



## 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
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#### 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:

<b>Subjects enrolled per age group</b>	
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  $UAS7 \geq 16$  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
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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 ( $UAS7 \geq 16$  at least once), they were transitioned to the treatment period. Participants with a  $UAS7 \geq 16$  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  $UAS7 \geq 16$  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 <sup>[1]</sup>
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

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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
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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 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 Units: Years			
median	45.0		
full range (min-max)	18 to 77	-	
Sex: Female, Male Units: Participants			
Female	165	165	
Male	64	64	
Race/Ethnicity, Customized 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.

<b>Reporting group values</b>	Treated cohort		
Number of subjects	194		
Age categorical			
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			
Units: Years			
median	45.0		
full range (min-max)	19 to 77		
Sex: Female, Male			
Units: Participants			
Female	139		
Male	55		
Race/Ethnicity, Customized			
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) <sup>[1]</sup>
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
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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
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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 ( $\pm$ 13.400)			

## Statistical analyses

No statistical analyses for this end point

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

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

<b>End point values</b>	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
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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	

<b>End point values</b>	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
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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
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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
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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
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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
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### Dictionary used

Dictionary name	MedDRA
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Dictionary version	25.0
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### Reporting groups

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

Participants with a UAS7 $\geq$ 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)
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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 $\geq$ 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 %

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