



Clinical trial results:

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

Summary

| | |
|--------------------------|-----------------|
| EudraCT number | 2020-002961-32 |
| Trial protocol | NL DK BE PL ES |
| Global end of trial date | 06 January 2023 |

Results information

| | |
|--------------------------------|-----------------|
| Result version number | v1 |
| This version publication date | 18 January 2024 |
| First version publication date | 18 January 2024 |

Trial information

Trial identification

| | |
|-----------------------|-------------|
| Sponsor protocol code | LP0133-1402 |
|-----------------------|-------------|

Additional study identifiers

| | |
|------------------------------------|---|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | - |
| 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, disclosure@leo-pharma.com |
| Scientific contact | Clinical Disclosure, LEO Pharma A/S, 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 | 25 January 2023 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 27 December 2022 |
| Global end of trial reached? | Yes |
| Global end of trial date | 06 January 2023 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

To confirm the efficacy of twice-daily applications of delgocitinib cream 20 mg/g compared with cream vehicle in the treatment of adult subjects with moderate to severe chronic hand eczema (CHE).

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 | 25 May 2021 |
| 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 | Canada: 97 |
| Country: Number of subjects enrolled | Netherlands: 24 |
| Country: Number of subjects enrolled | Poland: 96 |
| Country: Number of subjects enrolled | Spain: 65 |
| Country: Number of subjects enrolled | Belgium: 22 |
| Country: Number of subjects enrolled | Denmark: 22 |
| Country: Number of subjects enrolled | Germany: 147 |
| Worldwide total number of subjects | 473 |
| EEA total number of subjects | 376 |

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) | 436 |
| From 65 to 84 years | 36 |
| 85 years and over | 1 |

Subject disposition

Recruitment

Recruitment details:

473 participants from 49 sites in 7 countries (Belgium, Canada, Denmark, Germany, the Netherlands, Poland, and Spain) were randomised in this trial. The first participant was screened on 25-May-2021 and the last participant completed the trial on 06-Jan-2023.

Pre-assignment

Screening details:

557 participants were screened in this trial. Of these, 84 participants (15.1%) were excluded prior to randomisation. The main reason for exclusion prior to randomisation was screening failure (12.4%).

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 | Subject, Investigator, Assessor |

Blinding implementation details:

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

Arms

| | |
|--|----------------------------|
| Are arms mutually exclusive? | Yes |
| Arm title | Delgocitinib cream 20 mg/g |
| Arm description: - | |
| Arm type | Experimental |
| Investigational medicinal product name | Delgocitinib cream |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Cream |
| Routes of administration | Topical use |

Dosage and administration details:

A thin layer covering the affected areas twice daily for 16 weeks. The applications were to be performed approximately 12 hours apart to clean and dry skin of the affected areas of the hands and wrists.

| | |
|--|---------------|
| Arm title | Cream vehicle |
| Arm description: - | |
| Arm type | Placebo |
| Investigational medicinal product name | Cream vehicle |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Cream |
| Routes of administration | Topical use |

Dosage and administration details:

A thin layer covering the affected areas twice daily for 16 weeks. The applications were to be performed approximately 12 hours apart to clean and dry skin of the affected areas of the hands and wrists.

| Number of subjects in period 1 | Delgocitinib cream 20 mg/g | Cream vehicle |
|---------------------------------------|-------------------------------|---------------|
| Started | 314 | 159 |
| Completed | 291 | 122 |
| Not completed | 23 | 37 |
| Consent withdrawn by subject | 10 | 16 |
| Adverse event, non-fatal | 1 | 6 |
| Other | 1 | - |
| Pregnancy | 2 | - |
| Lost to follow-up | 2 | 1 |
| Not dosed | 1 | - |
| Lack of efficacy | 6 | 14 |

Baseline characteristics

Reporting groups

| | |
|--------------------------------|----------------------------|
| Reporting group title | Delgocitinib cream 20 mg/g |
| Reporting group description: - | |
| Reporting group title | Cream vehicle |
| Reporting group description: - | |

| Reporting group values | Delgocitinib cream 20 mg/g | Cream vehicle | Total |
|--|----------------------------|---------------|-------|
| Number of subjects | 314 | 159 | 473 |
| Age categorical 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) | 286 | 150 | 436 |
| From 65-84 years | 28 | 8 | 36 |
| 85 years and over | 0 | 1 | 1 |
| Age continuous Units: years | | | |
| arithmetic mean | 45.3 | 42.6 | |
| standard deviation | ± 14.6 | ± 14.3 | - |
| Gender categorical Units: Subjects | | | |
| Female | 204 | 108 | 312 |
| Male | 110 | 51 | 161 |
| Baseline IGA-CHE score Units: Subjects | | | |
| 0 - Clear | 0 | 0 | 0 |
| 1 - Almost clear | 0 | 0 | 0 |
| 2 - Mild | 0 | 0 | 0 |
| 3 - Moderate | 239 | 121 | 360 |
| 4 - Severe | 75 | 38 | 113 |
| Baseline HECSI score Units: Units on a scale | | | |
| arithmetic mean | 64.3 | 67.7 | |
| standard deviation | ± 37.9 | ± 39.5 | - |

End points

End points reporting groups

| | |
|--|----------------------------|
| Reporting group title | Delgocitinib cream 20 mg/g |
| Reporting group description: - | |
| Reporting group title | Cream vehicle |
| Reporting group description: - | |
| Subject analysis set title | Full analysis set |
| Subject analysis set type | Full analysis |
| Subject analysis set description: All participants randomized and exposed to IMP. | |
| Subject analysis set title | Safety analysis set |
| Subject analysis set type | Safety analysis |
| Subject analysis set description: All participants exposed to IMP. | |

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 from baseline (IGA-CHE treatment success [IGA-CHE TS]) at 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 from baseline (IGA-CHE treatment success [IGA-CHE TS]) at Week 16. |
| End point description: IGA-CHE rates the severity of the participant's global disease 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 20 mg/g | Cream vehicle | | |
|-------------------------------------|----------------------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 313 | 159 | | |
| Units: Participants with IGA-CHE TS | 91 | 11 | | |

Statistical analyses

| | |
|--|--|
| Statistical analysis title | Delgocitinib cream 20 mg/g vs. cream vehicle |
| Statistical analysis description: Based on the primary analysis of the primary estimand 'composite'. The difference in response rates between delgocitinib cream 20 mg/g and cream vehicle was analysed using the Cochran-Mantel-Haenszel test stratified by region and disease severity (baseline IGA-CHE score). Subjects with missing data, subjects who received rescue treatment, or subjects who permanently discontinued IMP were considered non-responders. | |
| Comparison groups | Delgocitinib cream 20 mg/g v Cream vehicle |

| | |
|---|-------------------------|
| Number of subjects included in analysis | 472 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 ^[1] |
| Method | Cochran-Mantel-Haenszel |
| Parameter estimate | Risk difference (RD) |
| Point estimate | 22.2 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 15.8 |
| upper limit | 28.5 |

Notes:

[1] - 5% significance level (two-sided).

Secondary: IGA-CHE TS at Week 8.

| | |
|--|-----------------------|
| End point title | IGA-CHE TS at Week 8. |
| End point description: | |
| IGA-CHE rates the severity of the participant's global disease and is based on a 5-point scale ranging from 0 (clear) to 4 (severe). | |
| End point type | Secondary |
| End point timeframe: | |
| Week 0 to Week 8 | |

| End point values | Delgocitinib cream 20 mg/g | Cream vehicle | | |
|-------------------------------------|----------------------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 313 | 159 | | |
| Units: Participants with IGA-CHE TS | 101 | 15 | | |

Statistical analyses

| | |
|---|--|
| Statistical analysis title | Delgocitinib cream 20 mg/g vs. cream vehicle |
| Statistical analysis description: | |
| Based on the primary analysis of the primary estimand 'composite'. The difference in response rates between delgocitinib cream 20 mg/g and cream vehicle was analysed using the Cochran-Mantel-Haenszel test stratified by region and disease severity (baseline IGA-CHE score). Subjects with missing data, subjects who received rescue treatment, or subjects who permanently discontinued IMP were considered non-responders. | |
| Comparison groups | Delgocitinib cream 20 mg/g v Cream vehicle |
| Number of subjects included in analysis | 472 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 ^[2] |
| Method | Cochran-Mantel-Haenszel |
| Parameter estimate | Risk difference (RD) |
| Point estimate | 22.9 |

| | |
|---------------------|---------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 16 |
| upper limit | 29.8 |

Notes:

[2] - Evaluated at 5% significance level (two-sided) and significant as per testing hierarchy using hierarchical tests, alpha splitting and alpha recycling controlling overall type 1 error at 5% (two-sided).

Secondary: IGA-CHE TS at Week 4.

| | |
|--|-----------------------|
| End point title | IGA-CHE TS at Week 4. |
| End point description: | |
| IGA-CHE rates the severity of the participant's global disease and is based on a 5-point scale ranging from 0 (clear) to 4 (severe). | |
| End point type | Secondary |
| End point timeframe: | |
| Week 0 to Week 4 | |

| End point values | Delgocitinib cream 20 mg/g | Cream vehicle | | |
|-------------------------------------|----------------------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 313 | 159 | | |
| Units: Participants with IGA-CHE TS | 46 | 13 | | |

Statistical analyses

| | |
|---|--|
| Statistical analysis title | Delgocitinib cream 20 mg/g vs. cream vehicle |
| Statistical analysis description: | |
| Based on the primary analysis of the primary estimand 'composite'. The difference in response rates between delgocitinib cream 20 mg/g and cream vehicle was analysed using the Cochran-Mantel-Haenszel test stratified by region and disease severity (baseline IGA-CHE score). Subjects with missing data, subjects who received rescue treatment, or subjects who permanently discontinued IMP were considered non-responders. | |
| Comparison groups | Delgocitinib cream 20 mg/g v Cream vehicle |
| Number of subjects included in analysis | 472 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.043 ^[3] |
| Method | Cochran-Mantel-Haenszel |
| Parameter estimate | Risk difference (RD) |
| Point estimate | 6.5 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.8 |
| upper limit | 12.3 |

Notes:

[3] - Evaluated at 5% significance level (two-sided) and significant as per testing hierarchy using hierarchical tests, alpha splitting and alpha recycling controlling overall type 1 error at 5% (two-sided).

Secondary: At least 75% improvement in Hand Eczema Severity Index (HECSI) score from baseline (HECSI-75) at Week 16.

| | |
|-----------------|---|
| End point title | At least 75% improvement in Hand Eczema Severity Index (HECSI) score from baseline (HECSI-75) at 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 20 mg/g | Cream vehicle | | |
|-----------------------------------|----------------------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 313 | 159 | | |
| Units: Participants with HECSI-75 | 155 | 29 | | |

Statistical analyses

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

Statistical analysis description:

Based on the primary analysis of the primary estimand 'composite'. The difference in response rates between delgocitinib cream 20 mg/g and cream vehicle was analysed using the Cochran-Mantel-Haenszel test stratified by region and disease severity (baseline IGA-CHE score). Subjects with missing data, subjects who received rescue treatment, or subjects who permanently discontinued IMP were considered non-responders.

| | |
|---|--|
| Comparison groups | Delgocitinib cream 20 mg/g v Cream vehicle |
| Number of subjects included in analysis | 472 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 ^[4] |
| Method | Cochran-Mantel-Haenszel |
| Parameter estimate | Risk difference (RD) |
| Point estimate | 31.3 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 23.1 |
| upper limit | 39.5 |

Notes:

[4] - Evaluated at 1% significance level (two-sided) and significant as per testing hierarchy using hierarchical tests, alpha splitting and alpha recycling controlling overall type 1 error at 5% (two-sided).

Secondary: HECSI-75 at Week 8.

| | |
|-----------------|---------------------|
| End point title | HECSI-75 at Week 8. |
|-----------------|---------------------|

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 8

| End point values | Delgocitinib cream 20 mg/g | Cream vehicle | | |
|-----------------------------------|----------------------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 313 | 159 | | |
| Units: Participants with HECSI-75 | 158 | 31 | | |

Statistical analyses

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

Statistical analysis description:

Based on the primary analysis of the primary estimand 'composite'. The difference in response rates between delgocitinib cream 20 mg/g and cream vehicle was analysed using the Cochran-Mantel-Haenszel test stratified by region and disease severity (baseline IGA-CHE score). Subjects with missing data, subjects who received rescue treatment, or subjects who permanently discontinued IMP were considered non-responders.

| | |
|---|--|
| Comparison groups | Delgocitinib cream 20 mg/g v Cream vehicle |
| Number of subjects included in analysis | 472 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 ^[5] |
| Method | Cochran-Mantel-Haenszel |
| Parameter estimate | Risk difference (RD) |
| Point estimate | 31 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 22.7 |
| upper limit | 39.3 |

Notes:

[5] - Evaluated at 1% significance level (two-sided) and significant as per testing hierarchy using hierarchical tests, alpha splitting and alpha recycling controlling overall type 1 error at 5% (two-sided).

Secondary: At least 90% improvement in HECSI score from baseline (HECSI-90) at Week 16.

| | |
|-----------------|--|
| End point title | At least 90% improvement in HECSI score from baseline (HECSI-90) at 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 20 mg/g | Cream vehicle | | |
|-----------------------------------|----------------------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 313 | 159 | | |
| Units: Participants with HECSI-90 | 97 | 14 | | |

Statistical analyses

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

Statistical analysis description:

Based on the primary analysis of the primary estimand 'composite'. The difference in response rates between delgocitinib cream 20 mg/g and cream vehicle was analysed using the Cochran-Mantel-Haenszel test stratified by region and disease severity (baseline IGA-CHE score). Subjects with missing data, subjects who received rescue treatment, or subjects who permanently discontinued IMP were considered non-responders.

| | |
|---|--|
| Comparison groups | Delgocitinib cream 20 mg/g v Cream vehicle |
| Number of subjects included in analysis | 472 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 ^[6] |
| Method | Cochran-Mantel-Haenszel |
| Parameter estimate | Risk difference (RD) |
| Point estimate | 22.2 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 15.4 |
| upper limit | 29 |

Notes:

[6] - Evaluated at 1% significance level (two-sided) and significant as per testing hierarchy using hierarchical tests, alpha splitting and alpha recycling controlling overall type 1 error at 5% (two-sided).

Secondary: Percentage change in HECSI score from baseline to Week 16.

| | |
|-----------------|--|
| End point title | Percentage change in HECSI score 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 20 mg/g | Cream vehicle | | |
|---|----------------------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 313 | 159 | | |
| Units: Percentage change in HECSI score | | | | |
| least squares mean (standard error) | -58.9 (± 3.2) | -13.4 (± 4.5) | | |

Statistical analyses

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

Statistical analysis description:

Primary analysis of primary estimand 'composite'. The percentage change from baseline was analysed using an ANCOVA model with effects of treatment group, region, baseline IGA-CHE score, and baseline HESCI value. Missing data for subjects who did not attend the visit was imputed as WOCF (including baseline value). For subjects who received rescue treatment or subjects who have permanently discontinued the IMP, observed data was considered non-response by using WOCF (including baseline value).

| | |
|---|--|
| Comparison groups | Delgocitinib cream 20 mg/g v Cream vehicle |
| Number of subjects included in analysis | 472 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 ^[7] |
| Method | ANCOVA |
| Parameter estimate | Mean difference (net) |
| Point estimate | -45.5 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -56.4 |
| upper limit | -34.6 |

Notes:

[7] - Evaluated at 1% significance level (two-sided) and significant as per testing hierarchy using hierarchical tests, alpha splitting and alpha recycling controlling overall type 1 error at 5% (two-sided).

Secondary: Reduction of Hand Eczema Symptom Diary (HESD) itch score (weekly average) of ≥4 points from baseline at Week 16.

| | |
|-----------------|--|
| End point title | Reduction of Hand Eczema Symptom Diary (HESD) itch score (weekly average) of ≥4 points from baseline at Week 16. |
|-----------------|--|

End point description:

HESD is a 6-item PRO instrument designed to assess severity of CHE signs and symptoms. Participants assess the worst severity of 6 individual signs and symptoms of CHE over the past 24 hours using an 11-point numeric rating scale with anchors of 0 = 'no (symptom)' and 10 = 'severe (symptom)'. The HESD score is derived as an average of the 6 items.

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

End point timeframe:

Week 0 to Week 16

| End point values | Delgocitinib cream 20 mg/g | Cream vehicle | | |
|--|----------------------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 309 | 156 | | |
| Units: Participants with ≥ 4 points reduction | 146 | 31 | | |

Statistical analyses

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

Statistical analysis description:

Based on the primary analysis of the primary estimand 'composite'. The difference in response rates between delgocitinib cream 20 mg/g and cream vehicle was analysed using the Cochran-Mantel-Haenszel test stratified by region and disease severity (baseline IGA-CHE score). Subjects with missing data, subjects who received rescue treatment, or subjects who permanently discontinued IMP were considered non-responders.

| | |
|---|--|
| Comparison groups | Cream vehicle v Delgocitinib cream 20 mg/g |
| Number of subjects included in analysis | 465 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 ^[8] |
| Method | Cochran-Mantel-Haenszel |
| Parameter estimate | Risk difference (RD) |
| Point estimate | 27.4 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 19 |
| upper limit | 35.8 |

Notes:

[8] - Evaluated at 5% significance level (two-sided) and significant as per testing hierarchy using hierarchical tests, alpha splitting and alpha recycling controlling overall type 1 error at 5% (two-sided).

Secondary: Reduction of HESD itch score (weekly average) of ≥ 4 points from baseline at Week 8.

| | |
|-----------------|---|
| End point title | Reduction of HESD itch score (weekly average) of ≥ 4 points from baseline at Week 8. |
|-----------------|---|

End point description:

HESD is a 6-item PRO instrument designed to assess severity of CHE signs and symptoms. Participants assess the worst severity of 6 individual signs and symptoms of CHE over the past 24 hours using an 11-point numeric rating scale with anchors of 0 = 'no (symptom)' and 10 = 'severe (symptom)'. The HESD score is derived as an average of the 6 items.

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

End point timeframe:

Week 0 to Week 8

| | | | | |
|--|----------------------------|-----------------|--|--|
| End point values | Delgocitinib cream 20 mg/g | Cream vehicle | | |
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 309 | 156 | | |
| Units: Participants with ≥ 4 points reduction | 131 | 21 | | |

Statistical analyses

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

Statistical analysis description:

Based on the primary analysis of the primary estimand 'composite'. The difference in response rates between delgocitinib cream 20 mg/g and cream vehicle was analysed using the Cochran-Mantel-Haenszel test stratified by region and disease severity (baseline IGA-CHE score). Subjects with missing data, subjects who received rescue treatment, or subjects who permanently discontinued IMP were considered non-responders.

| | |
|---|--|
| Comparison groups | Delgocitinib cream 20 mg/g v Cream vehicle |
| Number of subjects included in analysis | 465 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 ^[9] |
| Method | Cochran-Mantel-Haenszel |
| Parameter estimate | Risk difference (RD) |
| Point estimate | 29 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 21.3 |
| upper limit | 36.7 |

Notes:

[9] - Evaluated at 5% significance level (two-sided) and significant as per testing hierarchy using hierarchical tests, alpha splitting and alpha recycling controlling overall type 1 error at 5% (two-sided).

Secondary: Reduction of HESD itch score (weekly average) of ≥ 4 points from baseline at Week 4.

| | |
|-----------------|---|
| End point title | Reduction of HESD itch score (weekly average) of ≥ 4 points from baseline at Week 4. |
|-----------------|---|

End point description:

| | |
|----------------------|-----------|
| End point type | Secondary |
| End point timeframe: | |
| Week 0 to Week 4 | |

| | | | | |
|--|----------------------------|-----------------|--|--|
| End point values | Delgocitinib cream 20 mg/g | Cream vehicle | | |
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 309 | 156 | | |
| Units: Participants with ≥ 4 points reduction | 94 | 19 | | |

Statistical analyses

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

Statistical analysis description:

Based on the primary analysis of the primary estimand 'composite'. The difference in response rates between delgocitinib cream 20 mg/g and cream vehicle was analysed using the Cochran-Mantel-Haenszel test stratified by region and disease severity (baseline IGA-CHE score). Subjects with missing data, subjects who received rescue treatment, or subjects who permanently discontinued IMP were considered non-responders.

| | |
|---|--|
| Comparison groups | Delgocitinib cream 20 mg/g v Cream vehicle |
| Number of subjects included in analysis | 465 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 ^[10] |
| Method | Cochran-Mantel-Haenszel |
| Parameter estimate | Risk difference (RD) |
| Point estimate | 18.3 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 11 |
| upper limit | 25.6 |

Notes:

[10] - Evaluated at 5% significance level (two-sided) and significant as per testing hierarchy using hierarchical tests, alpha splitting and alpha recycling controlling overall type 1 error at 5% (two-sided).

Secondary: Reduction of HESD itch score (weekly average) of ≥ 4 points from baseline at Week 2.

| | |
|-----------------|---|
| End point title | Reduction of HESD itch score (weekly average) of ≥ 4 points from baseline at Week 2. |
|-----------------|---|

End point description:

HESD is a 6-item PRO instrument designed to assess severity of CHE signs and symptoms. Participants assess the worst severity of 6 individual signs and symptoms of CHE over the past 24 hours using an 11-point numeric rating scale with anchors of 0 = 'no (symptom)' and 10 = 'severe (symptom)'. The HESD score is derived as an average of the 6 items.

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

End point timeframe:

Week 0 to Week 2

| | | | | |
|--|----------------------------|-----------------|--|--|
| End point values | Delgocitinib cream 20 mg/g | Cream vehicle | | |
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 309 | 156 | | |
| Units: Participants with ≥ 4 points reduction | 40 | 10 | | |

Statistical analyses

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

Statistical analysis description:

Based on the primary analysis of the primary estimand 'composite'. The difference in response rates between delgocitinib cream 20 mg/g and cream vehicle was analysed using the Cochran-Mantel-Haenszel test stratified by region and disease severity (baseline IGA-CHE score). Subjects with missing data, subjects who received rescue treatment, or subjects who permanently discontinued IMP were considered non-responders.

| | |
|---|--|
| Comparison groups | Delgocitinib cream 20 mg/g v Cream vehicle |
| Number of subjects included in analysis | 465 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.031 ^[11] |
| Method | Cochran-Mantel-Haenszel |
| Parameter estimate | Risk difference (RD) |
| Point estimate | 6.6 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 1.1 |
| upper limit | 12 |

Notes:

[11] - Evaluated at 5% significance level (two-sided) and significant as per testing hierarchy using hierarchical tests, alpha splitting and alpha recycling controlling overall type 1 error at 5% (two-sided).

Secondary: Change in HESD itch score (weekly average) from baseline to Week 16.

| | |
|-----------------|--|
| End point title | Change in HESD itch score (weekly average) from baseline to Week 16. |
|-----------------|--|

End point description:

HESD is a 6-item PRO instrument designed to assess severity of CHE signs and symptoms. Participants assess the worst severity of 6 individual signs and symptoms of CHE over the past 24 hours using an 11-point numeric rating scale with anchors of 0 = 'no (symptom)' and 10 = 'severe (symptom)'. The HESD score is derived as an average of the 6 items.

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

End point timeframe:

Week 0 to Week 16

| | | | | |
|-------------------------------------|----------------------------|-----------------|--|--|
| End point values | Delgocitinib cream 20 mg/g | Cream vehicle | | |
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 312 | 157 | | |
| Units: Change in HESD itch score | | | | |
| least squares mean (standard error) | -3.4 (± 0.2) | -1.4 (± 0.2) | | |

Statistical analyses

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

Statistical analysis description:

Primary analysis of primary estimand 'composite'. The percentage change from baseline was analysed using an ANCOVA model with effects of treatment group, region, baseline IGA-CHE score, and baseline HESD itch value. Missing data for subjects who did not attend the visit was imputed as WOCF (including baseline value). For subjects who received rescue treatment or subjects who have permanently discontinued the IMP, observed data was considered non-response by using WOCF (including baseline value)

| | |
|---|--|
| Comparison groups | Delgocitinib cream 20 mg/g v Cream vehicle |
| Number of subjects included in analysis | 469 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 ^[12] |
| Method | ANCOVA |
| Parameter estimate | Mean difference (net) |
| Point estimate | -2 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -2.5 |
| upper limit | -1.4 |

Notes:

[12] - Evaluated at 1% significance level (two-sided) and significant as per testing hierarchy using hierarchical tests, alpha splitting and alpha recycling controlling overall type 1 error at 5% (two-sided).

Secondary: Reduction of HESD score (weekly average) of ≥4 points from baseline at Week 16.

| | |
|-----------------|---|
| End point title | Reduction of HESD score (weekly average) of ≥4 points from baseline at Week 16. |
|-----------------|---|

End point description:

HESD is a 6-item PRO instrument designed to assess severity of CHE signs and symptoms. Participants assess the worst severity of 6 individual signs and symptoms of CHE over the past 24 hours using an 11-point numeric rating scale with anchors of 0 = 'no (symptom)' and 10 = 'severe (symptom)'. The HESD score is derived as an average of the 6 items.

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

End point timeframe:

Week 0 to Week 16

| | | | | |
|--|----------------------------|-----------------|--|--|
| End point values | Delgocitinib cream 20 mg/g | Cream vehicle | | |
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 308 | 153 | | |
| Units: Participants with ≥ 4 points reduction | 137 | 32 | | |

Statistical analyses

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

Statistical analysis description:

Based on the primary analysis of the primary estimand 'composite'. The difference in response rates between delgocitinib cream 20 mg/g and cream vehicle was analysed using the Cochran-Mantel-Haenszel test stratified by region and disease severity (baseline IGA-CHE score). Subjects with missing data, subjects who received rescue treatment, or subjects who permanently discontinued IMP were considered non-responders.

| | |
|---|--|
| Comparison groups | Delgocitinib cream 20 mg/g v Cream vehicle |
| Number of subjects included in analysis | 461 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 ^[13] |
| Method | Cochran-Mantel-Haenszel |
| Parameter estimate | Risk difference (RD) |
| Point estimate | 23.7 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 15.1 |
| upper limit | 32.2 |

Notes:

[13] - Evaluated at 5% significance level (two-sided) and significant as per testing hierarchy using hierarchical tests, alpha splitting and alpha recycling controlling overall type 1 error at 5% (two-sided).

Secondary: Reduction of HESD score (weekly average) of ≥ 4 points from baseline at Week 8.

| | |
|-----------------|--|
| End point title | Reduction of HESD score (weekly average) of ≥ 4 points from baseline at Week 8. |
|-----------------|--|

End point description:

HESD is a 6-item PRO instrument designed to assess severity of CHE signs and symptoms. Participants assess the worst severity of 6 individual signs and symptoms of CHE over the past 24 hours using an 11-point numeric rating scale with anchors of 0 = 'no (symptom)' and 10 = 'severe (symptom)'. The HESD score is derived as an average of the 6 items.

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

End point timeframe:

Week 0 to Week 8

| | | | | |
|--|----------------------------|-----------------|--|--|
| End point values | Delgocitinib cream 20 mg/g | Cream vehicle | | |
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 308 | 153 | | |
| Units: Participants with ≥ 4 points reduction | 115 | 19 | | |

Statistical analyses

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

Statistical analysis description:

Based on the primary analysis of the primary estimand 'composite'. The difference in response rates between delgocitinib cream 20 mg/g and cream vehicle was analysed using the Cochran-Mantel-Haenszel test stratified by region and disease severity (baseline IGA-CHE score). Subjects with missing data, subjects who received rescue treatment, or subjects who permanently discontinued IMP were considered non-responders.

| | |
|---|--|
| Comparison groups | Delgocitinib cream 20 mg/g v Cream vehicle |
| Number of subjects included in analysis | 461 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 ^[14] |
| Method | Cochran-Mantel-Haenszel |
| Parameter estimate | Risk difference (RD) |
| Point estimate | 25 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 17.5 |
| upper limit | 32.5 |

Notes:

[14] - Evaluated at 5% significance level (two-sided) and significant as per testing hierarchy using hierarchical tests, alpha splitting and alpha recycling controlling overall type 1 error at 5% (two-sided).

Secondary: Reduction of HESD score (weekly average) of ≥ 4 points from baseline at Week 4.

| | |
|-----------------|--|
| End point title | Reduction of HESD score (weekly average) of ≥ 4 points from baseline at Week 4. |
|-----------------|--|

End point description:

HESD is a 6-item PRO instrument designed to assess severity of CHE signs and symptoms. Participants assess the worst severity of 6 individual signs and symptoms of CHE over the past 24 hours using an 11-point numeric rating scale with anchors of 0 = 'no (symptom)' and 10 = 'severe (symptom)'. The HESD score is derived as an average of the 6 items.

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

End point timeframe:

Week 0 to Week 4

| | | | | |
|--|----------------------------|-----------------|--|--|
| End point values | Delgocitinib cream 20 mg/g | Cream vehicle | | |
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 308 | 153 | | |
| Units: Participants with ≥ 4 points reduction | 80 | 14 | | |

Statistical analyses

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

Statistical analysis description:

Based on the primary analysis of the primary estimand 'composite'. The difference in response rates between delgocitinib cream 20 mg/g and cream vehicle was analysed using the Cochran-Mantel-Haenszel test stratified by region and disease severity (baseline IGA-CHE score). Subjects with missing data, subjects who received rescue treatment, or subjects who permanently discontinued IMP were considered non-responders.

| | |
|---|--|
| Comparison groups | Delgocitinib cream 20 mg/g v Cream vehicle |
| Number of subjects included in analysis | 461 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 ^[15] |
| Method | Cochran-Mantel-Haenszel |
| Parameter estimate | Risk difference (RD) |
| Point estimate | 16.9 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 10.2 |
| upper limit | 23.7 |

Notes:

[15] - Evaluated at 5% significance level (two-sided) and significant as per testing hierarchy using hierarchical tests, alpha splitting and alpha recycling controlling overall type 1 error at 5% (two-sided).

Secondary: Change in HESD score (weekly average) from baseline to Week 16.

| | |
|-----------------|---|
| End point title | Change in HESD score (weekly average) from baseline to Week 16. |
|-----------------|---|

End point description:

HESD is a 6-item PRO instrument designed to assess severity of CHE signs and symptoms. Participants assess the worst severity of 6 individual signs and symptoms of CHE over the past 24 hours using an 11-point numeric rating scale with anchors of 0 = 'no (symptom)' and 10 = 'severe (symptom)'. The HESD score is derived as an average of the 6 items.

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

End point timeframe:

Week 0 to Week 16

| | | | | |
|-------------------------------------|----------------------------|-----------------|--|--|
| End point values | Delgocitinib cream 20 mg/g | Cream vehicle | | |
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 312 | 157 | | |
| Units: Change in HESD score | | | | |
| least squares mean (standard error) | -3.2 (± 0.1) | -1.4 (± 0.2) | | |

Statistical analyses

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

Statistical analysis description:

Primary analysis of primary estimand 'composite'. The percentage change from baseline was analysed using an ANCOVA model with effects of treatment group, region, baseline IGA-CHE score, and baseline HESD value. Missing data for subjects who did not attend the visit was imputed as WOCF (including baseline value). For subjects who received rescue treatment or subjects who have permanently discontinued the IMP, observed data was considered non-response by using WOCF (including baseline value).

| | |
|---|--|
| Comparison groups | Delgocitinib cream 20 mg/g v Cream vehicle |
| Number of subjects included in analysis | 469 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 ^[16] |
| Method | ANCOVA |
| Parameter estimate | Mean difference (net) |
| Point estimate | -1.9 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -2.4 |
| upper limit | -1.4 |

Notes:

[16] - Evaluated at 1% significance level (two-sided) and significant as per testing hierarchy using hierarchical tests, alpha splitting and alpha recycling controlling overall type 1 error at 5% (two-sided).

Secondary: Reduction of HESD pain score (weekly average) of ≥4 points from baseline at Week 16.

| | |
|-----------------|--|
| End point title | Reduction of HESD pain score (weekly average) of ≥4 points from baseline at Week 16. |
|-----------------|--|

End point description:

HESD is a 6-item PRO instrument designed to assess severity of CHE signs and symptoms. Participants assess the worst severity of 6 individual signs and symptoms of CHE over the past 24 hours using an 11-point numeric rating scale with anchors of 0 = 'no (symptom)' and 10 = 'severe (symptom)'. The HESD score is derived as an average of the 6 items.

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

End point timeframe:

Week 0 to Week 16

| | | | | |
|--|----------------------------|-----------------|--|--|
| End point values | Delgocitinib cream 20 mg/g | Cream vehicle | | |
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 294 | 141 | | |
| Units: Participants with ≥ 4 points reduction | 143 | 32 | | |

Statistical analyses

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

Statistical analysis description:

Based on the primary analysis of the primary estimand 'composite'. The difference in response rates between delgocitinib cream 20 mg/g and cream vehicle was analysed using the Cochran-Mantel-Haenszel test stratified by region and disease severity (baseline IGA-CHE score). Subjects with missing data, subjects who received rescue treatment, or subjects who permanently discontinued IMP were considered non-responders.

| | |
|---|--|
| Comparison groups | Delgocitinib cream 20 mg/g v Cream vehicle |
| Number of subjects included in analysis | 435 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 ^[17] |
| Method | Cochran-Mantel-Haenszel |
| Parameter estimate | Risk difference (RD) |
| Point estimate | 26 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 17 |
| upper limit | 35.1 |

Notes:

[17] - Evaluated at 5% significance level (two-sided) and significant as per testing hierarchy using hierarchical tests, alpha splitting and alpha recycling controlling overall type 1 error at 5% (two-sided).

Secondary: Reduction of HESD pain score (weekly average) of ≥ 4 points from baseline at Week 8.

| | |
|-----------------|---|
| End point title | Reduction of HESD pain score (weekly average) of ≥ 4 points from baseline at Week 8. |
|-----------------|---|

End point description:

HESD is a 6-item PRO instrument designed to assess severity of CHE signs and symptoms. Participants assess the worst severity of 6 individual signs and symptoms of CHE over the past 24 hours using an 11-point numeric rating scale with anchors of 0 = 'no (symptom)' and 10 = 'severe (symptom)'. The HESD score is derived as an average of the 6 items.

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

End point timeframe:

Week 0 to Week 8

| | | | | |
|--|----------------------------|-----------------|--|--|
| End point values | Delgocitinib cream 20 mg/g | Cream vehicle | | |
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 294 | 141 | | |
| Units: Participants with ≥ 4 points reduction | 124 | 18 | | |

Statistical analyses

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

Statistical analysis description:

Based on the primary analysis of the primary estimand 'composite'. The difference in response rates between delgocitinib cream 20 mg/g and cream vehicle was analysed using the Cochran-Mantel-Haenszel test stratified by region and disease severity (baseline IGA-CHE score). Subjects with missing data, subjects who received rescue treatment, or subjects who permanently discontinued IMP were considered non-responders.

| | |
|---|--|
| Comparison groups | Delgocitinib cream 20 mg/g v Cream vehicle |
| Number of subjects included in analysis | 435 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 ^[18] |
| Method | Cochran-Mantel-Haenszel |
| Parameter estimate | Risk difference (RD) |
| Point estimate | 29.6 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 21.7 |
| upper limit | 37.4 |

Notes:

[18] - Evaluated at 5% significance level (two-sided) and significant as per testing hierarchy using hierarchical tests, alpha splitting and alpha recycling controlling overall type 1 error at 5% (two-sided).

Secondary: Reduction of HESD pain score (weekly average) of ≥ 4 points from baseline at Week 4.

| | |
|-----------------|---|
| End point title | Reduction of HESD pain score (weekly average) of ≥ 4 points from baseline at Week 4. |
|-----------------|---|

End point description:

HESD is a 6-item PRO instrument designed to assess severity of CHE signs and symptoms. Participants assess the worst severity of 6 individual signs and symptoms of CHE over the past 24 hours using an 11-point numeric rating scale with anchors of 0 = 'no (symptom)' and 10 = 'severe (symptom)'. The HESD score is derived as an average of the 6 items.

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

End point timeframe:

Week 0 to Week 4

| | | | | |
|--|----------------------------|-----------------|--|--|
| End point values | Delgocitinib cream 20 mg/g | Cream vehicle | | |
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 294 | 141 | | |
| Units: Participants with ≥ 4 points reduction | 91 | 15 | | |

Statistical analyses

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

Statistical analysis description:

Based on the primary analysis of the primary estimand 'composite'. The difference in response rates between delgocitinib cream 20 mg/g and cream vehicle was analysed using the Cochran-Mantel-Haenszel test stratified by region and disease severity (baseline IGA-CHE score). Subjects with missing data, subjects who received rescue treatment, or subjects who permanently discontinued IMP were considered non-responders.

| | |
|---|--|
| Comparison groups | Delgocitinib cream 20 mg/g v Cream vehicle |
| Number of subjects included in analysis | 435 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 ^[19] |
| Method | Cochran-Mantel-Haenszel |
| Parameter estimate | Risk difference (RD) |
| Point estimate | 20.5 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 13.1 |
| upper limit | 27.8 |

Notes:

[19] - Evaluated at 5% significance level (two-sided) and significant as per testing hierarchy using hierarchical tests, alpha splitting and alpha recycling controlling overall type 1 error at 5% (two-sided).

Secondary: Change in HESD pain score (weekly average) from baseline to Week 16.

| | |
|-----------------|--|
| End point title | Change in HESD pain score (weekly average) from baseline to Week 16. |
|-----------------|--|

End point description:

HESD is a 6-item PRO instrument designed to assess severity of CHE signs and symptoms. Participants assess the worst severity of 6 individual signs and symptoms of CHE over the past 24 hours using an 11-point numeric rating scale with anchors of 0 = 'no (symptom)' and 10 = 'severe (symptom)'. The HESD score is derived as an average of the 6 items.

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

End point timeframe:

Week 0 to Week 16

| | | | | |
|-------------------------------------|----------------------------|-----------------|--|--|
| End point values | Delgocitinib cream 20 mg/g | Cream vehicle | | |
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 312 | 157 | | |
| Units: Change in HESD pain score | | | | |
| least squares mean (standard error) | -3.3 (± 0.2) | -1.3 (± 0.2) | | |

Statistical analyses

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

Statistical analysis description:

Primary analysis of primary estimand 'composite'. The percentage change from baseline was analysed using an ANCOVA model with effects of treatment group, region, baseline IGA-CHE score, and baseline HESD pain value. Missing data for subjects who did not attend the visit was imputed as WOCF (including baseline value). For subjects who received rescue treatment or subjects who have permanently discontinued the IMP, observed data was considered non-response by using WOCF (including baseline value)

| | |
|---|--|
| Comparison groups | Delgocitinib cream 20 mg/g v Cream vehicle |
| Number of subjects included in analysis | 469 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 ^[20] |
| Method | ANCOVA |
| Parameter estimate | Mean difference (net) |
| Point estimate | -2 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -2.6 |
| upper limit | -1.5 |

Notes:

[20] - Evaluated at 1% significance level (two-sided) and significant as per testing hierarchy using hierarchical tests, alpha splitting and alpha recycling controlling overall type 1 error at 5% (two-sided).

Secondary: Reduction of Dermatology Life Quality Index (DLQI) score of ≥4 points from baseline at Week 16.

| | |
|-----------------|---|
| End point title | Reduction of Dermatology Life Quality Index (DLQI) score of ≥4 points from baseline at Week 16. |
|-----------------|---|

End point description:

DLQI is a validated questionnaire with content specific to those with dermatologic conditions. It consists of 10 items addressing the participant's perception of the impact of their skin disease on different aspects of their quality of life over the last week. Each item is scored on a 4-point Likert scale ranging from 0 = 'not at all /not relevant' to 3 = 'very much'. The DLQI score is the sum of the 10 items (score ranging from 0 to 30); a high score is indicative of a poor quality of life.

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

End point timeframe:

Week 0 to Week 16

| | | | | |
|--|----------------------------|-----------------|--|--|
| End point values | Delgocitinib cream 20 mg/g | Cream vehicle | | |
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 299 | 153 | | |
| Units: Participants with ≥ 4 points reduction | 216 | 70 | | |

Statistical analyses

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

Statistical analysis description:

Based on the primary analysis of the primary estimand 'composite'. The difference in response rates between delgocitinib cream 20 mg/g and cream vehicle was analysed using the Cochran-Mantel-Haenszel test stratified by region and disease severity (baseline IGA-CHE score). Subjects with missing data, subjects who received rescue treatment, or subjects who permanently discontinued IMP were considered non-responders.

| | |
|---|--|
| Comparison groups | Delgocitinib cream 20 mg/g v Cream vehicle |
| Number of subjects included in analysis | 452 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 ^[21] |
| Method | Cochran-Mantel-Haenszel |
| Parameter estimate | Risk difference (RD) |
| Point estimate | 26.4 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 17 |
| upper limit | 35.9 |

Notes:

[21] - Evaluated at 1% significance level (two-sided) and significant as per testing hierarchy using hierarchical tests, alpha splitting and alpha recycling controlling overall type 1 error at 5% (two-sided).

Secondary: Change in DLQI score from baseline to Week 16.

| | |
|-----------------|--|
| End point title | Change in DLQI score from baseline to Week 16. |
|-----------------|--|

End point description:

DLQI is a validated questionnaire with content specific to those with dermatologic conditions. It consists of 10 items addressing the participant's perception of the impact of their skin disease on different aspects of their quality of life over the last week. Each item is scored on a 4-point Likert scale ranging from 0 = 'not at all /not relevant' to 3 = 'very much'. The DLQI score is the sum of the 10 items (score ranging from 0 to 30); a high score is indicative of a poor quality of life.

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

End point timeframe:

Week 0 to Week 16

| | | | | |
|-------------------------------------|----------------------------|-----------------|--|--|
| End point values | Delgocitinib cream 20 mg/g | Cream vehicle | | |
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 310 | 159 | | |
| Units: Change in DLQI score | | | | |
| least squares mean (standard error) | -7.0 (± 0.3) | -3.1 (± 0.5) | | |

Statistical analyses

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

Statistical analysis description:

Primary analysis of primary estimand 'composite'. The percentage change from baseline was analysed using an ANCOVA model with effects of treatment group, region, baseline IGA-CHE score, and baseline DLQI value. Missing data for subjects who did not attend the visit was imputed as WOCF (including baseline value). For subjects who received rescue treatment or subjects who have permanently discontinued the IMP, observed data was considered non-response by using WOCF (including baseline value).

| | |
|---|--|
| Comparison groups | Delgocitinib cream 20 mg/g v Cream vehicle |
| Number of subjects included in analysis | 469 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 ^[22] |
| Method | ANCOVA |
| Parameter estimate | Mean difference (net) |
| Point estimate | -3.9 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -5 |
| upper limit | -2.8 |

Notes:

[22] - Evaluated at 1% significance level (two-sided) and significant as per testing hierarchy using hierarchical tests, alpha splitting and alpha recycling controlling overall type 1 error at 5% (two-sided).

Secondary: Change in Hand Eczema Impact Scale (HEIS) score from baseline to Week 16.

| | |
|-----------------|---|
| End point title | Change in Hand Eczema Impact Scale (HEIS) score from baseline to Week 16. |
|-----------------|---|

End point description:

HEIS includes 9 items addressing the participant's perception of the impact of hand eczema on their daily activities, embarrassment, frustration, sleep, work, and physical functioning over the past 7 days. Each item is scored on a 5-point scale ranging from 0='not at all' to 4='extremely'. The HEIS score is the average of the 9 items. The highest possible score is 4, and a high score is indicative of a high impact. 6 domain scores can be calculated for HEIS: Proximal Daily Activity Limitations (PDAL) (average of 3 items), embarrassment with the appearance of the hands (average of 2 items), frustration with CHE (1 item), sleep (1 item), work (1 item), and physical functioning (1 item).

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

End point timeframe:

Week 0 to Week 16

| | | | | |
|-------------------------------------|----------------------------|-----------------|--|--|
| End point values | Delgocitinib cream 20 mg/g | Cream vehicle | | |
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 310 | 159 | | |
| Units: Change in HEIS score | | | | |
| least squares mean (standard error) | -1.45 (± 0.06) | -0.64 (± 0.08) | | |

Statistical analyses

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

Statistical analysis description:

Primary analysis of primary estimand 'composite'. The percentage change from baseline was analysed using an ANCOVA model with effects of treatment group, region, baseline IGA-CHE score, and baseline HEIS value. Missing data for subjects who did not attend the visit was imputed as WOCF (including baseline value). For subjects who received rescue treatment or subjects who have permanently discontinued the IMP, observed data was considered non-response by using WOCF (including baseline value).

| | |
|---|--|
| Comparison groups | Delgocitinib cream 20 mg/g v Cream vehicle |
| Number of subjects included in analysis | 469 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 ^[23] |
| Method | ANCOVA |
| Parameter estimate | Mean difference (net) |
| Point estimate | -0.81 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.99 |
| upper limit | -0.62 |

Notes:

[23] - Evaluated at 1% significance level (two-sided) and significant as per testing hierarchy using hierarchical tests, alpha splitting and alpha recycling controlling overall type 1 error at 5% (two-sided).

Secondary: Change in HEIS PDAL score from baseline to Week 16.

| | |
|-----------------|---|
| End point title | Change in HEIS PDAL score from baseline to Week 16. |
|-----------------|---|

End point description:

HEIS includes 9 items addressing the participant's perception of the impact of hand eczema on their daily activities, embarrassment, frustration, sleep, work, and physical functioning over the past 7 days. Each item is scored on a 5-point scale ranging from 0='not at all' to 4='extremely'. The HEIS score is the average of the 9 items. The highest possible score is 4, and a high score is indicative of a high impact. 6 domain scores can be calculated for HEIS: Proximal Daily Activity Limitations (PDAL) (average of 3 items), embarrassment with the appearance of the hands (average of 2 items), frustration with CHE (1 item), sleep (1 item), work (1 item), and physical functioning (1 item).

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

End point timeframe:

Week 0 to Week 16

| | | | | |
|-------------------------------------|----------------------------|-----------------|--|--|
| End point values | Delgocitinib cream 20 mg/g | Cream vehicle | | |
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 310 | 159 | | |
| Units: Change in HEIS PDAL score | | | | |
| least squares mean (standard error) | -1.48 (± 0.06) | -0.66 (± 0.08) | | |

Statistical analyses

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

Statistical analysis description:

Primary analysis of primary estimand 'composite'. The percentage change from baseline was analysed using an ANCOVA model with effects of treatment group, region, baseline IGA-CHE score, and baseline HEIS PDAL value. Missing data for subjects who did not attend the visit was imputed as WOCF (including baseline value). For subjects who received rescue treatment or subjects who have permanently discontinued the IMP, observed data was considered non-response by using WOCF (including baseline value)

| | |
|---|--|
| Comparison groups | Delgocitinib cream 20 mg/g v Cream vehicle |
| Number of subjects included in analysis | 469 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 ^[24] |
| Method | ANCOVA |
| Parameter estimate | Mean difference (net) |
| Point estimate | -0.82 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -1.01 |
| upper limit | -0.62 |

Notes:

[24] - Evaluated at 1% significance level (two-sided) and significant as per testing hierarchy using hierarchical tests, alpha splitting and alpha recycling controlling overall type 1 error at 5% (two-sided).

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Week 0 to Week 16

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

Dictionary used

| | |
|-----------------|--------|
| Dictionary name | MedDRA |
|-----------------|--------|

| | |
|--------------------|------|
| Dictionary version | 24.0 |
|--------------------|------|

Reporting groups

| | |
|-----------------------|----------------------------|
| Reporting group title | Delgocitinib cream 20 mg/g |
|-----------------------|----------------------------|

Reporting group description: -

| | |
|-----------------------|---------------|
| Reporting group title | Cream vehicle |
|-----------------------|---------------|

Reporting group description: -

| Serious adverse events | Delgocitinib cream 20 mg/g | Cream vehicle | |
|---|----------------------------|-----------------|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 5 / 313 (1.60%) | 3 / 159 (1.89%) | |
| number of deaths (all causes) | 0 | 0 | |
| number of deaths resulting from adverse events | 0 | 0 | |
| Cardiac disorders | | | |
| Cardiac tamponade | | | |
| subjects affected / exposed | 0 / 313 (0.00%) | 1 / 159 (0.63%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Nervous system disorders | | | |
| Epilepsy | | | |
| subjects affected / exposed | 1 / 313 (0.32%) | 0 / 159 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Migraine | | | |
| subjects affected / exposed | 1 / 313 (0.32%) | 0 / 159 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Notalgia paraesthetica | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 313 (0.00%) | 1 / 159 (0.63%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Pulmonary oedema | | | |
| subjects affected / exposed | 0 / 313 (0.00%) | 1 / 159 (0.63%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Skin and subcutaneous tissue disorders | | | |
| Hand dermatitis | | | |
| subjects affected / exposed | 1 / 313 (0.32%) | 1 / 159 (0.63%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Infections and infestations | | | |
| COVID-19 pneumonia | | | |
| subjects affected / exposed | 1 / 313 (0.32%) | 0 / 159 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Peritonsillar abscess | | | |
| subjects affected / exposed | 1 / 313 (0.32%) | 0 / 159 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

Frequency threshold for reporting non-serious adverse events: 2 %

| Non-serious adverse events | Delgocitinib cream 20 mg/g | Cream vehicle | |
|---|-------------------------------|-------------------|--|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 70 / 313 (22.36%) | 43 / 159 (27.04%) | |
| Nervous system disorders | | | |
| Headache | | | |
| subjects affected / exposed | 19 / 313 (6.07%) | 9 / 159 (5.66%) | |
| occurrences (all) | 25 | 11 | |
| Skin and subcutaneous tissue disorders | | | |
| Hand dermatitis | | | |

| | | | |
|--|----------------------|----------------------|--|
| subjects affected / exposed occurrences (all) | 2 / 313 (0.64%) 2 | 5 / 159 (3.14%) 5 | |
| Infections and infestations | | | |
| COVID-19 | | | |
| subjects affected / exposed | 36 / 313 (11.50%) | 20 / 159 (12.58%) | |
| occurrences (all) | 36 | 20 | |
| Nasopharyngitis | | | |
| subjects affected / exposed | 21 / 313 (6.71%) | 10 / 159 (6.29%) | |
| occurrences (all) | 24 | 10 | |
| Pharyngitis | | | |
| subjects affected / exposed | 3 / 313 (0.96%) | 5 / 159 (3.14%) | |
| occurrences (all) | 3 | 6 | |
| Herpes simplex | | | |
| subjects affected / exposed | 1 / 313 (0.32%) | 4 / 159 (2.52%) | |
| occurrences (all) | 1 | 4 | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|----------------|--|
| 20 August 2021 | This amendment was written to comply with requests from health authorities and to proceed with administrative and editorial changes. |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported