# Clinical trial results:
# A phase 2b, double-blind, randomised, 5-arm, vehicle-controlled, dose-ranging trial to evaluate the efficacy and safety of twice daily topical application of delgocitinib cream 1, 3, 8, and 20 mg/g for 16 weeks in adult subjects with mild to severe chronic hand eczema

## Summary

| | |
|---|---|
| EudraCT number | 2018-000900-40 |
| Trial protocol | DK |
| Global end of trial date | 20 April 2020 |

**Results information**

| | |
|---|---|
| Result version number | v1 (current) |
| This version publication date | 12 June 2021 |
| First version publication date | 12 June 2021 |

## Trial information

**Trial identification**

| | |
|---|---|
| Sponsor protocol code | LP0133-1273 |

**Additional study identifiers**

| | |
|---|---|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT03683719 |
| WHO universal trial number (UTN) | - |

Notes:

**Sponsors**

| | |
|---|---|
| Sponsor organisation name | LEO Pharma A/S |
| Sponsor organisation address | Industriparken 55, Ballerup, Denmark, 2750 |
| Public contact | Clinical Disclosure, LEO Pharma A/S, +45 44945888, disclosure@leo-pharma.com |
| Scientific contact | Clinical Disclosure, LEO Pharma A/S, +45 44945888, disclosure@leo-pharma.com |

Notes:

**Paediatric regulatory details**

| | |
|---|---|
| Is trial part of an agreed paediatric investigation plan (PIP) | No |
| Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial? | No |
| Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial? | No |

Notes:

## Results analysis stage

| | |
|---|---|
| Analysis stage | Final |
| Date of interim/final analysis | 14 October 2020 |
| Is this the analysis of the primary completion data? | No |

| | |
|---|---|
| Global end of trial reached? | Yes |
| Global end of trial date | 20 April 2020 |
| Was the trial ended prematurely? | No |

Notes:

## General information about the trial

Main objective of the trial:

The purpose of this research trial was to test different strengths of a new trial medication, delgocitinib cream 1, 3, 8, and 20 mg/g, and to investigate how treatment with delgocitinib cream affects chronic hand eczema. This was judged by a range of assessments that rate the severity and extent of chronic hand eczema and its symptoms, as well as general health status and quality of life.

Protection of trial subjects:

This clinical trial was conducted to conform to the principles of the Declaration of Helsinki, the International Council for Harmonisation (ICH) Good Clinical Practice (GCP) guidelines, in compliance with the approved protocol, and applicable regulatory requirements.

Background therapy: -

Evidence for comparator: -

| | |
|---|---|
| Actual start date of recruitment | 28 November 2018 |
| Long term follow-up planned | No |
| Independent data monitoring committee (IDMC) involvement? | No |

Notes:

## Population of trial subjects

### Subjects enrolled per country

| | |
|---|---|
| Country: Number of subjects enrolled | Denmark: 58 |
| Country: Number of subjects enrolled | Germany: 179 |
| Country: Number of subjects enrolled | United States: 21 |
| Worldwide total number of subjects | 258 |
| EEA total number of subjects | 237 |

Notes:

### Subjects enrolled per age group

| | |
|---|---|
| In utero | 0 |
| Preterm newborn - gestational age < 37 wk | 0 |
| Newborns (0-27 days) | 0 |
| Infants and toddlers (28 days-23 months) | 0 |
| Children (2-11 years) | 0 |
| Adolescents (12-17 years) | 0 |
| Adults (18-64 years) | 233 |

| | |
|---|---|
| From 65 to 84 years | 25 |
| 85 years and over | 0 |

## Subject disposition

### Recruitment

Recruitment details:

258 participants from 26 sites in 3 countries (U.S., Denmark, Germany) were randomised in this trial. The first participant was screened on 28-Nov-2018 and the last participant completed the trial on 20-Apr-2020.

### Pre-assignment

Screening details:

305 participants were screened for this trial. Of these, 47 participants (15.4%) were screening failures. The main reason for screening failure was failure to meet eligibility criteria (11.8%). The eligibility criterion most frequently not met was exclusion criterion 21 (positive HBsAg, HBsAb, HBcAb, or antiHCV serology at screening [3.3%].

### Period 1

| | |
|---|---|
| Period 1 title | Overall study (overall period) |
| Is this the baseline period? | Yes |
| Allocation method | Randomised - controlled |
| Blinding used | Double blind |
| Roles blinded | Investigator, Assessor, Subject |

Blinding implementation details:

This was a double-blind study in which it was not possible to differentiate between the IMPs solely by sensory evaluation. Neither the participant nor any of the investigators or LEO Pharma staff involved in the treatment or clinical evaluation and monitoring of the participants were aware of the treatment received. The packaging and labelling of the IMPs contained no evidence of their identity.

### Arms

| | |
|---|---|
| Are arms mutually exclusive? | Yes |
| **Arm title** | Delgocitinib cream 1 mg/g |

Arm description: -

| | |
|---|---|
| Arm type | Experimental |
| Investigational medicinal product name | Delgocitinib cream |
| Investigational medicinal product code | |
| Other name | LEO 124249 cream |
| Pharmaceutical forms | Cream |
| Routes of administration | Topical use |

Dosage and administration details:

Applied twice daily for 16 weeks.

| | |
|---|---|
| **Arm title** | Delgocitinib cream 3 mg/g |

Arm description: -

| | |
|---|---|
| Arm type | Experimental |
| Investigational medicinal product name | Delgocitinib cream |
| Investigational medicinal product code | |
| Other name | LEO 124249 cream |
| Pharmaceutical forms | Cream |
| Routes of administration | Topical use |

Dosage and administration details:

Applied twice daily for 16 weeks.

| | |
|---|---|
| **Arm title** | Delgocitinib cream 8 mg/g |

Arm description: -

| | |
|---|---|
| Arm type | Experimental |

| | |
|---|---|
| Investigational medicinal product name | Delgocitinib cream |
| Investigational medicinal product code | |
| Other name | LEO 124249 cream |
| Pharmaceutical forms | Cream |
| Routes of administration | Topical use |

Dosage and administration details:

Applied twice daily for 16 weeks.

| | |
|---|---|
| **Arm title** | Delgocitinib cream 20 mg/g |

Arm description: -

| | |
|---|---|
| Arm type | Experimental |
| Investigational medicinal product name | Delgocitinib cream |
| Investigational medicinal product code | |
| Other name | LEO 124249 cream |
| Pharmaceutical forms | Cream |
| Routes of administration | Topical use |

Dosage and administration details:

Applied twice daily for 16 weeks.

| | |
|---|---|
| **Arm title** | Delgocitinib cream vehicle |

Arm description: -

| | |
|---|---|
| Arm type | Placebo |
| Investigational medicinal product name | Delgocitinib cream vehicle |
| Investigational medicinal product code | |
| Other name | LEO 124249 cream |
| Pharmaceutical forms | Cream |
| Routes of administration | Topical use |

Dosage and administration details:

Participants applied the investigational medicinal product (delgocitinib cream 1, 3, 8, or 20 mg/g or delgocitinib cream vehicle) as a twice daily cutaneous application for 16 weeks. The applications were performed approximately 12 hours apart.

| **Number of subjects in period 1** | Delgocitinib cream 1 mg/g | Delgocitinib cream 3 mg/g | Delgocitinib cream 8 mg/g |
|---|---|---|---|
| Started | 52 | 51 | 52 |
| Completed | 40 | 38 | 44 |
| Not completed | 12 | 13 | 8 |
| Consent withdrawn by subject | 4 | 4 | 3 |
| Adverse event, non-fatal | 6 | 6 | - |
| Lost to follow-up | 1 | - | - |
| Other personal reasons | - | - | 1 |
| Lack of efficacy | 1 | 3 | 4 |

| **Number of subjects in period 1** | Delgocitinib cream 20 mg/g | Delgocitinib cream vehicle |
|---|---|---|
| Started | 53 | 50 |
| Completed | 46 | 36 |
| Not completed | 7 | 14 |
| Consent withdrawn by subject | 5 | 5 |

| | | |
|---|---|---|
| Adverse event, non-fatal | 1 | 3 |
| Lost to follow-up | 1 | 1 |
| Other personal reasons | - | 1 |
| Lack of efficacy | - | 4 |

## Baseline characteristics

| Reporting groups | |
|---|---|
| Reporting group title | Delgocitinib cream 1 mg/g |
| Reporting group description: - | |
| Reporting group title | Delgocitinib cream 3 mg/g |
| Reporting group description: - | |
| Reporting group title | Delgocitinib cream 8 mg/g |
| Reporting group description: - | |
| Reporting group title | Delgocitinib cream 20 mg/g |
| Reporting group description: - | |
| Reporting group title | Delgocitinib cream vehicle |
| Reporting group description: - | |

| Reporting group values | Delgocitinib cream 1 mg/g | Delgocitinib cream 3 mg/g | Delgocitinib cream 8 mg/g |
|---|---|---|---|
| Number of subjects | 52 | 51 | 52 |
| Age categorical<br>Units: Subjects | | | |
| In utero | 0 | 0 | 0 |
| Preterm newborn infants (gestational age < 37 wks) | 0 | 0 | 0 |
| Newborns (0-27 days) | 0 | 0 | 0 |
| Infants and toddlers (28 days-23 months) | 0 | 0 | 0 |
| Children (2-11 years) | 0 | 0 | 0 |
| Adolescents (12-17 years) | 0 | 0 | 0 |
| Adults (18-64 years) | 48 | 45 | 46 |
| From 65-84 years | 4 | 6 | 6 |
| 85 years and over | 0 | 0 | 0 |
| Age continuous<br>Units: years | | | |
| arithmetic mean | 44.3 | 46.1 | 47.9 |
| standard deviation | ± 13.6 | ± 14.6 | ± 12.9 |
| Gender categorical<br>Units: Subjects | | | |
| Female | 37 | 28 | 32 |
| Male | 15 | 23 | 20 |
| Baseline IGA-CHE score<br>Units: Subjects | | | |
| 0 - Clear | 0 | 0 | 0 |
| 1 - Almost clear | 0 | 0 | 0 |
| 2 - Mild | 13 | 13 | 11 |
| 3 - Moderate | 29 | 29 | 29 |
| 4 - Severe | 10 | 9 | 12 |
| Baseline HECSI score<br>Units: Units on a scale | | | |
| arithmetic mean | 59.0 | 52.4 | 49.5 |
| standard deviation | ± 48.0 | ± 35.9 | ± 29.3 |

| **Reporting group values** | Delgocitinib cream 20 mg/g | Delgocitinib cream vehicle | Total |
|---|---|---|---|
| Number of subjects | 53 | 50 | 258 |
| Age categorical<br>Units: Subjects | | | |
| In utero | 0 | 0 | 0 |
| Preterm newborn infants (gestational age < 37 wks) | 0 | 0 | 0 |
| Newborns (0-27 days) | 0 | 0 | 0 |
| Infants and toddlers (28 days-23 months) | 0 | 0 | 0 |
| Children (2-11 years) | 0 | 0 | 0 |
| Adolescents (12-17 years) | 0 | 0 | 0 |
| Adults (18-64 years) | 50 | 44 | 233 |
| From 65-84 years | 3 | 6 | 25 |
| 85 years and over | 0 | 0 | 0 |
| Age continuous<br>Units: years | | | |
| arithmetic mean | 43.9 | 47.8 | |
| standard deviation | ± 15.1 | ± 16.2 | - |
| Gender categorical<br>Units: Subjects | | | |
| Female | 34 | 27 | 158 |
| Male | 19 | 23 | 100 |
| Baseline IGA-CHE score<br>Units: Subjects | | | |
| 0 - Clear | 0 | 0 | 0 |
| 1 - Almost clear | 0 | 0 | 0 |
| 2 - Mild | 12 | 12 | 61 |
| 3 - Moderate | 31 | 27 | 145 |
| 4 - Severe | 10 | 11 | 52 |
| Baseline HECSI score<br>Units: Units on a scale | | | |
| arithmetic mean | 65.7 | 52.7 | |
| standard deviation | ± 58.3 | ± 34.9 | - |

## End points

### End points reporting groups

| | |
|---|---|
| Reporting group title | Delgocitinib cream 1 mg/g |
| Reporting group description: - | |
| Reporting group title | Delgocitinib cream 3 mg/g |
| Reporting group description: - | |
| Reporting group title | Delgocitinib cream 8 mg/g |
| Reporting group description: - | |
| Reporting group title | Delgocitinib cream 20 mg/g |
| Reporting group description: - | |
| Reporting group title | Delgocitinib cream vehicle |
| Reporting group description: - | |

### Primary: Investigator's Global Assessment for Chronic Hand Eczema (IGA-CHE) score of 0 (clear) or 1 (almost clear) with at least a 2-step improvement (IGA-CHE treatment success) from baseline to Week 16.

| | |
|---|---|
| End point title | Investigator's Global Assessment for Chronic Hand Eczema (IGA-CHE) score of 0 (clear) or 1 (almost clear) with at least a 2-step improvement (IGA-CHE treatment success) from baseline to Week 16. |

End point description:

IGA-CHE is an instrument used in clinical trials to rate the severity of participant's global disease stage and is based on a 5-point scale ranging from 0 (clear) to 4 (severe).

| | |
|---|---|
| End point type | Primary |

End point timeframe:

Week 0 to Week 16

| End point values | Delgocitinib cream 1 mg/g | Delgocitinib cream 3 mg/g | Delgocitinib cream 8 mg/g | Delgocitinib cream 20 mg/g |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 52 | 51 | 52 | 53 |
| Units: Participants reaching IGA-CHE success | 11 | 4 | 19 | 20 |

| End point values | Delgocitinib cream vehicle | | | |
|---|---|---|---|---|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 50 | | | |
| Units: Participants reaching IGA-CHE success | 4 | | | |

## Statistical analyses

| **Statistical analysis title** | Delgocitinib cream 1 mg/g vs. vehicle cream |
|---|---|

Statistical analysis description:

The difference in response rates between the active delgocitinib cream doses and delgocitinib cream vehicle was analysed separately for each of the active dose groups using the Cochran-Mantel-Haenszel test stratified by region and disease severity (baseline IGA-CHE score). The null hypothesis of no difference in response rates between the delgocitinib cream active doses and delgocitinib cream vehicle was tested against the 2-sided alternative that there is a difference.

| | |
|---|---|
| Comparison groups | Delgocitinib cream vehicle v Delgocitinib cream 1 mg/g |
| Number of subjects included in analysis | 102 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | > 0.05 [1] |
| Method | Cochran-Mantel-Haenszel |
| Parameter estimate | Risk difference (RD) |
| Point estimate | 13.29 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.34 |
| upper limit | 26.24 |

Notes:

[1] - The statistical test was not controlled for multiplicity. Data at visits following premature discont. of IMP or initiation of rescue medication before Week 16 were considered missing and imputed as non-responders (as were any other missing data).

| **Statistical analysis title** | Delgocitinib cream 3 mg/g vs. vehicle cream |
|---|---|

Statistical analysis description:

The difference in response rates between the active delgocitinib cream doses and delgocitinib cream vehicle was analysed separately for each of the active dose groups using the Cochran-Mantel-Haenszel test stratified by region and disease severity (baseline IGA-CHE score). The null hypothesis of no difference in response rates between the delgocitinib cream active doses and delgocitinib cream vehicle was tested against the 2-sided alternative that there is a difference.

| | |
|---|---|
| Comparison groups | Delgocitinib cream vehicle v Delgocitinib cream 3 mg/g |
| Number of subjects included in analysis | 101 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | > 0.05 [2] |
| Method | Cochran-Mantel-Haenszel |
| Parameter estimate | Risk difference (RD) |
| Point estimate | -0.03 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -10.44 |
| upper limit | 10.39 |

Notes:

[2] - The statistical test was not controlled for multiplicity. Data at visits following premature discont. of IMP or initiation of rescue medication before Week 16 were considered missing and imputed as non-responders (as were any other missing data).

| **Statistical analysis title** | Delgocitinib cream 8 mg/g vs. vehicle cream |
|---|---|

Statistical analysis description:

The difference in response rates between the active delgocitinib cream doses and delgocitinib cream vehicle was analysed separately for each of the active dose groups using the Cochran-Mantel-Haenszel test stratified by region and disease severity (baseline IGA-CHE score). The null hypothesis of no difference in response rates between the delgocitinib cream active doses and delgocitinib cream vehicle

was tested against the 2-sided alternative that there is a difference.

| | |
|---|---|
| Comparison groups | Delgocitinib cream vehicle v Delgocitinib cream 8 mg/g |
| Number of subjects included in analysis | 102 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 [3] |
| Method | Cochran-Mantel-Haenszel |
| Parameter estimate | Risk difference (RD) |
| Point estimate | 28.22 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 13.8 |
| upper limit | 42.64 |

Notes:

[3] - The statistical test was not controlled for multiplicity. Data at visits following premature discont. of IMP or initiation of rescue medication before Week 16 were considered missing and imputed as non-responders (as were any other missing data).

| **Statistical analysis title** | Delgocitinib cream 20 mg/g vs. vehicle cream |
|---|---|

Statistical analysis description:

The difference in response rates between the active delgocitinib cream doses and delgocitinib cream vehicle was analysed separately for each of the active dose groups using the Cochran-Mantel-Haenszel test stratified by region and disease severity (baseline IGA-CHE score). The null hypothesis of no difference in response rates between the delgocitinib cream active doses and delgocitinib cream vehicle was tested against the 2-sided alternative that there is a difference.

| | |
|---|---|
| Comparison groups | Delgocitinib cream vehicle v Delgocitinib cream 20 mg/g |
| Number of subjects included in analysis | 103 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 [4] |
| Method | Cochran-Mantel-Haenszel |
| Parameter estimate | Risk difference (RD) |
| Point estimate | 29.61 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 14.56 |
| upper limit | 44.67 |

Notes:

[4] - The statistical test was not controlled for multiplicity. Data at visits following premature discont. of IMP or initiation of rescue medication before Week 16 were considered missing and imputed as non-responders (as were any other missing data).

| **Statistical analysis title** | Dose-response analysis |
|---|---|

Statistical analysis description:

The primary endpoint was evaluated by determining if there was a dose-response relationship between the IGA-CHE response rate at Week 16 and the dose administered, using the Multiple Comparison Procedure - Modelling (MCP-Mod) methodology. Several candidate parametric models were assumed and multiple comparison techniques were used to choose the model(s) most likely to represent the true underlying dose-response curve.

| | |
|---|---|
| Comparison groups | Delgocitinib cream 1 mg/g v Delgocitinib cream 3 mg/g v Delgocitinib cream 8 mg/g v Delgocitinib cream 20 mg/g v Delgocitinib cream vehicle |

| | |
|---|---|
| Number of subjects included in analysis | 258 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 [5] |
| Method | Multiple contrast test |

Notes:

[5] - P-values were adjusted for multiple comparisons. Models with an adjusted p-value <0.025 were statistically sign. different from a flat dose-response model. Model: IGA-CHE TS = Treatment + Region + Baseline IGA-CHE.

## Secondary: Change in Hand Eczema Severity Index (HECSI) from baseline to Week 16.

| | |
|---|---|
| End point title | Change in Hand Eczema Severity Index (HECSI) from baseline to Week 16. |

End point description:

HECSI is an instrument used in clinical trials to rate the severity of 6 clinical signs of hand eczema and the extent of the lesions on each of 5 hand areas by use of standard scales. The total HECSI score is based on a 4-point severity scale ranging from 0 (none/absent) to 3 (severe) and a 5-point scale rating the affected area(s) ranging from 0 (0% affected area) to 4 (76% to 100% affected area). The highest possible HECSI score is 360.

| | |
|---|---|
| End point type | Secondary |

End point timeframe:

Week 0 to Week 16

| End point values | Delgocitinib cream 1 mg/g | Delgocitinib cream 3 mg/g | Delgocitinib cream 8 mg/g | Delgocitinib cream 20 mg/g |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 52 | 51 | 52 | 53 |
| Units: Change in HECSI from baseline to Week 16 | | | | |
| least squares mean (standard error) | -39.81 (± 3.71) | -35.93 (± 3.77) | -46.69 (± 3.63) | -41.99 (± 3.59) |

| End point values | Delgocitinib cream vehicle | | | |
|---|---|---|---|---|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 50 | | | |
| Units: Change in HECSI from baseline to Week 16 | | | | |
| least squares mean (standard error) | -26.40 (± 3.80) | | | |

### Statistical analyses

| Statistical analysis title | Delgocitinib cream 1 mg/g vs. vehicle cream |
|---|---|

Statistical analysis description:

Least Square (LS) Means were calculated using a mixed model for repeated measurements on the post-baseline responses up to Week 16 with an unstructured covariance matrix, Kenward-Roger approximation to estimate denominator degrees of freedom, and the mean modelled as follows:

Change from baseline in HECSI
= treatment × visit + baseline HECSI × visit + region + baseline IGA-CHE.

The primary comparison between each active delgocitinib dose and vehicle was at Week 16.

| | |
|---|---|
| Comparison groups | Delgocitinib cream 1 mg/g v Delgocitinib cream vehicle |
| Number of subjects included in analysis | 102 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.01 [6] |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (net) |
| Point estimate | -13.41 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -22.82 |
| upper limit | -4.01 |

Notes:

[6] - The statistical test was not controlled for multiplicity.

| **Statistical analysis title** | Delgocitinib cream 3 mg/g vs. vehicle cream |
|---|---|

Statistical analysis description:

Least Square (LS) Means were calculated using a mixed model for repeated measurements on the post-baseline responses up to Week 16 with an unstructured covariance matrix, Kenward-Roger approximation to estimate denominator degrees of freedom, and the mean modelled as follows:

Change from baseline in HECSI
= treatment × visit + baseline HECSI × visit + region + baseline IGA-CHE.

The primary comparison between each active delgocitinib dose and vehicle was at Week 16.

| | |
|---|---|
| Comparison groups | Delgocitinib cream vehicle v Delgocitinib cream 3 mg/g |
| Number of subjects included in analysis | 101 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.05 [7] |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (net) |
| Point estimate | -9.53 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -19.04 |
| upper limit | -0.02 |

Notes:

[7] - The statistical test was not controlled for multiplicity.

| **Statistical analysis title** | Delgocitinib cream 8 mg/g vs. vehicle cream |
|---|---|

Statistical analysis description:

Least Square (LS) Means were calculated using a mixed model for repeated measurements on the post-baseline responses up to Week 16 with an unstructured covariance matrix, Kenward-Roger approximation to estimate denominator degrees of freedom, and the mean modelled as follows:

Change from baseline in HECSI
= treatment × visit + baseline HECSI × visit + region + baseline IGA-CHE.

The primary comparison between each active delgocitinib dose and vehicle was at Week 16.

| | |
|---|---|
| Comparison groups | Delgocitinib cream vehicle v Delgocitinib cream 8 mg/g |
| Number of subjects included in analysis | 102 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.0001 [8] |
| Method | Mixed models analysis |
| Parameter estimate | Median difference (net) |
| Point estimate | -20.29 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -29.56 |
| upper limit | -11.02 |

Notes:

[8] - The statistical test was not controlled for multiplicity.

| **Statistical analysis title** | Delgocitinib cream 20 mg/g vs. vehicle cream |
|---|---|

Statistical analysis description:

Least Square (LS) Means were calculated using a mixed model for repeated measurements on the post-baseline responses up to Week 16 with an unstructured covariance matrix, Kenward-Roger approximation to estimate denominator degrees of freedom, and the mean modelled as follows:

Change from baseline in HECSI
= treatment × visit + baseline HECSI × visit + region + baseline IGA-CHE.

The primary comparison between each active delgocitinib dose and vehicle was at Week 16.

| | |
|---|---|
| Comparison groups | Delgocitinib cream vehicle v Delgocitinib cream 20 mg/g |
| Number of subjects included in analysis | 103 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.001 [9] |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (net) |
| Point estimate | -15.59 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -24.82 |
| upper limit | -6.36 |

Notes:

[9] - The statistical test was not controlled for multiplicity.

| **Statistical analysis title** | Dose-response analysis |
|---|---|

Statistical analysis description:

The secondary endpoint "Change from baseline to Week 16 in HECSI score" was evaluated by determining if there was a dose-response relationship between the change from baseline in HECSI score at Week 16 and the dose administered, using the Multiple Comparison Procedure - Modelling (MCP-Mod) methodology. Several candidate parametric models were assumed and multiple comparison techniques were used to choose the model(s) most likely to represent the true underlying dose-response curve.

| | |
|---|---|
| Comparison groups | Delgocitinib cream 1 mg/g v Delgocitinib cream 3 mg/g v Delgocitinib cream 8 mg/g v Delgocitinib cream 20 mg/g v Delgocitinib cream vehicle |

| | |
|---|---|
| Number of subjects included in analysis | 258 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.0001 [10] |
| Method | Multiple contrast test |

Notes:

[10] - P-values were adj. for multiple comparisons. Models with an adj. p-value <0.025 were statistically sign. different from a flat dose-response model. Model: Change = Treatment + Baseline + Region + Baseline IGA-CHE.

### Secondary: Time to IGA-CHE treatment success.

| | |
|---|---|
| End point title | Time to IGA-CHE treatment success. |

End point description:

Time to IGA-CHE treatment success response is defined as the time from baseline to first assessment of an IGA-CHE score of 0 (clear) or 1 (almost clear) with at least a 2-step improvement. The median time to achieve success in IGA-CHE was not estimable in all groups, as fewer participants (less than 50 percent) reached success in IGA-CHE in delgocitinib cream 1 mg/g, delgocitinib cream 3 mg/g, and delgocitinib cream vehicle. Therefore, values are only reported for delgocitinib cream 8 mg/g and delgocitinib cream 20 mg/g.

| | |
|---|---|
| End point type | Secondary |

End point timeframe:

Week 0 to Week 16

| End point values | Delgocitinib cream 1 mg/g | Delgocitinib cream 3 mg/g | Delgocitinib cream 8 mg/g | Delgocitinib cream 20 mg/g |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 52[11] | 51[12] | 52 | 53 |
| Units: Median time to achieve treatment success | | | | |
| number (not applicable) | 9999 | 9999 | 82 | 98 |

Notes:

[11] - 9999=number NA. IGA-CHE TS was reached in <50% of participants, therefore median time not estimable

[12] - 9999=number NA. IGA-CHE TS was reached in <50% of participants, therefore median time not estimable

| End point values | Delgocitinib cream vehicle | | | |
|---|---|---|---|---|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 50[13] | | | |
| Units: Median time to achieve treatment success | | | | |
| number (not applicable) | 9999 | | | |

Notes:

[13] - 9999=number NA. IGA-CHE TS was reached in <50% of participants, therefore median time not estimable

### Statistical analyses

| Statistical analysis title | Delgocitinib cream 1 mg/g vs. vehicle cream |
|---|---|

Statistical analysis description:

Time to IGA-CHE TS was defined as the time from the date of the first IMP application to first assessment of IGA-CHE TS. Subjects without baseline observation were censored at the date of the first IMP application. Subjects with baseline observation not achieving IGA-CHE TS during the treatment period were censored at the date of the last visit with a valid post-baseline assessment on or prior to the

date of discontinuation of IMP or initiation of rescue medication, whichever occurred first.

| | |
|---|---|
| Comparison groups | Delgocitinib cream 1 mg/g v Delgocitinib cream vehicle |
| Number of subjects included in analysis | 102 |
| Analysis specification | Pre-specified |
| Analysis type | other[14] |
| P-value | < 0.05 [15] |
| Method | Logrank |

Notes:

[14] - Treatment groups were compared using a 2-sided log-rank test stratified by region and baseline IGA-CHE score. An event was defined as the first time achieving IGA-CHE TS.
[15] - IGA-CHE TS was reached in less than 50% of participants, therefore the median time was not estimable.
The statistical test was not controlled for multiplicity.

| **Statistical analysis title** | Delgocitinib cream 3 mg/g vs. vehicle cream |
|---|---|

Statistical analysis description:

Time to IGA-CHE TS was defined as the time from the date of the first IMP application to first assessment of IGA-CHE TS. Subjects without baseline observation were censored at the date of the first IMP application. Subjects with baseline observation not achieving IGA-CHE TS during the treatment period were censored at the date of the last visit with a valid post-baseline assessment on or prior to the date of discontinuation of IMP or initiation of rescue medication, whichever occurred first.

| | |
|---|---|
| Comparison groups | Delgocitinib cream 3 mg/g v Delgocitinib cream vehicle |
| Number of subjects included in analysis | 101 |
| Analysis specification | Pre-specified |
| Analysis type | other[16] |
| P-value | > 0.1 [17] |
| Method | Logrank |

Notes:

[16] - Treatment groups were compared using a 2-sided log-rank test stratified by region and baseline IGA-CHE score. An event was defined as the first time achieving IGA-CHE TS.
[17] - IGA-CHE TS was reached in less than 50% of participants, therefore the median time was not estimable.
The statistical test was not controlled for multiplicity.

| **Statistical analysis title** | Delgocitinib cream 8 mg/g vs. vehicle cream |
|---|---|

Statistical analysis description:

Time to IGA-CHE TS was defined as the time from the date of the first IMP application to first assessment of IGA-CHE TS. Subjects without baseline observation were censored at the date of the first IMP application. Subjects with baseline observation not achieving IGA-CHE TS during the treatment period were censored at the date of the last visit with a valid post-baseline assessment on or prior to the date of discontinuation of IMP or initiation of rescue medication, whichever occurred first.

| | |
|---|---|
| Comparison groups | Delgocitinib cream 8 mg/g v Delgocitinib cream vehicle |
| Number of subjects included in analysis | 102 |
| Analysis specification | Pre-specified |
| Analysis type | other[18] |
| P-value | < 0.0001 [19] |
| Method | Logrank |

Notes:

[18] - Treatment groups were compared using a 2-sided log-rank test stratified by region and baseline IGA-CHE score. An event was defined as the first time achieving IGA-CHE TS.
[19] - The statistical test was not controlled for multiplicity.

| **Statistical analysis title** | Delgocitinib cream 20 mg/g vs. vehicle cream |
|---|---|

Statistical analysis description:

Time to IGA-CHE TS was defined as the time from the date of the first IMP application to first assessment of IGA-CHE TS. Subjects without baseline observation were censored at the date of the first IMP application. Subjects with baseline observation not achieving IGA-CHE TS during the treatment period were censored at the date of the last visit with a valid post-baseline assessment on or prior to the

date of discontinuation of IMP or initiation of rescue medication, whichever occurred first.

| | |
|---|---|
| Comparison groups | Delgocitinib cream 20 mg/g v Delgocitinib cream vehicle |
| Number of subjects included in analysis | 103 |
| Analysis specification | Pre-specified |
| Analysis type | other[20] |
| P-value | < 0.01 [21] |
| Method | Logrank |

Notes:

[20] - Treatment groups were compared using a 2-sided log-rank test stratified by region and baseline IGA-CHE score. An event was defined as the first time achieving IGA-CHE TS.
[21] - The statistical test was not controlled for multiplicity.

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

18 weeks (from first application of IMP up until the last visit (safety follow-up visit))

Adverse event reporting additional description:

At all visits/phone call, the participants were asked a non-leading question by the investigator about AEs, for example: "How have you felt since I saw you last?" No specific symptoms were to be asked for.

| | |
|---|---|
| Assessment type | Non-systematic |

### Dictionary used

| | |
|---|---|
| Dictionary name | MedDRA |
| Dictionary version | 21.1 |

### Reporting groups

| | |
|---|---|
| Reporting group title | Delgocitinib cream 1 mg/g |
| Reporting group description: - | |
| Reporting group title | Delgocitinib cream 3 mg/g |
| Reporting group description: - | |
| Reporting group title | Delgocitinib cream 8 mg/g |
| Reporting group description: - | |
| Reporting group title | Delgocitinib cream 20 mg/g |
| Reporting group description: - | |
| Reporting group title | Delgocitinib cream vehicle |
| Reporting group description: - | |

| Serious adverse events | Delgocitinib cream 1 mg/g | Delgocitinib cream 3 mg/g | Delgocitinib cream 8 mg/g |
|---|---|---|---|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 0 / 52 (0.00%) | 2 / 51 (3.92%) | 1 / 52 (1.92%) |
| number of deaths (all causes) | 0 | 0 | 0 |
| number of deaths resulting from adverse events | 0 | 0 | 0 |
| Nervous system disorders | | | |
| Dizziness postural | | | |
| subjects affected / exposed | 0 / 52 (0.00%) | 1 / 51 (1.96%) | 0 / 52 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Skin and subcutaneous tissue disorders | | | |
| Pemphigoid | | | |
| subjects affected / exposed | 0 / 52 (0.00%) | 1 / 51 (1.96%) | 0 / 52 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Psychiatric disorders | | | |
| Anxiety | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 52 (0.00%) | 0 / 51 (0.00%) | 1 / 52 (1.92%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| **Serious adverse events** | Delgocitinib cream 20 mg/g | Delgocitinib cream vehicle | |
|---|---|---|---|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 0 / 53 (0.00%) | 0 / 50 (0.00%) | |
| number of deaths (all causes) | 0 | 0 | |
| number of deaths resulting from adverse events | 0 | 0 | |
| Nervous system disorders | | | |
| Dizziness postural | | | |
| subjects affected / exposed | 0 / 53 (0.00%) | 0 / 50 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Skin and subcutaneous tissue disorders | | | |
| Pemphigoid | | | |
| subjects affected / exposed | 0 / 53 (0.00%) | 0 / 50 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Psychiatric disorders | | | |
| Anxiety | | | |
| subjects affected / exposed | 0 / 53 (0.00%) | 0 / 50 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

Frequency threshold for reporting non-serious adverse events: 5 %

| **Non-serious adverse events** | Delgocitinib cream 1 mg/g | Delgocitinib cream 3 mg/g | Delgocitinib cream 8 mg/g |
|---|---|---|---|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 20 / 52 (38.46%) | 25 / 51 (49.02%) | 25 / 52 (48.08%) |
| Nervous system disorders | | | |
| Headache | | | |
| subjects affected / exposed | 2 / 52 (3.85%) | 2 / 51 (3.92%) | 6 / 52 (11.54%) |
| occurrences (all) | 2 | 4 | 7 |
| Gastrointestinal disorders | | | |

| | | | |
|---|---|---|---|
| Toothache | | | |
| subjects affected / exposed | 3 / 52 (5.77%) | 1 / 51 (1.96%) | 0 / 52 (0.00%) |
| occurrences (all) | 3 | 1 | 0 |
| Skin and subcutaneous tissue disorders | | | |
| Eczema | | | |
| subjects affected / exposed | 5 / 52 (9.62%) | 4 / 51 (7.84%) | 3 / 52 (5.77%) |
| occurrences (all) | 5 | 5 | 7 |
| Pruritus | | | |
| subjects affected / exposed | 3 / 52 (5.77%) | 2 / 51 (3.92%) | 1 / 52 (1.92%) |
| occurrences (all) | 3 | 2 | 1 |
| Dermatitis atopic | | | |
| subjects affected / exposed | 1 / 52 (1.92%) | 3 / 51 (5.88%) | 0 / 52 (0.00%) |
| occurrences (all) | 1 | 3 | 0 |
| Musculoskeletal and connective tissue disorders | | | |
| Back pain | | | |
| subjects affected / exposed | 1 / 52 (1.92%) | 0 / 51 (0.00%) | 2 / 52 (3.85%) |
| occurrences (all) | 1 | 0 | 2 |
| Infections and infestations | | | |
| Nasopharyngitis | | | |
| subjects affected / exposed | 9 / 52 (17.31%) | 15 / 51 (29.41%) | 15 / 52 (28.85%) |
| occurrences (all) | 11 | 22 | 16 |
| Influenza | | | |
| subjects affected / exposed | 1 / 52 (1.92%) | 1 / 51 (1.96%) | 0 / 52 (0.00%) |
| occurrences (all) | 1 | 1 | 0 |

| **Non-serious adverse events** | Delgocitinib cream 20 mg/g | Delgocitinib cream vehicle | |
|---|---|---|---|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 26 / 53 (49.06%) | 24 / 50 (48.00%) | |
| Nervous system disorders | | | |
| Headache | | | |
| subjects affected / exposed | 4 / 53 (7.55%) | 2 / 50 (4.00%) | |
| occurrences (all) | 5 | 2 | |
| Gastrointestinal disorders | | | |
| Toothache | | | |
| subjects affected / exposed | 0 / 53 (0.00%) | 0 / 50 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Skin and subcutaneous tissue disorders | | | |

| | | | |
|---|---|---|---|
| Eczema | | | |
| subjects affected / exposed | 6 / 53 (11.32%) | 8 / 50 (16.00%) | |
| occurrences (all) | 7 | 9 | |
| Pruritus | | | |
| subjects affected / exposed | 3 / 53 (5.66%) | 1 / 50 (2.00%) | |
| occurrences (all) | 3 | 1 | |
| Dermatitis atopic | | | |
| subjects affected / exposed | 0 / 53 (0.00%) | 0 / 50 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Musculoskeletal and connective tissue disorders | | | |
| Back pain | | | |
| subjects affected / exposed | 3 / 53 (5.66%) | 1 / 50 (2.00%) | |
| occurrences (all) | 3 | 1 | |
| Infections and infestations | | | |
| Nasopharyngitis | | | |
| subjects affected / exposed | 14 / 53 (26.42%) | 20 / 50 (40.00%) | |
| occurrences (all) | 20 | 20 | |
| Influenza | | | |
| subjects affected / exposed | 4 / 53 (7.55%) | 0 / 50 (0.00%) | |
| occurrences (all) | 4 | 0 | |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|---|---|
| 11 July 2018 | The main reason for the amendment was to add an exclusion criterion to ensure that participants who previously participated in a clinical trial with delgocitinib were not allowed to participate in this trial. The amendment was approved prior to first participant first visit. |
| 07 December 2018 | The main reason for the amendment was to address comments to the protocol received from the U.S. Food and Drug Administration (FDA). Exclusion criterion 1 was revised to ensure exclusion of participants with a diagnosis of tinea manuum. The participant's Global Assessment of disease severity (PaGa) scale was updated. The Patient Global Impression of Change (PGI-C) questionnaire was added as a PRO to support the planned psychometric properties analyses. A tuberculosis test was added to further safeguard participants in risk of (re)activation of latent tuberculosis. Participant assessment of local tolerability (stinging/burning) was added as an active safety assessment. Miscellaneous other changes/updates have also been implemented. |

Notes:

### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported