# Clinical trial results:
# An open-label, multicenter, extension study to evaluate the long-term safety and tolerability of LOU064 in eligible subjects with CSU who have participated in CLOU064A2201

## Summary

| | |
|---|---|
| EudraCT number | 2019-001074-29 |
| Trial protocol | GB HU CZ SK FR DK ES |
| Global end of trial date | 09 September 2022 |

**Results information**

| | |
|---|---|
| Result version number | v1 (current) |
| This version publication date | 21 September 2023 |
| First version publication date | 21 September 2023 |

## Trial information

**Trial identification**

| | |
|---|---|
| Sponsor protocol code | CLOU064A2201E1 |

**Additional study identifiers**

| | |
|---|---|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT04109313 |
| WHO universal trial number (UTN) | - |

Notes:

**Sponsors**

| | |
|---|---|
| Sponsor organisation name | Novartis Pharma AG |
| Sponsor organisation address | Novartis Campus, Basel, Switzerland, |
| Public contact | Clinical Disclosure Office, Novartis Pharma AG, 41 613241111, Novartis.email@Novartis.com |
| Scientific contact | Clinical Disclosure Office, Novartis Pharma AG, 41 613241111, Novartis.email@Novartis.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 | 09 September 2022 |
| Is this the analysis of the primary completion data? | No |

| | |
|---|---|
| Global end of trial reached? | Yes |
| Global end of trial date | 09 September 2022 |
| Was the trial ended prematurely? | No |

Notes:

## General information about the trial

Main objective of the trial:

The main objective of this trial is to assess the long-term safety and tolerability of LOU064 in patients with CSU who have participated in Study CLOU064A2201

Protection of trial subjects:

The study was in compliance with the ethical principles derived from the Declaration of Helsinki and the International Conference on Harmonization (ICH) Good Clinical Practice (GCP) guidelines. All the local regulatory requirements pertinent to safety of trial subjects were also followed during the conduct of the trial.

Background therapy:

Background therapy was a second generation H1-antihistamine at a locally approved licensed posology given with a stable treatment regimen. Administration/discontinuation of the background H1-antihistamine was at the discretion of the investigator. Background therapy could not be taken from Day 1 until Week 4 of the Treatment period. It could be re-initiated at Week 4 if deemed necessary.
Rescue therapy was a second generation H1-antihistamine at a locally approved licensed posology that was eliminated primarily via renal excretion (e.g. cetirizine, levocetirizine or bilastine). The rescue H1-antihistamine had to differ from the background H1-antihistamine and could only be given to treat unbearable symptoms (itch) of CSU on a day-to-day basis.

Evidence for comparator: -

| | |
|---|---|
| Actual start date of recruitment | 24 October 2019 |
| 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 | Argentina: 10 |
| Country: Number of subjects enrolled | Canada: 21 |
| Country: Number of subjects enrolled | Czechia: 10 |
| Country: Number of subjects enrolled | Spain: 19 |
| Country: Number of subjects enrolled | France: 10 |
| Country: Number of subjects enrolled | Hungary: 12 |
| Country: Number of subjects enrolled | Japan: 40 |
| Country: Number of subjects enrolled | Poland: 35 |
| Country: Number of subjects enrolled | Russian Federation: 20 |
| Country: Number of subjects enrolled | Turkey: 6 |
| Country: Number of subjects enrolled | United States: 23 |
| Country: Number of subjects enrolled | Belgium: 4 |
| Country: Number of subjects enrolled | Denmark: 5 |

| | |
|---|---|
| Country: Number of subjects enrolled | United Kingdom: 6 |
| Country: Number of subjects enrolled | Slovakia: 8 |
| Worldwide total number of subjects | 229 |
| EEA total number of subjects | 103 |

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) | 203 |
| From 65 to 84 years | 26 |
| 85 years and over | 0 |

## Subject disposition

### Recruitment

Recruitment details:

229 subjects were enrolled in the observational period or the treatment period across 72 sites in 15 countries.
One subject was a screening failure and, as a result, was not enrolled in either the observational or treatment period.

### Pre-assignment

Screening details:

Participants with UAS7<16 at Week 16 of CLOU064A2201 (NCT03926611) entered a 12-week observational period.
Participants with UAS7≥16 at Week 12 or Week 16 of CLOU064A2201, as well as those who relapsed during the observational period, entered the treatment period.

### Period 1

| | |
|---|---|
| Period 1 title | Overall Study (overall period) |
| Is this the baseline period? | Yes |
| Allocation method | Not applicable |
| Blinding used | Not blinded |

### Arms

| | |
|---|---|
| **Arm title** | All participants |

Arm description:

Participants with UAS7<16 at Week 16 of CLOU064A2201 were followed up to 12 weeks without receiving treatment (observational period). If participants relapsed (UAS7≥16 at least once), they were transitioned to the treatment period. Participants with a UAS7≥16 at Week 12 or Week 16 in the CLOU064A2201, as well as participants who experienced a relapse during the 12-week observational period, were administered 100 mg of LOU064 b.i.d. open-label for up to 52 weeks.

| | |
|---|---|
| Arm type | Experimental |
| Investigational medicinal product name | LOU064 |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Capsule |
| Routes of administration | Oral use |

Dosage and administration details:

Participants with a UAS7≥16 at Week 12 or Week 16 in the CLOU064A2201, as well as participants who experienced a relapse during the 12-week observational period, were administered LOU064 50mg capsules b.i.d. (i.e. two capsules of LOU064 50mg in the morning and two capsules of LOU064 50mg in the evening) from Day 1 up to Week 52 of the Treatment period.

| **Number of subjects in period 1** | All participants |
|---|---|
| Started | 229 |
| Treatment-free Cohort | 68 [1] |
| Treatment Cohort | 194 |
| Completed | 188 |
| Not completed | 41 |
| Physician decision | 2 |
| Subject Decision | 13 |

| | |
|---|---|
| Adverse event, non-fatal | 11 |
| Pregnancy | 1 |
| Covid-19 situation | 2 |
| Lost to follow-up | 1 |
| Lack of efficacy | 11 |

Notes:

[1] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: This is a sub-group of participants (i.e. participants who entered the treatment free cohort)

## Baseline characteristics

### Reporting groups

| Reporting group title | All participants |
|---|---|

Reporting group description:

Participants with UAS7<16 at Week 16 of CLOU064A2201 were followed up to 12 weeks without receiving treatment (observational period). If participants relapsed (UAS7≥16 at least once), they were transitioned to the treatment period. Participants with a UAS7≥16 at Week 12 or Week 16 in the CLOU064A2201, as well as participants who experienced a relapse during the 12-week observational period, were administered 100 mg of LOU064 b.i.d. open-label for up to 52 weeks.

| Reporting group values | All participants | Total | |
|---|---|---|---|
| Number of subjects | 229 | 229 | |
| Age categorical<br>Units: Subjects | | | |
| In utero | 0 | 0 | |
| Preterm newborn infants (gestational age < 37 wks) | 0 | 0 | |
| Newborns (0-27 days) | 0 | 0 | |
| Infants and toddlers (28 days-23 months) | 0 | 0 | |
| Children (2-11 years) | 0 | 0 | |
| Adolescents (12-17 years) | 0 | 0 | |
| Adults (18-64 years) | 203 | 203 | |
| From 65-84 years | 26 | 26 | |
| 85 years and over | 0 | 0 | |
| Age Continuous<br>Units: Years | | | |
| median | 45.0 | | |
| full range (min-max) | 18 to 77 | - | |
| Sex: Female, Male<br>Units: Participants | | | |
| Female | 165 | 165 | |
| Male | 64 | 64 | |
| Race/Ethnicity, Customized<br>Units: Subjects | | | |
| White | 181 | 181 | |
| Black | 2 | 2 | |
| Asian | 44 | 44 | |
| Multiple | 1 | 1 | |
| American Indian or Alaska Native | 1 | 1 | |

### Subject analysis sets

| Subject analysis set title | Treated cohort |
|---|---|
| Subject analysis set type | Sub-group analysis |

Subject analysis set description:

Participants with a UAS7≥16 at Week 12 or Week 16 in the CLOU064A2201, as well as participants who experienced a relapse during the 12-week observational period, were administered 100 mg of LOU064 b.i.d. open-label for up to 52 weeks.

| **Reporting group values** | Treated cohort | | |
|---|---|---|---|
| Number of subjects | 194 | | |
| Age categorical<br>Units: Subjects | | | |
| In utero | 0 | | |
| Preterm newborn infants (gestational age < 37 wks) | 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) | 172 | | |
| From 65-84 years | 22 | | |
| 85 years and over | 0 | | |
| Age Continuous<br>Units: Years | | | |
| median | 45.0 | | |
| full range (min-max) | 19 to 77 | | |
| Sex: Female, Male<br>Units: Participants | | | |
| Female | 139 | | |
| Male | 55 | | |
| Race/Ethnicity, Customized<br>Units: Subjects | | | |
| White | 152 | | |
| Black | 2 | | |
| Asian | 38 | | |
| Multiple | 1 | | |
| American Indian or Alaska Native | 1 | | |

## End points

### End points reporting groups

| Reporting group title | All participants |
|---|---|

Reporting group description:

Participants with UAS7<16 at Week 16 of CLOU064A2201 were followed up to 12 weeks without receiving treatment (observational period). If participants relapsed (UAS7≥16 at least once), they were transitioned to the treatment period. Participants with a UAS7≥16 at Week 12 or Week 16 in the CLOU064A2201, as well as participants who experienced a relapse during the 12-week observational period, were administered 100 mg of LOU064 b.i.d. open-label for up to 52 weeks.

| Subject analysis set title | Treated cohort |
|---|---|
| Subject analysis set type | Sub-group analysis |

Subject analysis set description:

Participants with a UAS7≥16 at Week 12 or Week 16 in the CLOU064A2201, as well as participants who experienced a relapse during the 12-week observational period, were administered 100 mg of LOU064 b.i.d. open-label for up to 52 weeks.

### Primary: Number of participants with treatment-emergent Adverse Events (AEs)

| End point title | Number of participants with treatment-emergent Adverse Events (AEs)[1] |
|---|---|

End point description:

An AE refers to any undesirable medical occurrence, such as an unintended sign (including abnormal laboratory findings), symptom, or disease, experienced by a participant. Serious AEs (SAEs) is defined as any AE that results in death, is life-threatening, requires hospitalization or prolongation of existing hospitalization, results in persistent or significant disability/incapacity, results in a congenital anomaly/birth defect, or any other medically significant condition.
Treatment-emergent AEs were defined as AEs that either begin on the same day or after the first dose of study medication during the treatment period in the extension study or worsen on the same day or after the first dose of study medication in the extension study and within the minimum of either 28 days post last dose or the end of the study visit. The number of participants with treatment-emergent AEs was summarized.

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

End point timeframe:

From first dose of treatment up to 28 days after last dose, assessed up to 56 weeks

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No statistical analyses were planned for the primary endpoint

| End point values | Treated cohort | | | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 194 | | | |
| Units: Participants | | | | |
| AEs | 139 | | | |
| Deaths | 0 | | | |
| Non-fatal Serious AEs (SAEs) | 6 | | | |
| SAE(s) | 6 | | | |
| Discontinued treatment due to any AE(s) | 11 | | | |
| Discontinued treatment due to any SAE(s) | 2 | | | |
| Treatment interruption due to AE(s) | 13 | | | |
| Treatment interruption due to SAE(s) | 1 | | | |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Change from baseline in weekly Urticaria Activity Score (UAS7) at Week 4 of the treatment period

| End point title | Change from baseline in weekly Urticaria Activity Score (UAS7) at Week 4 of the treatment period |
|---|---|

End point description:

The Urticaria Activity Score (UAS) is a composite, diary-recorded score with numeric severity intensity ratings (0=none to 3=intense/severe) for the number of wheals (hives) and the intensity of the pruritus (itch) over the past 12 hours (twice daily). The daily UAS is calculated as the average of the morning and evening scores. The UAS7 is the weekly sum of the daily UAS, which is the composite score of the intensity of pruritus and the number of wheals. UAS7 scores ranged from 0 to 42. A higher UAS7 indicated greater urticaria disease activity. A minimum of 4 out of 7 daily scores were needed to calculate the UAS7 values. Otherwise, the weekly score was missing for that week.
The change from baseline in UAS7 at Week 4 of the treatment period was calculated. A negative change score from baseline indicates improvement. The UAS7 at baseline was considered as the UAS7 derived over the last 7 days before day 1 of the treatment period.

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

End point timeframe:

Baseline, Week 4 of treatment period

| **End point values** | Treated cohort | | | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 187 | | | |
| Units: Score on a Scale | | | | |
| arithmetic mean (standard deviation) | -17.58 (± 13.400) | | | |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Percentage of participants with well-controlled disease (UAS7≤6) at Week 4 of the treatment period

| End point title | Percentage of participants with well-controlled disease (UAS7≤6) at Week 4 of the treatment period |
|---|---|

End point description:

The Urticaria Activity Score (UAS) is a composite, diary-recorded score with numeric severity intensity ratings (0=none to 3=intense/severe) for the number of wheals (hives) and the intensity of the pruritus (itch) over the past 12 hours (twice daily). The daily UAS is calculated as the average of the morning and evening scores. The UAS7 is the weekly sum of the daily UAS, which is the composite score of the intensity of pruritus and the number of wheals. UAS7 scores ranged from 0 to 42. A higher UAS7 indicated greater urticaria disease activity.

A minimum of 4 out of 7 daily scores were needed to calculate the UAS7 values. Otherwise, the weekly score was missing for that week. Missing values were imputed by non-responder imputation method regardless of the reason for missingness.
The percentage of subjects with UAS7≤ 6 at Week 4 of the treatment period was calculated. The 90% confidence interval was derived based on the score method with continuity correction.

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

End point timeframe:

Week 4 of the treatment period

| **End point values** | Treated cohort | | | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 194 | | | |
| Units: Percentage of participants | | | | |
| number (confidence interval 90%) | 51.0 (44.9 to 57.1) | | | |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Percentage of participants with complete response (UAS7=0) at Week 4 of the treatment period

| End point title | Percentage of participants with complete response (UAS7=0) at Week 4 of the treatment period |
|---|---|

End point description:

The Urticaria Activity Score (UAS) is a composite, diary-recorded score with numeric severity intensity ratings (0=none to 3=intense/severe) for the number of wheals (hives) and the intensity of the pruritus (itch) over the past 12 hours (twice daily). The daily UAS is calculated as the average of the morning and evening scores. The UAS7 is the weekly sum of the daily UAS, which is the composite score of the intensity of pruritus and the number of wheals. UAS7 scores ranged from 0 to 42. A higher UAS7 indicated greater urticaria disease activity.
A minimum of 4 out of 7 daily scores were needed to calculate the UAS7 values. Otherwise, the weekly score was missing for that week. Missing values were imputed by non-responder imputation method regardless of the reason for missingness.
The percentage of subjects with UAS7= 0 at Week 4 of the treatment period was calculated. The 90% confidence interval was derived based on the score method with continuity correction.

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

End point timeframe:

Week 4 of the treatment period

| **End point values** | Treated cohort | | | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 194 | | | |
| Units: Percentage of participants | | | | |
| number (confidence interval 90%) | 27.3 (22.2 to 33.1) | | | |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Percentage of participants with well-controlled disease (UAS7≤ 6) overtime

| End point title | Percentage of participants with well-controlled disease (UAS7≤ 6) overtime |
|---|---|

End point description:

The Urticaria Activity Score (UAS) is a composite, diary-recorded score with numeric severity intensity ratings (0=none to 3=intense/severe) for the number of wheals (hives) and the intensity of the pruritus (itch) over the past 12 hours (twice daily). The daily UAS is calculated as the average of the morning and evening scores. The UAS7 is the weekly sum of the daily UAS, which is the composite score of the intensity of pruritus and the number of wheals. UAS7 scores ranged from 0 to 42. A higher UAS7 indicated greater urticaria disease activity.
A minimum of 4 out of 7 daily scores were needed to calculate the UAS7 values. Otherwise, the weekly score was missing for that week.
The percentage of subjects with UAS7≤ 6 during the treatment period was calculated. The 90% confidence interval was derived based on the score method with continuity correction. The UAS7 at baseline was considered as the UAS7 derived over the last 7 days before day 1 of the treatment period.

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

End point timeframe:

From baseline until Week 52 of the treatment period

| **End point values** | Treated cohort | | | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 194 | | | |
| Units: Percentage of participants | | | | |
| number (confidence interval 90%) | | | | |
| Baseline (n=193) | 1.0 (0.2 to 3.5) | | | |
| Week 1 (n=179) | 37.4 (31.4 to 43.8) | | | |
| Week 4 (n=188) | 52.7 (46.4 to 58.8) | | | |
| Week 12 (n=173) | 56.6 (50.1 to 63.0) | | | |
| Week 20 (n=169) | 62.7 (56.1 to 68.9) | | | |
| Week 28 (n=162) | 68.5 (61.9 to 74.5) | | | |
| Week 40 (n=155) | 66.5 (59.6 to 72.7) | | | |
| Week 52 (n=147) | 68.0 (61.1 to 74.3) | | | |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Change from baseline in UAS7 overtime

| End point title | Change from baseline in UAS7 overtime |
|---|---|

End point description:

The Urticaria Activity Score (UAS) is a composite, diary-recorded score with numeric severity intensity ratings (0=none to 3=intense/severe) for the number of wheals (hives) and the intensity of the pruritus (itch) over the past 12 hours (twice daily). The daily UAS is calculated as the average of the morning and evening scores. The UAS7 is the weekly sum of the daily UAS, which is the composite score of the intensity of pruritus and the number of wheals. UAS7 scores ranged from 0 to 42. A higher UAS7 indicated greater urticaria disease activity.
A minimum of 4 out of 7 daily scores were needed to calculate the UAS7 values. Otherwise, the weekly score was missing for that week.
The change from baseline in UAS7 during the treatment period was calculated. A negative change score from baseline indicates improvement. The UAS7 at baseline was considered as the UAS7 derived over the last 7 days before day 1 of the treatment period.

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

End point timeframe:

From baseline until Week 52 of the treatment period

| **End point values** | Treated cohort | | | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 193 | | | |
| Units: Score on a Scale | | | | |
| arithmetic mean (standard deviation) | | | | |
| Week 1 (n=178) | -14.76 (± 11.502) | | | |
| Week 4 (n=187) | -17.58 (± 13.400) | | | |
| Week 12 (n=172) | -19.37 (± 12.502) | | | |
| Week 20 (n=168) | -20.61 (± 11.634) | | | |
| Week 28 (n= 161) | -21.54 (± 11.525) | | | |
| Week 40 (n=154) | -21.25 (± 11.400) | | | |
| Week 52 (n=146) | -21.82 (± 10.699) | | | |

## Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Treated cohort: AEs from first dose to 28 days post last dose, up to 56 weeks; deaths until end of study, up to 68 weeks.
Treatment-free cohort: AEs and deaths from start of observation period until relapse or end of observation period, up to 12 weeks

Adverse event reporting additional description:

An AE refers to any undesirable medical occurrence, such as an unintended sign (including abnormal laboratory findings), symptom, or disease, experienced by a participant.

| | |
|---|---|
| Assessment type | Systematic |

### Dictionary used

| | |
|---|---|
| Dictionary name | MedDRA |
| Dictionary version | 25.0 |

### Reporting groups

| | |
|---|---|
| Reporting group title | Treated cohort (treatment+follow-up period) |

Reporting group description:

Participants with a UAS7≥16 at Week 12 or Week 16 in the CLOU064A2201, as well as participants who experienced a relapse during the 12-week observational period, were administered 100 mg of LOU064 b.i.d. open-label for up to 52 weeks.

| | |
|---|---|
| Reporting group title | Treatment-free cohort (observational period) |

Reporting group description:

Participants with UAS7<16 at Week 16 of CLOU064A2201 were followed up to 12 weeks without receiving treatment (observational period). If participants relapsed (UAS7≥16 at least once), they were transitioned to the treatment period (treated cohort).

| **Serious adverse events** | Treated cohort (treatment+follow-up period) | Treatment-free cohort (observational period) | |
|---|---|---|---|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 6 / 194 (3.09%) | 1 / 68 (1.47%) | |
| number of deaths (all causes) | 0 | 0 | |
| number of deaths resulting from adverse events | 0 | 0 | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Superficial spreading melanoma stage unspecified | | | |
| subjects affected / exposed | 0 / 194 (0.00%) | 1 / 68 (1.47%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Injury, poisoning and procedural complications | | | |
| Tibia fracture | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 194 (0.52%) | 0 / 68 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| General disorders and administration site conditions | | | |
| Chest pain | | | |
| subjects affected / exposed | 1 / 194 (0.52%) | 0 / 68 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastrointestinal disorders | | | |
| Melaena | | | |
| subjects affected / exposed | 1 / 194 (0.52%) | 0 / 68 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Reproductive system and breast disorders | | | |
| Ovarian cyst | | | |
| subjects affected / exposed | 1 / 194 (0.52%) | 0 / 68 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Infections and infestations | | | |
| Appendicitis | | | |
| subjects affected / exposed | 1 / 194 (0.52%) | 0 / 68 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| COVID-19 pneumonia | | | |
| subjects affected / exposed | 2 / 194 (1.03%) | 0 / 68 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 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** | Treated cohort (treatment+follow-up period) | Treatment-free cohort (observational period) | |
|---|---|---|---|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 56 / 194 (28.87%) | 0 / 68 (0.00%) | |

| | | | |
|---|---|---|---|
| Nervous system disorders<br>Headache<br>subjects affected / exposed<br>occurrences (all) | <br><br>13 / 194 (6.70%)<br>44 | <br><br>0 / 68 (0.00%)<br>0 | |
| Skin and subcutaneous tissue disorders<br>Eczema<br>subjects affected / exposed<br>occurrences (all)<br><br>Chronic spontaneous urticaria<br>subjects affected / exposed<br>occurrences (all) | <br><br>10 / 194 (5.15%)<br>10<br><br><br>22 / 194 (11.34%)<br>25 | <br><br>0 / 68 (0.00%)<br>0<br><br><br>0 / 68 (0.00%)<br>0 | |
| Infections and infestations<br>COVID-19<br>subjects affected / exposed<br>occurrences (all) | <br><br>16 / 194 (8.25%)<br>17 | <br><br>0 / 68 (0.00%)<br>0 | |

## More information

## Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|---|---|
| 02 October 2019 | The main purpose of this amendment was to address requests from health authorities and to align eligibility criteria of this study with amended eligibility criteria of the preceding core study (Study CLOU064A2201): Deletion of inclusion criterion #4 (this change triggered several changes throughout the document, including changing the study title, modification of inclusion criterion #3 and deletion of the 2nd interim analysis). Lowering the minimum required resting heart rate to 50 bpm (from 60 bpm) to align with amended exclusion criterion #6b in Study CLOU064A2201. This also aligned the eligibility criterion for resting heart rate with normal resting heart rates of CSU patients and did not impact patient safety as LOU064 does not have a negative chronotropic effect. Clarification that investigators needed to assess the benefit-risk ratio for each subject throughout the study. Both, lack of or inadequate treatment response and/or emergence of adverse events that outweighed the benefits, could lead to study treatment discontinuation. Added urine pregnancy testing every 4 weeks with at home assessments between study visits for women of childbearing potential starting after the Week 20 visit of the treatment period. |
| 05 April 2021 | The main purpose of this amendment was to implement two changes related to the addition of optional interim analyses and the removal of the male contraception requirement. Updated the statistical analysis section to allow additional optional interim analyses, with the purpose to enable further benefit-risk assessment to support clinical trials in other indications under development and/or potential Health Authority interactions and requests. The requirement for male contraception in this study was removed following the reproductive toxicity assessment |
| 08 September 2021 | The main purpose of this amendment was to inform about a possibility for potential drug-drug interactions (DDIs) for efflux and uptake transporters (as noted in the Investigator's Brochure Ed. 7.0). The update was due to new in vitro data on transporters in line with the FDA guidance and pending results from a planned DDI study (Study CLOU064A02103). |

Notes:

## Interruptions (globally)

Were there any global interruptions to the trial? No

## Limitations and caveats

None reported