly average) ≥3 points.
5) Among subjects with a baseline HESD pain score (weekly average) ≥4 points.
6) Among subjects with a baseline HESD pain score (weekly average) ≥3 points.
7) Among subjects with a baseline HESD score (weekly average) ≥4 points.
8) Among subjects with a baseline HESD score (weekly average) ≥3 points.
9) 'Number of treatment-emergent AEs from baseline up to Week 18' will be analysed descriptively according to the specifications in section 5.8.1.

Abbreviations: AE = adverse event; cDLQI = Children's Dermatology Life Quality Index; CHE = chronic hand eczema; 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; HESD = Hand Eczema Symptom Diary©.

1.2 Trial design

This trial is a phase 3, randomised, double-blind, vehicle-controlled, parallel-group, multi-site trial. The trial is designed to evaluate the efficacy and safety of delgocitinib cream 20 mg/g applied twice-daily for 16 weeks in adolescents 12-17 years of age with moderate to severe chronic hand eczema. The trial design is illustrated in Panel 3.

Panel 3: Trial design



* For subjects using treatments that are listed as exclusion criteria, the duration of the screening period will depend on the required wash-out period. In view of a 28-day wash-out for some of these treatments and the allowed visit window (+3 days), the screening period can be extended up to 31 days.

Abbreviations: d = day; IGA-CHE = Investigator's Global Assessment for chronic hand eczema©; N = number of subjects; w = week.

Protocol amendment

The original protocol was dated 13-Jan-2022. The amendment was considered substantial and was mainly written to change the statistical methodology to a Bayesian analysis, where data from the adult population from recently completed pivotal phase 3 trials (LP0133-1401 and LP0133-1402) will be leveraged to analyse efficacy endpoints in the adolescent population. The change in the statistical methodology was done as LEO Pharma believes that, based on results from the completed clinical development program for delgocitinib, there is sufficient

understanding of CHE pathophysiology and the pharmacology of delgocitinib to support using efficacy results from the adult trials as prior information to the Bayesian analysis of the adolescent data.

2 Testing strategy

2.1 Testing hierarchy and statistical hypothesis

The Bayesian analyses of the primary estimand for the primary and key secondary endpoints are considered the confirmatory evidence for the trial.

The treatment effect (defined as proportion of responders for delgocitinib cream 20 mg/g minus the proportion of responders for cream vehicle) for all the binary confirmatory endpoints will be evaluated based on the calculated difference of posterior distributions for delgocitinib cream 20 mg/g and cream vehicle.

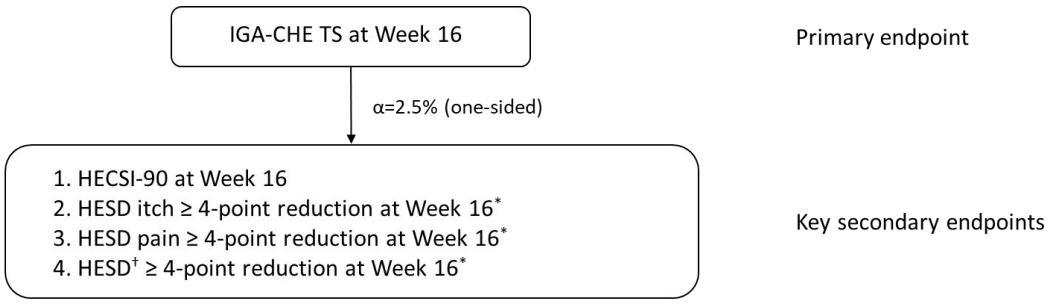
Delgocitinib cream 20 mg/g is considered superior to cream vehicle if the 2.5% percentile of the posterior distribution of the treatment difference is ≥0.

Hierarchical evaluation, which is applied for the Bayesian analyses, will be used to control the overall type I error at a nominal one sided 2.5% level. This is built on the principle that the IGA-CHE TS superiority at Week 16 will have to be established before sequential testing for additional benefits (key secondary endpoints) related to efficacy.

If superiority is claimed for the primary endpoint, then evaluation of the next endpoints will be done in a fixed sequential order as specified in Panel 4. This process will be repeated until no further tests are significant.

Only analyses based on the Bayesian approach will be part of the testing hierarchy.

Panel 4:Graphical display of the testing procedure for primary and secondary endpoints



* From baseline in subjects with baseline ≥ threshold of response
† Average score of 6 symptom items, i.e., itch, pain, cracking of the skin, redness, dryness, and flaking

Abbreviations: HECSI-90 = at least 90% improvement in HECSI score from baseline; 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.

3 Sample size

Sample size documentation is provided in the CTP Section 14.1.

4 Trial analysis sets

For the purposes of analysis, the analysis sets presented in Panel 5 are defined.

Panel 5: Trial analysis sets

Trial analysis set	Description
FAS	• All randomised to treatment and exposed subjects. Subjects will be included in the analyses according to the planned treatment.
SAF	• All subjects who are exposed to IMP. Subjects will be included in the analyses according to the treatment they actually received.

Abbreviations: FAS = full analysis set, IMP = investigational medicinal product, SAF = safety analysis set.

The FAS is used to analyse endpoints related to the efficacy objectives, and the SAF is used to analyse the endpoints and assessments related to safety.

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

Exclusions from the FAS can be considered in special cases as described in ICH E9, Section 5.2.1., Full Analysis Set. If it is decided to exclude a randomized subject from the FAS, a justification addressing ICH E9 will be given in the Classification Brief before breaking the randomization code.

5 Statistical analysis

5.1 General principles

All frequentist significance tests will be one-sided using the 2.5% significance level. Operationally, the one-sided (superiority) hypotheses will be evaluated by deriving the two-sided p value; the null hypothesis will be rejected if the p value is smaller than 5% and if the point estimate is in favor of the alternative hypothesis.

All confidence intervals will be presented with 95% degree of confidence, unless otherwise specified.

An observed-cases approach will be used for tabulations of data by visit (that is, involving only those subjects who attended each specific visit).

Categorical data will be summarised using the number and percentage of subjects in each category and treatment group. Continuous data will be summarised using the mean, median, SD, 1st quartile, 3rd quartile, minimum, and maximum values.

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

In case of randomization in wrong stratum with respect to baseline IGA-CHE score, the statistical analyses will use 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.

Simulation seed used for MI will be 1331426 for both types of imputation (MI based on MAR and MI based on Bernoulli distribution).

5.1.1 Handling of missing values

5.1.1.1 Multiple imputation

5.1.1.1.1 Multiple imputation based on missing at random assumption (MAR)

Multiple imputation will only be performed for the primary endpoint.

For the treatment policy estimands' analyses the MI method includes the use of the FCS method assuming MAR to impute missing data. When analyses require MI procedures of data, 100 complete datasets will be generated.

MI under the MAR assumption will be performed using PROC MI in SAS with the FCS method 'logistics' for arbitrary missing patterns (1). Section 7.2 provides an example of SAS code to perform MI.

When analyses require MI procedures of data, the multiple-imputed datasets will be created in the following way:

1. A dataset will be created with longitudinal data in wide format (one row per patient).
2. For each timepoint missing (weeks 2, 4, 8, 12 and 16) values will be imputed using PROC MI within treatment group for IGA-CHE. The regression model for a certain timepoint will include the 2 preceding and 2 subsequent timepoints as predictors, in addition to baseline IGA-CHE score. Exceptions being the first 2 and last 2 timepoints, where the number of previous and subsequent timepoints are reduced to zero or one.
3. IGA-CHE TS is derived based on the imputed score for each of the 100 datasets and will be derived from imputation of the underlying ordinal score.
4. The relevant model is fitted for the 100 complete datasets, and Rubin's rule is applied, in order to derive the estimated treatment difference, associated SE and CI.

If there are no between-imputation variance, i.e., all the 100 imputed datasets are identical, it will not be feasible to estimate the variance using Rubin's rule for MI. Instead, the first imputed dataset will be used for analysis.

For imputation of IGA-CHE scores, it may occur that the observed data from which the imputation model is fitted does not contain all categories of the IGA-CHE predictors necessary for the imputation. For example, if all subjects with an IGA-CHE score of 3 at Week 12 have missing data at Week 16, then a regression model based on Week 12 data cannot predict the Week 16 outcome in those subjects, unless the IGA-CHE score of 3 at Week 12 is combined with other IGA-CHE scores. To avoid this situation, in this example

IGA-CHE scores of 2 and 3 at Week 12 will be combined into a single category for the purpose of the imputation.

If this situation arises, IGA-CHE categories will be combined into a single category at the specific visit for the purpose of the specific imputation, according to the rules in Panel 6.

Panel 6: Adjacent IGA-CHE scores combined in case of missing predictors in observed data

IGA-CHE score(s) missing in imputation model	IGA-CHE scores combined
0	(0,1) scores combined to 1
1	(0,1) scores combined to 1
2	(2,3) scores combined to 3
3	(2,3) scores combined to 3
4	(3,4) scores combined to 3

5.1.1.1.2 Multiple imputation based on Bernoulli distribution

For imputation of missing IGA-CHE scores using the Bernoulli distribution the following will be applied: In both treatment groups missing data will be imputed from a Bernoulli distribution with parameter p = 0.1. A MI procedure (100 iterations) will be used.

5.1.1.2 Worst observation carried forward

For the analyses of continuous data WOCF is used to impute missing data and data treated as missing. When WOCF is used, missing values are imputed with the subject's worst-case non-missing value (including the baseline value) and thereby represents no treatment effect.

5.2 Extent of exposure

The duration of exposure to treatment will be calculated as the number of days from date of first application of IMP to the date of last application of IMP, both days included.

Exposure to IMP will be presented for the SAF as days of exposure per treatment group. In addition, patient years of exposure and patient years of observation are presented per treatment group. Patient years of exposure will be calculated as the number of days from date of first application of IMP to the date of last application of IMP (both days included) divided by 365.25. Patient years of observation is calculated as number of days from date of randomisation to date of end of trial divided by 365.25.

In case subjects come in after end of trial (the safety follow-up visit) to e.g., hand in slates or update information on adverse events the time between end of trial and this last contact will not be added to the years of observation.

5.3 Intercurrent events

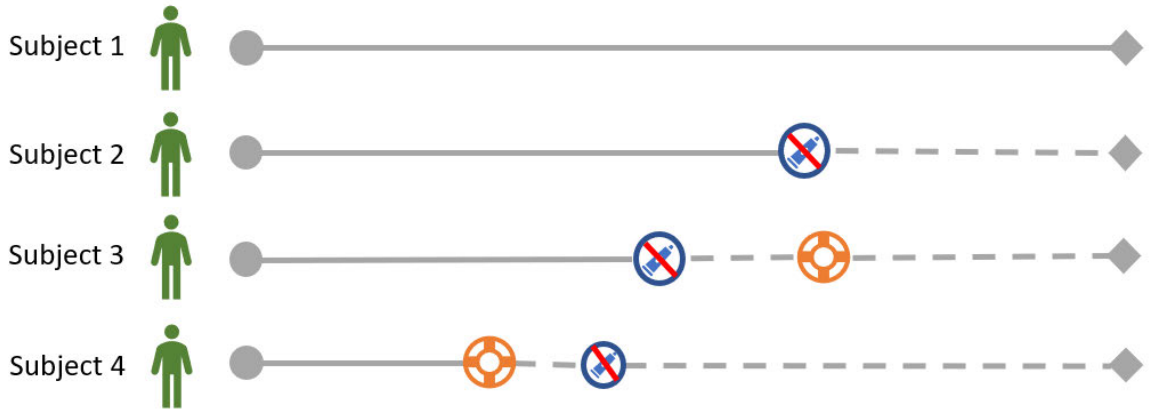
The following intercurrent events are considered to affect the interpretation of the estimated treatment effects.

- **Initiation of rescue treatment:** This IE occurs when a subject initiates rescue treatment. This IE can occur at the discretion of the investigator. If rescue treatment is initiated, 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. For further information about the definition of rescue treatment see Appendix 7.3.5.

- **Permanent discontinuation of IMP:** This IE occurs when a subject permanently discontinues IMP. This IE can occur at the subject's own initiative, at the subject's parent's/guardian's 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.

Journeys of 4 subjects from randomization to primary endpoint visit are illustrated in Panel 7.

Panel 7: Subject journeys with intercurrent events



Notes: Subject 1 completes the treatment period, subject 2 permanently discontinues IMP, subject 3 discontinues IMP and then initiates rescue treatment, while subject 4 initiates rescue treatment and subsequently discontinues IMP.

If a subject experiences more than one IE, the first IE occurring will be used when addressing IEs in the statistical analyses. If both types of IEs occur on the same day, handling of observed and missing data will be done in accordance with Panel 8, as methods described are identical for the two IEs. The number of IEs and type of IEs will be summarized by treatment group and visit interval. For further information about how permanent discontinuation of IMP and rescue treatment data will be summarized see Appendix 7.3.2 and 7.3.5, respectively.

5.3.1 Handling of observed and missing data according to intercurrent events

An overview of how observed and missing data will be handled according to the IEs for all analyses for the two estimands are presented in Panel 8.

Panel 8: Handling of observed and missing data in the analyses according to the intercurrent events

		Estimand strategy for binary endpoints					Estimand strategy for continuous endpoints
		Composite strategy			Treatment policy strategy		Composite strategy
Intercurrent event	**Data observed or missing**	**Bayes:** • **Primary endpoint primary analysis** • **Key secondary endpoints[1] analyses**	**Frequentist:** • **Primary endpoint primary analysis** • **Primary endpoint supplementary analysis using historical data** • **Primary endpoint additional analysis** • **Key secondary endpoints[1] analyses** • **Secondary endpoints[2] analyses** • **Exploratory endpoints[3] analyses**	**Frequentist:** • **Primary endpoint sensitivity analysis** • **Sensitivity analysis of primary endpoint additional analysis**	**Frequentist:** • **Primary endpoint analysis** • **Primary endpoint additional analysis**	**Frequentist:** • **Primary endpoint sensitivity analysis** • **Sensitivity analysis of primary endpoint additional analysis**	**Frequentist:** • **Secondary endpoints[2] analyses** • **Exploratory endpoints[3] analyses**
Initiation of rescue treatment	Observed	Non-response		Non-response	Value will be used as observed	Value will be used as observed	WOCF (including baseline value)
	Missing	Non-response		Non-response	MI (MAR)	Non-response	WOCF (including baseline value)
Permanent discontinuation of IMP	Observed	Non-response		Non-response	Value will be used as observed	Value will be used as observed	WOCF (including baseline value)
	Missing	Non-response		Non-response	MI (MAR)	Non-response	WOCF (including baseline value)
No intercurrent events	Observed	Value will be used as observed		Value will be used as observed	Value will be used as observed	Value will be used as observed	Value will be used as observed

	Missing	Non-response	MI using Bernoulli distribution	MI (MAR)	Non-response	WOCF (including baseline value)

1. Key secondary endpoints:
    - HECSI-90 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 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 score (weekly average) of ≥4 points from baseline at Week 16 (among subjects with a baseline HESD score (weekly average) ≥4 points).
2. Secondary endpoints:
    - IGA CHE TS at Weeks 2, 4, 8, and 12.
    - Change in cDLQI score from baseline to Week 16.
3. Exploratory endpoints:
    - HECSI-75 at Weeks 4, 8, and 16.
    - HECSI-90 at Weeks 4 and 8.
    - Percentage change in HECSI score from baseline to Weeks 4, 8, and 16.
    - Reduction of HESD itch score (weekly average) of ≥3 points from baseline at Weeks 2, 4, 8 and 16 (among subjects with a baseline HESD itch score (weekly average) ≥3 points).
    - Reduction of HESD itch score (weekly average) of ≥4 points from baseline at Weeks 2, 4, and 8 (among subjects with a baseline HESD itch score (weekly average) ≥4 points).
    - Change in HESD itch score (weekly average) from baseline to Weeks 2, 4, 8, and 16.
    - Reduction of HESD pain score (weekly average) of ≥3 points from baseline at Weeks 2, 4, 8 and 16 (among subjects with a baseline HESD pain score (weekly average) ≥3 points).
    - Reduction of HESD pain score (weekly average) of ≥4 points from baseline at Weeks 2, 4, and 8 (among subjects with a baseline HESD pain score (weekly average) ≥4 points).
    - Change in HESD pain score (weekly average) from baseline to Weeks 2, 4, 8, and 16.
    - Reduction of HESD score (weekly average) of ≥3 points from baseline at Weeks 2, 4, 8, and 16 (among subjects with a baseline HESD score (weekly average) ≥3 points).
    - Reduction of HESD score (weekly average) of ≥4 points from baseline at Weeks 2, 4, and 8 (among subjects with a baseline HESD score (weekly average) ≥4 points).
    - Change in HESD score (weekly average) from baseline to Weeks 2, 4, 8, and 16;
    - Change in cDLQI score from baseline to Week 4.

Abbreviations: IMP = investigational medicinal product; MAR = missing at random; MI = multiple imputation; WOCF = worst observation carried forward.

5.4 Estimand overview

The primary endpoint for LP0133-1426 is IGA-CHE TS at Week 16, and the primary estimand uses the composite strategy when handling intercurrent events. With a composite strategy, the occurrence of an IE is a component of the endpoint.

For the analyses based on the Bayesian approach, only the primary estimand using the composite strategy will be used.

For the analyses based on the Frequentist approach, both the primary estimand (using the composite strategy) and the supplementary estimand (using the treatment policy strategy) will be considered for the primary endpoint. For the other endpoints the primary estimand will be the only one used.

The supplementary estimand uses a treatment policy strategy which attempts to quantify the effect of the randomised treatment, ignoring the occurrence of IEs. Data collected for the endpoint of interest are used regardless of whether an IE occurred.

5.5 Primary estimand

The primary estimand defined for the binary and continuous endpoints uses the composite strategy.

5.5.1 Primary estimand for binary endpoints: composite strategy, used for both the Bayesian approach and the Frequentist approach

The primary estimand “Composite strategy” evaluates the treatment effect in adolescents 12-17 years of age with moderate to severe CHE as the risk difference for achieving a response, without initiation of rescue treatment or permanent discontinuation of IMP.

For subjects who received rescue treatment or who have permanently discontinued IMP prior to the endpoint of interest, observed data after the IEs will be considered non-response, reflecting an assumption that initiation of rescue treatment and permanent discontinuation of IMP indicate failure of the randomised treatment.

For example, the primary composite endpoint of IGA-CHE TS at Week 16 without initiation of rescue treatment or permanent discontinuation of IMP can take the values:

- ‘1’ (response), if the subject achieves IGA-CHE TS at Week 16 and has neither initiated rescue treatment nor permanently discontinued IMP prior to Week 16.

- '0' (non-response), if the subject has not achieved IGA-CHE TS at Week 16 or has initiated rescue treatment or permanently discontinued IMP prior to Week 16.

Missing data for subjects who do not experience an IE prior to the visit for the endpoint of interest will be imputed as non-response, except in the sensitivity analysis where these are imputed from a Bernoulli distribution. Similarly, missing data at the endpoint of interest for subjects who do experience an IE prior to this visit will be imputed as non-response.

5.5.1.1 Definition of binary endpoints

The primary endpoint for LP0133-1426 is the binary endpoint "IGA CHE TS at Week 16 (IGA CHE TS refers to a score of 0 [clear] or 1 [almost clear] with a ≥2 step improvement from baseline)".

The remaining binary endpoints (key secondary, secondary, and exploratory) are:

- HECSI 90 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 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 score (weekly average) of ≥4 points from baseline at Week 16 (Among subjects with a baseline HESD score (weekly average) ≥4 points).
- IGA-CHE TS at Weeks 2, 4, 8, and 12.
- HECSI-90 at Weeks 4, 8 and 16.
- HECSI-75 at Weeks 4, 8, and 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 itch score (weekly average) of ≥3 points from baseline at Weeks 2, 4, 8, and 16 (Among subjects with a baseline HESD itch score (weekly average) ≥3 points.).
- Reduction of HESD pain score (weekly average) of ≥4 points from baseline at Weeks 2, 4, 8 and 16 (Among subjects with a baseline HESD pain score (weekly average) ≥4 points).
- Reduction of HESD pain score (weekly average) of ≥3 points from baseline at Weeks 2, 4, 8, and 16 (Among subjects with a baseline HESD pain score (weekly average) ≥3 points.).

- Reduction of HESD score (weekly average) of ≥4 points from baseline at Weeks 2, 4, 8 and 16 (Among subjects with a baseline HESD score (weekly average) ≥4 points).
- Reduction of HESD score (weekly average) of ≥3 points from baseline at Weeks 2, 4, 8, and 16 (Among subjects with a baseline HESD score (weekly average) ≥3 points.).

5.5.1.2 Primary endpoint analysis using the primary estimand, Frequentist approach

The primary endpoint will be analysed as follows: Let the treatment effect be defined as the risk difference μ = (delgocitinib cream 20 mg/g minus cream vehicle), then the hypothesis to be tested is:

- $H_0: \mu \leq 0$ against $H_a: \mu > 0$.

The hypothesis will be tested for delgocitinib cream 20 mg/g vs. cream vehicle based on the primary analysis for the primary estimand.

Missing data for subjects who do not attend the visit for the endpoint of interest and do not experience an IE prior to this visit will be imputed as non-response.

The risk difference between the 2 treatment groups will be based on a logistic regression model including treatment group and baseline IGA-CHE score as factors. The logistic regression model will be used to estimate the risk difference and associated 95% confidence interval based on the standardised estimator presented in Ge M et al. (2) and the variance estimator presented in Bartlett JW (3).

5.5.1.3 Sensitivity analysis of the primary estimand for the primary endpoint analysis, Frequentist approach

For subjects who received rescue treatment or who have permanently discontinued IMP prior to the endpoint of interest, observed data after the IEs will be considered non-response. Any missing data for such subjects will be imputed as non-response.

Missing data at the endpoint of interest, for subjects who do not experience the IEs prior to that, will be handled as follows; For subjects in the delgocitinib cream 20 mg/g group and the cream vehicle group, missing data will be imputed from a Bernoulli distribution with parameter p value 0.1. The same parameter p will be used for both treatment groups. The parameter value 0.1 is based on the response rate of IGA-CHE TS at Week 16 in the cream vehicle group in the phase 2b trial in adults (LP0133-1273) and will introduce uncertainty due to missing data. A MI procedure (100 iterations) will be used.

For each of the 100 complete datasets, the risk difference will be based on a logistic regression model including treatment group and baseline IGA-CHE score as factors. The logistic regression model will be used to estimate the risk difference and associated 95% confidence interval based on the standardised estimator presented in Ge M et al. (2) and the variance estimator presented in Bartlett JW (3). The results of the analyses will be combined using Rubin's rule to provide the estimated treatment difference and associated standard error, and the 95% CI for the treatment difference will be calculated. In case of no missing data this analysis will not be performed.

5.5.1.4 Supplementary analysis of the primary endpoint using the primary estimand along with historical and trial data, Frequentist approach

Historical data used for this analysis is from trials LP0133-1401 and LP0133-1402. Missing data for subjects who do not experience an IE prior to the Week 16 visit will be imputed as non-response.

The risk difference between the 2 treatment groups will be based on a logistic regression model including treatment group, baseline IGA-CHE score, trial ID [i.e., trials LP0133-1401, LP0133-1402, and LP0133-1426] and interaction between treatment and trial ID as factors. Vehicle will be used as reference for treatment and LP0133-1426 as the reference for trial ID. The logistic regression model will be used to estimate the risk difference and associated 95% confidence interval will be estimated based on the delta method (https://www.stata.com/support/faqs/statistics/delta-method/).

Additionally, the estimate and 95% CI of interaction between treatment and trial ID for the logistic regression model, (including the factors: treatment group, baseline IGA-CHE score, trial ID and interaction between treatment and trial ID) will be presented.

5.5.1.5 Additional analyses for the primary endpoint using the primary estimand and the sensitivity analysis of the primary estimand, Frequentist approach

To be able to compare the results from LP0133-1426 with the analyses performed in LP0133-1401 and LP0133-1402 two additional analyses will be performed for the primary endpoint using the primary estimand.

In the primary endpoint additional analysis, missing data for subjects who do not experience an IE prior to Week 16 will be imputed as non-response (see Panel 8). The difference in response rates between the two treatment groups will be analysed using the CMH test stratified by baseline IGA-CHE score. The difference in response rates with 95% CI will be calculated by the Mantel-Haenszel method stratified by baseline IGA-CHE score.

In the sensitivity analysis of primary endpoint additional analysis, missing data for subjects who do not experience an IE prior to Week 16 will be imputed based on a Bernoulli distribution as described in section 5.5.1.3.

For each of the 100 complete datasets, the difference in response rates will be analysed by the Mantel-Haenszel method stratified by baseline IGA-CHE score. The results of the analyses will be combined using Rubin's rule to provide the estimated treatment difference and associated standard error, and the 95% CI for the treatment difference will be calculated.

5.5.1.6 Binary endpoint analyses using the primary estimand, Frequentist approach

The remaining binary endpoints will be analysed in a similar manner as the primary endpoint (that is including treatment group and baseline IGA-CHE score as factors), see section 5.5.1.2.

5.5.1.7 Primary endpoint analysis using the primary estimand, Bayesian approach

For the Bayesian analysis of the primary endpoint the estimand used is the primary estimand i.e., the composite strategy. The treatment effect (defined as proportion of responders for delgocitinib cream 20 mg/g minus the proportion of responders for cream vehicle) will be evaluated based on the calculated posterior distribution of the treatment difference. Delgocitinib cream 20 mg/g is considered superior to cream vehicle if the 2.5% percentile of the posterior distribution of the treatment difference is ≥ 0. Appendix 7.2.2 provides an example of R code to perform the Bayesian analyses.

The MAP approach using a hierarchical model for the between-study heterogeneity is used to derive the informative priors from historical data. The prior for the between-trial heterogeneity for the primary endpoint IGA-CHE TS, which controls the amount of borrowing from historical information, is set to $\tau = 0.5$ and the prior weight on the non-informative part of the prior is set to 0.2 (20%).

The 'gMAP' function in the statistical package 'RBesT' in R is used for the calculations. The seed used for both vehicle and delgocitinib cream 20 mg/g is 1331426, the number of iterations is set to 50.000 and the warmup is set to 5000.

For IGA-CHE the historical response rates from LP0133-1401 and LP0133-1402 (see Panel 9) are used to calculate the informative MAP prior both for the cream vehicle as well as for the delgocitinib cream 20 mg/g.

Panel 9: IGA-CHE responders from LP0133-1401 and LP0133-1402

	LP0133-1401[a]		LP0133-1402[b]	
	Vehicle	Delgocitinib 20 mg/g	Vehicle	Delgocitinib 20 mg/g
Number of responders	16	64	11	91
Total number of subjects randomised	162	325	159	313

Notes: a = 1401 numbers are from final_20230308, t_20100_igat_byvis.txt. **b** = 1402 numbers are from final_20230324, t_20100_igats_byvis.txt.

After calculation of the MAP prior, the expectation maximization algorithm is used to approximate the parametric mixture density with the 'automixfit' function in the statistical package 'RBesT'.

Finally, the prior is robustified (to control the type-1 error) by adding a non-informative component to the MAP prior in case the historical data deviate from the adolescent data. The non-informative mixture component weight is set to 20% as previously mentioned.

The univariate beta mixture components of the map prior for vehicle and delgocitinib 20 mg/g calculated for IGA-CHE can be seen in a rounded version with 2 decimal points in Panel 10 and Panel 11. The actual numbers are used in the further calculations. The prior distributions shown in the SAP are fixed and will not change after un-blinding.

Panel 10: Beta mix components for the prior distribution for IGA-CHE vehicle responders from LP0133-1401 and LP0133-1402

	Component 1	Component 2	Component 3	Component 4	Robust
W	0.42	0.28	0.06	0.04	0.20
A	16.36	3.44	5.86	1.16	1.00
B	180.23	39.78	35.60	5.07	1.00

Note: Not rounded data can be found in /leo/clinical/lp0133/1426/stat/sap/rob_viga.xpt.

Panel 11: Beta mix components for the prior distribution for IGA-CHE delgocitinib 20 mg/g responders from LP0133-1401 and LP0133-1402

	Component 1	Component 2	Component 3	Component 4	Robust
W	0.38	0.16	0.13	0.12	0.20
A	21.30	6.35	1.55	14.15	1.00
B	66.59	30.83	3.26	27.17	1.00

Note: Not rounded data can be found in /leo/clinical/lp0133/1426/stat/sap/rob_diga.xpt.

Once the trial is unblinded the posterior distributions for the proportion of responders for vehicle and delgocitinib 20 mg/g for IGA-CHE given the robust mixture priors can be calculated with the 'postmix' function in the statistical package 'RBesT'.

The conclusion on treatment effect will be based on the calculated difference (based on 1.000.000 samples) in the posterior distributions. A statistically significant treatment effect is concluded if the probability that the difference (delgocitinib cream 20 mg/g minus cream vehicle) is larger than zero, is larger than 0.975. That is if P(delgocitinib cream 20 mg/g - cream vehicle > 0) > 0.975. The 95% credibility interval (generated as the 2.5% and 97.5% quantiles of the difference in posterior distributions) will be presented along with the mean and median.

5.5.1.8 Binary key secondary endpoints analyses using the primary estimand, Bayesian approach

The Bayesian analyses of the primary estimand for the key secondary endpoints will be performed in a similar manner as for the primary endpoint IGA-CHE. The various number of responders and beta mix components for vehicle and delgocitinib 20 mg/g can be found in the following subsections.

The prior for the between-trial heterogeneity τ is set to 0.5 and the prior for the weight on the non-informative part of the prior is set to 0.2 for all key secondary endpoints.

As for the Bayesian approach of the primary endpoint analysis using the primary estimand the prior distributions for the key secondary endpoints shown in the SAP are fixed and will not change after un-blinding.

5.5.1.8.1 HECSI-90 responders

Panel 12: HECSI-90 responders from LP0133-1273, LP0133-1401 and LP0133-1402

	LP0133-1401[a]		LP0133-1402[b]		LP0133-1273[c]	
	Vehicle	Delgocitinib 20 mg/g	Vehicle	Delgocitinib 20 mg/g	Vehicle	Delgocitinib 20 mg/g
Responders	20	96	14	97	5	12
Total	162	325	159	313	38	41

Notes: a = 1401 numbers are from final_20230308, t_20240_hecsi90_byvis.txt., **b** = 1402 numbers are from final_20230324, t_20240_hecsi90_byvis.txt., **c** = 1273 numbers are from exploratory/output, t_60072_hecsi90_cmh_iga34_fas.txt.

Panel 13: Beta mix components for the prior distribution for HECSI-90 vehicle responders from LP0133-1273, LP0133-1401 and LP0133-1402

	Component 1	Component 2	Component 3	Component 4	Robust
W	0.43	0.24	0.07	0.06	0.20
A	25.96	7.22	16.14	1.46	1.00
B	211.47	69.47	80.24	7.16	1.00

Note: Not rounded data can be found in /leo/clinical/lp0133/1426/stat/sap/rob_vh90.xpt.

Panel 14: Beta mix components for the prior distribution for HECSI-90 delgocitinib 20 mg/g responders from LP0133-1273, LP0133-1401 and LP0133-1402

	Component 1	Component 2	Component 3	Component 4	Robust
W	0.45	0.27	0.08		0.20
A	106.68	14.57	3.01		1.00
B	246.79	33.77	6.07		1.00

Note: Not rounded data can be found in /leo/clinical/lp0133/1426/stat/sap/rob_dh90.xpt.

5.5.1.8.2 HESD itch ≥ 4-point reduction responders

Panel 15: HESD itch ≥ 4-point reduction responders from LP0133-1273, LP0133-1401 and LP0133-1402

	LP0133-1401[a]		LP0133-1402[b]		LP0133-1273[c]	
	Vehicle	Delgocitinib 20 mg/g	Vehicle	Delgocitinib 20 mg/g	Vehicle	Delgocitinib 20 mg/g
Responders	37	152	31	146	4	14
Total	161	323	156	309	24	26

Notes: a = 1401 numbers are from final_20230308, t_20520_hesd_itchr4_byvis.txt, **b** = 1402 numbers are from final_20230324, t_20520_hesd_itchr4_byvis.txt, **c** = 1273 numbers are from efficacy/output, t_20230_hesd_pruri_cmh_fas.txt.

Panel 16: Beta mix components for the prior distribution for HESD itch ≥ 4-point reduction vehicle responders from LP0133-1273, LP0133-1401 and LP0133-1402

	Component 1	Component 2	Component 3	Component 4	Robust
W	0.47	0.13	0.12	0.09	0.20
A	42.15	19.75	11.67	2.05	1.00
B	159.56	57.20	61.56	6.17	1.00

Note: Not rounded data can be found in /leo/clinical/lp0133/1426/stat/sap/rob_vitc.xpt.

Panel 17: Beta mix components for the prior distribution for HESD itch ≥ 4-point reduction delgocitinib 20 mg/g responders from LP0133-1273, LP0133-1401 and LP0133-1402

	Component 1	Component 2	Component 3	Component 4	Robust
W	0.37	0.21	0.15	0.07	0.20
A	135.80	85.18	7.10	7.02	1.00
B	154.36	87.39	6.75	9.26	1.00

Note: Not rounded data can be found in /leo/clinical/lp0133/1426/stat/sap/rob_ditc.xpt.

5.5.1.8.3 HESD pain ≥ 4-point reduction responders

Panel 18: HESD pain ≥ 4-point reduction responders from LP0133-1273, LP0133-1401 and LP0133-1402

	LP0133-1401[a]		LP0133-1402[b]		LP0133-1273[c]	
	Vehicle	Delgocitinib 20 mg/g	Vehicle	Delgocitinib 20 mg/g	Vehicle	Delgocitinib 20 mg/g
Responders	41	143	32	143	1	14
Total	149	291	141	294	15	20

Notes: a = 1401 numbers are from final_20230308, t_20630_hesd_painr4_byvis.txt, **b** = 1402 numbers are from final_20230324, t_20630_hesd_painr4_byvis.txt, **c** = 1273 numbers are from exploratory/output, t_70014_pain4_modsev.txt.

Panel 19: Beta mix components for the prior distribution for HESD pain ≥ 4-point reduction vehicle responders from LP0133-1273, LP0133-1401 and LP0133-1402

	Component 1	Component 2	Component 3	Component 4	Robust
W	0.34	0.33	0.13		0.20
A	5.34	36.96	1.67		1.00
B	18.89	117.43	4.82		1.00

Note: Not rounded data can be found in /leo/clinical/lp0133/1426/stat/sap/rob_vpai.xpt.

Panel 20: Beta mix components for the prior distribution for HESD pain ≥ 4-point reduction delgocitinib 20 mg/g responders from LP0133-1273, LP0133-1401 and LP0133-1402

	Component 1	Component 2	Component 3	Component 4	Robust
W	0.35	0.35	0.10		0.20
A	12.16	123.97	2.53		1.00
B	11.04	124.54	1.94		1.00

Note: Not rounded data can be found in /leo/clinical/lp0133/1426/stat/sap/rob_dpai.xpt.

5.5.1.8.4 HESD total score ≥ 4-point reduction responders

Panel 21: HESD total score ≥ 4-point reduction responders from LP0133-1273, LP0133-1401 and LP0133-1402

	LP0133-1401[a]		LP0133-1402[b]		LP0133-1273[c]	
	Vehicle	Delgocitinib 20 mg/g	Vehicle	Delgocitinib 20 mg/g	Vehicle	Delgocitinib 20 mg/g
Responders	38	146	32	137	2	10
Total	156	309	153	308	24	27

Notes: a = 1401 numbers are from final_20230308, t_20400_hesdr4_byvis.txt, **b** = 1402 numbers are from final_20230324, t_20400_hesdr4_byvis.txt, **c** = 1273 numbers are from exploratory/output, t_70017_comp4_modsev.txt.

Panel 22: Beta mix components for the prior distribution for HESD total score ≥ 4-point reduction vehicle responders from LP0133-1273, LP0133-1401 and LP0133-1402

	Component 1	Component 2	Component 3	Component 4	Robust
W	0.37	0.31	0.12		0.20
A	33.12	5.26	1.72		1.00
B	122.77	21.36	5.48		1.00

Note: Not rounded data can be found in /leo/clinical/lp0133/1426/stat/sap/rob_vhes.xpt.

Panel 23: Beta mix components for the prior distribution for HESD total score ≥ 4-point reduction delgocitinib 20 mg/g responders from LP0133-1273, LP0133-1401 and LP0133-1402

	Component 1	Component 2	Component 3	Component 4	Robust
W	0.34	0.23	0.16	0.07	0.20
A	128.18	58.31	6.89	4.79	1.00
B	149.81	76.14	7.44	8.13	1.00

Note: Not rounded data can be found in /leo/clinical/lp0133/1426/stat/sap/rob_dhes.xpt.

5.5.1.9 Sensitivity analysis of the chosen between-trial heterogeneity τ and the weight on the non-informative part of the prior, Bayesian approach

Once the trial is unblinded sensitivity analyses will be performed for the primary endpoint and all key secondary endpoints in order to evaluate the influence of the prespecified selected prior for τ and the prespecified selected prior weight parameter for the non-informative part of the prior.

The values of the prior for the between-trial heterogeneity τ tested are 0.2, 0.3, 0.4, 0.5, 0.75 and 1.0. The values of the weight on the non-informative part of the prior tested are 0 to 1 by 0.1.

5.5.2 Primary estimand for continuous endpoints: composite strategy

This primary estimand evaluates the treatment effect in adolescents with moderate to severe CHE, without initiation of rescue treatment or permanent discontinuation of IMP.

For subjects who received rescue treatment or who have permanently discontinued IMP prior to the endpoint of interest, observed data after the IEs will be imputed by using WOCF (including the baseline value) which is considered an extremely unfavourable value.

5.5.2.1 Definition of continuous endpoints

The continuous endpoints (secondary and exploratory) to be analysed with the composite strategy estimand are:

- Change in cDLQI score from baseline to Week 16.
- Percentage change in HECSI score from baseline to Weeks 4, 8, and 16.
- Change in HESD itch score (weekly average) from baseline to Weeks 2, 4, 8, and 16.
- Change in HESD pain score (weekly average) from baseline to Weeks 2, 4, 8, and 16.
- Change in HESD score (weekly average) from baseline to Weeks 2, 4, 8, and 16.
- Change in cDLQI score from baseline to Week 4.

5.5.2.2 Analysis of continuous endpoints for the primary estimand

For subjects who received rescue treatment or who have permanently discontinued IMP prior to the endpoint of interest, observed data after the IEs will be considered non-response by using WOCF (including the baseline value).

Missing data for subjects who do not experience an IE prior to the visit for the endpoint of interest will be imputed as WOCF (including the baseline value). Similarly, missing data at the endpoint of interest for subjects who do experience an IE prior to this visit will be imputed as WOCF (including the baseline value).

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

5.6 Supplementary estimand

The following supplementary estimand is defined for the primary binary endpoint.

5.6.1 Supplementary estimand for binary primary endpoint: treatment policy strategy, Frequentist approach

The supplementary estimand "Treatment policy" evaluates the treatment effect in adolescents 12-17 years of age with moderate to severe CHE as the risk difference for achieving a response, regardless of initiation of rescue treatment or permanent discontinuation of IMP.

5.6.1.1 Definition of binary endpoints

The primary endpoint (IGA CHE TS at Week 16) for LP0133-1426 will be the only endpoint analysed with the treatment policy strategy estimand.

5.6.1.2 Analysis for the supplementary estimand

Observed data will be used in the analysis, including the data observed after the occurrence of IEs. To support the treatment policy strategy, subjects who experience IEs prior to Week 16 will be asked to attend the primary endpoint visit at Week 16 for collection of data.

Missing data at Week 16 will be imputed using MI (100 iterations) assuming MAR within treatment group. For further detail on the MI procedure see section 5.1.1.1.1. For each of the 100 imputed datasets, the risk difference will be based on a logistic regression model including treatment group and baseline IGA-CHE score as factors. The results of the analyses will be combined using Rubin's rule to provide the estimated treatment difference and associated standard error, and the 95% CI for the treatment difference will be calculated. In case of no missing data this analysis will not be performed.

5.6.1.3 Sensitivity analysis of the supplementary estimand

Observed data will be used in the analysis, including the data observed after the occurrence of IEs. Missing data at Week 16 will be imputed as non-response.

The risk difference will be analysed as described above for the analysis of the supplementary estimand. In case of no missing data this analysis will not be performed.

5.6.1.4 Additional analyses for the primary endpoint using the supplementary estimand and the sensitivity analysis of the supplementary estimand

To be able to compare the results from LP0133-1426 with the analyses performed in LP0133-1401 and LP0133-1402 two additional analyses will be performed for the primary endpoint using the supplementary estimand.

In the primary endpoint additional analysis using the supplementary estimand, observed data including data observed after the occurrence of IE will be used in the analysis, and missing data at Week 16 will be imputed using MI (100 iterations) assuming MAR within treatment group (see Panel 8). The difference in response rates between the two treatment groups will be analysed using the CMH test stratified by baseline IGA-CHE score. The difference in response rates with 95% CI will be calculated by the Mantel-Haenszel method stratified by baseline IGA-CHE score.

In the sensitivity analysis of primary endpoint additional analysis using the supplementary estimand, observed data including the data observed after the occurrence of IEs will be used in the analysis. Missing data at Week 16 will be imputed as non-response.

The risk difference will be analysed as described above for the analysis of the supplementary estimand. In case of no missing data this analysis will not be performed.

5.7 Analysis of pharmacokinetics

The pharmacokinetics analysis is tabulated as described in the CTP Section 14.3.12.

5.8 Safety analysis

The analysis of safety will be based on the safety analysis set.

5.8.1 Adverse events

AEs will be coded during the course of the trial according to MedDRA version 24.0. AEs will be presented by PTs and primary SOC.

If an AE worsens in severity, the new severity, including date of severity change, will be recorded. If an AE with onset prior to initiation of IMP worsens after administration of IMP, a new AE will be recorded according to CTP Appendix 2. If an AE worsens in severity, the worst severity will be tabulated.

An event will be considered treatment-emergent if started after the first application of IMP or if started before the first application of IMP and worsened in severity after first application of IMP. If an AE started on the same date as the first IMP application, the tick mark from the eCRF indicating if the AE started before the first application of IMP is used to define, if the AE is treatment emergent. The tabulations described in the following will only include the treatment-emergent AEs.

For information about handling of missing data for AEs see the ADRG.

Treatment-emergent AEs will be summarised; however, all non-treatment emergent AEs will be listed for the SAF and for all screened subjects not in the SAF.

Treatment-related AEs are defined as AEs for which the investigator has described the causal relationship to IMP as possibly or probably related.

An overall summary of AEs, deaths, SAEs, premature discontinuations from IMP and/ or withdrawals from the trial due to AEs, treatment-related AEs, most frequent AEs (5%), severe AEs, outcome of AEs and severity will be presented.

The following AE types will as a minimum be summarized:

- AEs.
- AEs with possible or probable relation to IMP.
- Most frequent AEs (≥5% in any treatment group).
- SAEs.
- AEs leading to withdrawal from trial.
- AEs leading to permanent discontinuation of IMP.

Evaluation of events will be tabulated by treatment group and be based on the following: Number of subjects (N), number of subjects with events (n), percent of subjects with events (%), number of events (E), and rate of events per 100 patient years of observation (R).

The overview of AEs will be evaluated as above and will include the following information: seriousness, severity, relatedness, outcome, action taken with IMP, permanent discontinuations from IMP and/or withdrawals from the trial due to AEs.

As a minimum, listings will be provided for:

- AEs.
- SAEs.
- Deaths.
- AEs leading to withdrawal from trial.
- AEs leading to permanent discontinuation of IMP.
- AESIs.
- Other events involving IMP, and AEs originating from other events involving IMP.

The detailed listings will provide an overview of the individual cases and include the age and sex of the participant, whether treatment has been received at the time of AE onset, the AE preferred and reported terms, causality and severity of the AE, the action taken with the IMP, AE outcome, start and stop date of AE, duration of AE, and number of days since first and last IMP administration.

Narratives will be provided for SAEs and pregnancies.

AESIs will be listed by treatment group. No narratives will be given.

Other events (medication error, misuse, and abuse of IMP) will be tabulated and listed. No narratives will be given.

5.8.2 Vital signs and physical examination

Vital signs will be summarized as described in the CTP Section 14.3.13.2 Physical examination will be tabulated in a shift table and in a listing.

5.8.3 Clinical laboratory evaluation

Laboratory parameters will be presented by subgroupings of hematology, chemistry, urinalysis and serology parameters.

For the chemistry parameters and the hematology parameters the absolute values and the changes from baseline will be presented by visit for each treatment group.

Shift tables will be produced for chemistry and hematology parameters showing the thresholds at baseline against those at end of treatment (Week 16), as specified in the ADRG.

Selected chemistry and hematology parameters will be presented by thresholds at end of treatment and at max post-baseline according to the thresholds specified in the ADRG. For each threshold level the number and percentage of subjects with at least one value within the threshold will be summarized by treatment group with denominator being all subjects in the SAF. All post-baseline measurements (including samples from unscheduled visits) are considered in the max post-baseline thresholds tables.

All laboratory results (including serology and urinalysis) will be presented in the listings.

5.8.4 Local laboratory evaluation

Local laboratory results including urine dipsticks and urine pregnancy tests will be listed. Furthermore, urine dipsticks results will be presented in a shift table.

5.8.5 Electrocardiography

The investigator evaluation of ECG will be tabulated using a shift table from baseline to end of treatment, by treatment group. ECG measurements will also be presented in a listing.

5.8.6 Assessment of local tolerability

Subject assessment of local tolerability will be summarized in a table by week and treatment group. Subject assessment of local tolerability will also be presented in a listing.

5.8.7 New CHE lesions

New CHE lesions after baseline will be listed for randomised subjects.

5.9 Subgroup analyses

No subgroup analysis planned.

5.10 Interim analysis

No interim analysis planned.

6 Changes to analyses described in the protocol

In the analysis with the historical data, it is described that the associated 95% confidence interval will be based on the standardised estimator presented in Ge M et al. (2).

This has been changed so the associated 95% confidence interval will be estimated based on the delta method instead.

7 Supporting documentation

7.1 Appendix 1: Patient reported outcome scoring algorithms

The PROs scoring algorithms are specified in Panel 24.

Panel 24: Patient reported outcome scoring algorithms

cDLQI	Scored according to: https://www.cardiff.ac.uk/medicine/resources/quality-of-life-questionnaires/childrens-dermatology-life-quality-index.
HESD	HESD includes 6 items (itch, pain, cracking, redness, dryness, and flaking). HESD score is derived as an average of the 6 items. The daily HESD score may only be calculated if at least 3 items are available per day. The weekly HESD score is then calculated as the average of the daily HESD scores for the week, if at least 4 days are available. For the individual HESD items an average per week can be calculated if data from at least 4 days is available. The HESD weekly average scores at baseline and Week 16 will be calculated from daily assessments of HESD during the 7 days immediately preceding the baseline visit (Day -7 to Day -1) and the Week 16 visit (Day of Week 16 visit -7 to Day of Week 16 visit -1). For the HESD weekly average scores between baseline and Week 16 it will be the nominal weekly averages, meaning that the average isn't related to the actual visit. For further details on the derivation of the HESD weekly average scores refer to the ADRG.(4)

7.2 Appendix 2: SAS- and R-code

7.2.1 SAS code for multiple imputation

```
proc mi data = inddata nimpute = 100 out = uddata seed = 1331426;
    where trt01pn=treatment;
    class w0 w30 w40 w50 w60 w70;
    var w0 w30 w40 w50 w60 w70;
    fcs logistic(W30 = W0 W40 W50 / likelihood=augment);
    fcs logistic(W40 = W0 W30 W50 W60 / likelihood=augment);
    fcs logistic(W50 = W0 W30 W40 W60 W70 / likelihood=augment);
    fcs logistic(W60 = W0 W40 W50 W70 / likelihood=augment);
    fcs logistic(W70 = W0 W50 w60 / likelihood=augment);
run;
```

where IGA-CHE score at baseline (Week 0) is contained in the variable IGABL, the score of the variable of interest at Week 1 is contained in the variable w1, and similarly for other visits.

7.2.2 R code for Bayesian analyses

Calculation of Beta-mix components for prior distribution done before DBL and unblinding of data:

```
seed.Veh<-1331426
seed.del<-1331426
weight.value <- 0.2
tau.priorvalue <- 0.5

map_mcmc_veh <- gMAP(cbind(r, n-r) ~ 1 | study, data=xxx,
tau.dist="HalfNormal",
                     tau.prior=tau.priorvalue, beta.prior=100,
family=binomial, iter=50000, warmup=5000,
                     thin=5, init = 1, chains=6,cores=1L)
```

Conversion of the MAP prior to a parametric representation with the automixfit function:

```
map <- automixfit(map_mcmc_veh, k=10)
```

Robustification of parametric representation of the prior:

```
map_robust <- robustify(map, weight=weight.value,
mean=1/2,tau.prior=tau.priorvalue)
```

The parameter settings and number of iterations mentioned above will not be changed after DBL. The code mentioned below will be run on unblinded data. Here, the number of iterations may be increased if results are not clearly interpretable.

Calculation of the posterior distribution

```
post <- postmix(prior, r = number of responders, n = number of randomised)
```

Calculation of probability that the difference is smaller than 0

```
prob_smaller_iga <- pmixdiff(post_trt1, post_trt2, 0, lower.tail=FALSE)
prob_smaller_iga > 0.975
```

Sampling of 1.000.000 differences between posteriors

```
rM_iga <- rmixdiff(post_trt1, post_trt2, n=1E6)
rM_mean_iga<- mean(rM_iga)
```

7.3 Appendix 3: Subject disposition and other baseline characteristics

7.3.1 Demographics and other baseline characteristics

Demographics and other baseline characteristics will be summarized as described in the CTP Section 14.3.2.

7.3.2 Subject disposition

Subject disposition is summarized as described in the CTP Section 14.3.1.

In addition, time to permanent discontinuation of IMP will be presented for subjects in FAS by treatment group using Kaplan-Meier plots. Subjects completing the treatment period will be censored at the day of the Week 16 visit (administrative censoring).

7.3.3 Medical history

Medical history will be coded using MedDRA.

Medical history will be split between past and current medical history. Past medical history is medical history confirmed not to be ongoing at screening. Current medical history is medical history confirmed to be ongoing at screening.

Past and current medical history will be tabulated by SOC and PT per treatment group and for all randomized subjects.

CHE treatment history will be tabulated by treatment group for all randomized subjects.

All CHE treatment history will be listed.

7.3.4 Concomitant medication

Concomitant medication will be coded up to ATC level 4 using the WHODrug.

Concomitant medication will be split between prior medication and concomitant medication. Prior medication is medication with a stop date prior to first IMP application, concomitant medication is a medication that is ongoing at the date of first IMP application, or with a start date on or after the date of first IMP application.

ATC level 1-4 will be presented for prior medication and concomitant medication by treatment group for all randomized subjects.

7.3.5 Rescue treatment

Rescue treatment is defined as treatment (medication or procedure) initiated to treat intolerable CHE symptoms during the treatment and follow-up periods, see CTP Section 9.5. Rescue medication will be coded up to ATC level 4 using WHODrug. Rescue procedures will be coded using MedDRA.

Rescue treatment initiated on or after the date of first IMP application (most often the baseline visit) and until Week 16 will be tabulated by treatment for the FAS. All rescue treatment will be listed.

Time to initiation of rescue treatment will be presented for subjects in the FAS by treatment group. Subjects completing the treatment period without initiating rescue treatment will be censored at day of the Week 16 visit. Subjects who permanently discontinue IMP without initiation of rescue treatment will be censored at the day of their last visit. Kaplan-Meier curves of time to initiation of rescue treatment will be estimated by treatment group.

7.3.6 Treatment compliance and drug accountability

Treatment compliance will be presented for the safety analysis set by treatment group. Analysis of treatment compliance will be based on assessments from the eDiary.

Treatment compliance will be presented as the percentage of days where the subjects did not apply IMP as instructed or did not fill in the eDiary out of the expected number of days for specific periods of time (Day 1-7, Day 8-14, Day 15-28, Day 29-56, Day 57-84, Day 85-112 days, total treatment period).

Drug accountability is based on the weight of the returned tubes, and only returned tubes are considered. The total amount of IMP used and the average weekly amount of IMP used during the trial will be presented for the safety analysis set. Calculation of total amount of IMP and the average weekly amount of IMP used is described in the ADRG.

7.3.7 Protocol deviations

Important subject level protocol deviations will be summarized by country and site for all screened subjects.

Important trial level, country level, site level and subject level protocol deviations will be listed for all screened subjects.

8 References

1. van Buuren S. Multiple imputation of discrete and continuous data by fully conditional specification. Stat Methods Med Res. 2007;16(3):219-242.

2. Ge M, Durham LK, Meyer RD, Xie W, Thomas N. Covariate-Adjusted Difference in Proportions from Clinical Trials Using Logistic Regression and Weighted Risk Differences. Drug Information Journal. 2011;45(4):481-493.

3. Bartlett JW. Covariate adjustment and estimation of mean response in randomised trials. Pharm Stat. 2018;17(5):648-666.

4. LEO Pharma. Psychometric Analysis Plan for the Chronic Hand Eczema Symptom Diary (HESD) using blinded Phase 3 LP0133-1401 data. 2021.

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