Clinical trial results:
A multicenter, randomized, double-blind, placebo-controlled Phase 3 study of remibrutinib (LOU064) to investigate the efficacy, safety and tolerability for 52 weeks in adult chronic spontaneous urticaria (CSU) patients inadequately controlled by H1-antihistamines

Summary

EudraCT number	2021-000424-35
Trial protocol	SK DE DK AT
Global end of trial date	05 January 2024

Results information

Result version number	v1 (current)
This version publication date	31 October 2024
First version publication date	31 October 2024

Trial information

Trial identification

Sponsor protocol code	CLOU064A2302

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT05032157
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	05 January 2024
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	05 January 2024
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The purpose of this study was to establish the efficacy, safety, and tolerability of Remibrutinib 25 mg b.i.d. in adult patients suffering from chronic spontaneous urticaria (CSU) inadequately controlled by second generation H1-antihistamines (H1-AHs) in comparison to placebo.

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: -

Evidence for comparator: -

Actual start date of recruitment	01 December 2021
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Germany: 62
Country: Number of subjects enrolled	United States: 86
Country: Number of subjects enrolled	Austria: 2
Country: Number of subjects enrolled	Brazil: 4
Country: Number of subjects enrolled	Canada: 35
Country: Number of subjects enrolled	China: 65
Country: Number of subjects enrolled	Denmark: 5
Country: Number of subjects enrolled	India: 54
Country: Number of subjects enrolled	Malaysia: 24
Country: Number of subjects enrolled	Poland: 28
Country: Number of subjects enrolled	Russian Federation: 5
Country: Number of subjects enrolled	Slovakia: 10
Country: Number of subjects enrolled	South Africa: 14
Country: Number of subjects enrolled	Switzerland: 4
Country: Number of subjects enrolled	Taiwan: 15
Country: Number of subjects enrolled	Thailand: 25
Country: Number of subjects enrolled	United Kingdom: 5
Country: Number of subjects enrolled	Viet Nam: 12

Worldwide total number of subjects	455
EEA total number of subjects	107

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)	420
From 65 to 84 years	35
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The study was conducted globally across 18 countries.

Pre-assignment

Screening details:

Participants underwent a screening period of up to 4 weeks.

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, Carer, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	LOU064 25 mg b.i.d.

Arm description:

Patients initially randomized to Remibrutinib during the Double-blind treatment period and continued Remibrutinib during the Open-label treatment period (Up to Week 52)

Arm type	Experimental
Investigational medicinal product name	Remibrutinib
Investigational medicinal product code	LOU064
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Remibrutinib 25 mg b.i.d.

Arm title	Placebo

Arm description:

Patients initially randomized to Placebo (Up to Week 24)

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Placebo

Number of subjects in period 1	LOU064 25 mg b.i.d.	Placebo
Started	300	155
Full Analysis Set (FAS)	297	153
Safety Set (SAF)	297	153
Completed	230	111
Not completed	70	44
Physician decision	7	2
Adverse event, non-fatal	12	7
Protocol Deviation	8	4
Patient Decision	38	19
Unsatisfactory therapeutic effect	4	7
Pregnancy	-	2
Lost to follow-up	1	3

Baseline characteristics

Reporting groups	
Reporting group title	LOU064 25 mg b.i.d.
Reporting group description:	
Patients initially randomized to Remibrutinib during the Double-blind treatment period and continued Remibrutinib during the Open-label treatment period (Up to Week 52)	
Reporting group title	Placebo
Reporting group description:	
Patients initially randomized to Placebo (Up to Week 24)	

Reporting group values	LOU064 25 mg b.i.d.	Placebo	Total
Number of subjects	300	155	455
Age Categorical Units: Participants			
>= 18 and < 65 years	276	144	420
>= 65 and < 85 years	24	11	35
Age Continuous Units: Years			
arithmetic mean	41.9	41.3	
standard deviation	± 14.52	± 14.58	-
Sex: Female, Male Units: Participants			
Female	197	100	297
Male	103	55	158
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	0	0	0
Asian	130	72	202
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	7	3	10
White	159	79	238
More than one race	3	1	4
Unknown or Not Reported	1	0	1

End points

End points reporting groups

Reporting group title	LOU064 25 mg b.i.d.
Reporting group description:	
Patients initially randomized to Remibrutinib during the Double-blind treatment period and continued Remibrutinib during the Open-label treatment period (Up to Week 52)	
Reporting group title	Placebo
Reporting group description:	
Patients initially randomized to Placebo (Up to Week 24)	
Subject analysis set title	Double-blind treatment period: LOU064 25 mg b.i.d.
Subject analysis set type	Full analysis
Subject analysis set description:	
Patients initially randomized to Remibrutinib (Up to Week 24)	
Subject analysis set title	Double-blind treatment period: Placebo
Subject analysis set type	Full analysis
Subject analysis set description:	
Patients initially randomized to Placebo (Up to Week 24)	
Subject analysis set title	Transitioned to LOU064 25 mg b.i.d.
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Patients initially randomized to placebo during the Double-blind treatment period and switched to Remibrutinib during the Open-label treatment period (Weeks 25-52)	

Primary: Mean change from Baseline in Weekly Urticaria Activity Score (UAS7) at Week 12 (Scenario 1 with UAS7 as primary efficacy endpoint)

End point title	Mean change from Baseline in Weekly Urticaria Activity Score (UAS7) at Week 12 (Scenario 1 with UAS7 as primary efficacy endpoint)
End point description:	
The Weekly Urticaria Activity Score (UAS7) is a simple scoring system to evaluate urticaria signs and symptoms. It is based on scoring wheals (hive severity score) and itch (itch severity score) separately on a scale of 0 (no signs/symptoms) to 3 (intense signs/symptoms) over 7 days. The final score is calculated by adding together the daily scores, which can range from 0 to 6, for 7 days. This results in a maximum total score of 42 (highest urticaria severity), and a minimum possible score of 0. This endpoint is a secondary endpoint for testing strategy Scenario 2 with Weekly Itch Severity Score (ISS7) and Weekly Hives Severity Score (HSS7) as co-primary efficacy endpoints).	
End point type	Primary
End point timeframe:	
Baseline, Week 12	

End point values	LOU064 25 mg b.i.d.	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	297	153		
Units: Unit on a scale				
least squares mean (standard error)	-19.41 (± 0.702)	-11.73 (± 0.948)		

Statistical analyses

Statistical analysis title	UAS7 at Week 12 (Scenario 1)
Comparison groups	LOU064 25 mg b.i.d. v Placebo
Number of subjects included in analysis	450
Analysis specification	Pre-specified
Analysis type	
P-value	< 0.001
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-7.68
Confidence interval	
level	95 %
sides	2-sided
lower limit	-9.91
upper limit	-5.46
Variability estimate	Standard error of the mean
Dispersion value	1.136

Primary: Mean change from Baseline in Weekly Itch Severity Score (ISS7) at Week 12 (Scenario 2 with ISS7 and HSS7 as co-primary efficacy endpoints)

End point title	Mean change from Baseline in Weekly Itch Severity Score (ISS7) at Week 12 (Scenario 2 with ISS7 and HSS7 as co-primary efficacy endpoints)

End point description:

The severity of the itch was recorded by the participant twice daily in their electronic Diary, on a scale of 0 (none) to 3 (severe). A weekly score (ISS7) was derived by adding up the average daily scores of the 7 days preceding the visit. The possible range of the weekly score was therefore 0 - 21 (highest itch severity).
This endpoint is a secondary endpoint for testing strategy Scenario 1 with Weekly Urticaria Activity Score (UAS7) as the primary efficacy endpoint).

End point type	Primary

End point timeframe:

Baseline, Week 12

End point values	LOU064 25 mg b.i.d.	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	297	153		
Units: Unit on a scale				
least squares mean (standard error)	-8.95 (± 0.335)	-5.72 (± 0.454)		

Statistical analyses

Statistical analysis title	ISS7 at Week 12 (Scenario 2)
Comparison groups	LOU064 25 mg b.i.d. v Placebo

Number of subjects included in analysis	450
Analysis specification	Pre-specified
Analysis type	
P-value	< 0.001
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-3.23
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.29
upper limit	-2.16
Variability estimate	Standard error of the mean
Dispersion value	0.545

Primary: Mean change from Baseline in Weekly Hives Severity Score (HSS7) at Week 12 (Scenario 2 with ISS7 and HSS7 as co-primary efficacy endpoints)

End point title	Mean change from Baseline in Weekly Hives Severity Score (HSS7) at Week 12 (Scenario 2 with ISS7 and HSS7 as co-primary efficacy endpoints)

End point description:

The hives (wheals) severity score, defined by number of hives, was recorded by the participant twice daily in their electronic Diary, on a scale of 0 (none) to 3 (> 12 hives/12 hours). A weekly score (HSS7) was derived by adding up the average daily scores of the 7 days preceding the visit. The possible range of the weekly score was therefore 0 - 21 (highest hives activity).
This endpoint is a secondary endpoint for testing strategy Scenario 1 with Weekly Urticaria Activity Score (UAS7) as the primary efficacy endpoint).

End point type	Primary

End point timeframe:

Baseline, Week 12

End point values	LOU064 25 mg b.i.d.	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	297	153		
Units: Unit on a scale				
least squares mean (standard error)	-10.47 (± 0.394)	-6.00 (± 0.531)		

Statistical analyses

Statistical analysis title	HSS7 at Week 12 (Scenario 2)
Comparison groups	LOU064 25 mg b.i.d. v Placebo

Number of subjects included in analysis	450
Analysis specification	Pre-specified
Analysis type	
P-value	< 0.001
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-4.47
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.71
upper limit	-3.23
Variability estimate	Standard error of the mean
Dispersion value	0.634

Secondary: Number of Participants who achieved disease activity control (UAS7 =< 6) at Week 12

End point title	Number of Participants who achieved disease activity control (UAS7 =< 6) at Week 12

End point description:

The percentage of patients achieving disease activity control (UAS7 =< 6) at Week 12 was assessed to evaluate the efficacy of Remibrutinib in Chronic Spontaneous Urticaria (CSU) patients. The UAS7 is the sum of the Weekly Hives Severity Score (HSS7) and the Weekly Itch Severity Score (ISS7). The possible range of the UAS7 score is 0 – 42 (highest hives and itch severity).

End point type	Secondary

End point timeframe:

Week 12

End point values	LOU064 25 mg b.i.d.	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	297	153		
Units: Participants	139	30		

Statistical analyses

Statistical analysis title	Disease activity control (UAS7 =< 6) at Week 12
Comparison groups	LOU064 25 mg b.i.d. v Placebo
Number of subjects included in analysis	450
Analysis specification	Pre-specified
Analysis type	
P-value	< 0.001
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	3.84

Confidence interval	
level	95 %
sides	2-sided
lower limit	2.39
upper limit	6.18

Secondary: Number of Participants who achieved complete absence of hives and itch (UAS7 = 0) at Week 12

End point title	Number of Participants who achieved complete absence of hives and itch (UAS7 = 0) at Week 12

End point description:

The proportion of patients achieving complete absence of hives and itch (UAS7 = 0) at Week 12 was assessed to evaluate the efficacy of Remibrutinib in Chronic Spontaneous Urticaria (CSU) patients. The UAS7 is the sum of the Weekly Hives Severity Score (HSS7) and the Weekly Itch Severity Score (ISS7). The possible range of the UAS7 score is 0 – 42 (highest hives and itch severity).

End point type	Secondary

End point timeframe:

Week 12

End point values	LOU064 25 mg b.i.d.	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	297	153		
Units: Participants	83	10		

Statistical analyses

Statistical analysis title	UAS7 = 0 at Week 12
Comparison groups	LOU064 25 mg b.i.d. v Placebo
Number of subjects included in analysis	450
Analysis specification	Pre-specified
Analysis type	
P-value	< 0.001
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	5.78
Confidence interval	
level	95 %
sides	2-sided
lower limit	2.83
upper limit	11.78

Secondary: Number of Participants who achieved early onset of disease activity

control (UAS7 =< 6) at Week 2

End point title	Number of Participants who achieved early onset of disease activity control (UAS7 =< 6) at Week 2

End point description:

The percentage of patients achieving disease activity control (UAS7 =< 6) at Week 2 was assessed to evaluate the efficacy of Remibrutinib in Chronic Spontaneous Urticaria (CSU) patients. The UAS7 is the sum of the Weekly Hives Severity Score (HSS7) and the Weekly Itch Severity Score (ISS7). The possible range of the UAS7 score is 0 – 42 (highest hives and itch severity).

End point type	Secondary

End point timeframe:

Week 2

End point values	LOU064 25 mg b.i.d.	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	297	153		
Units: Participants	89	9		

Statistical analyses

Statistical analysis title	UAS7 =< 6 at Week 2
Comparison groups	LOU064 25 mg b.i.d. v Placebo
Number of subjects included in analysis	450
Analysis specification	Pre-specified
Analysis type	
P-value	< 0.001
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	7.92
Confidence interval	
level	95 %
sides	2-sided
lower limit	3.72
upper limit	16.85

Secondary: Number of Participants who achieved Dermatology Life Quality Index (DLQI) = 0-1 at Week 12

End point title	Number of Participants who achieved Dermatology Life Quality Index (DLQI) = 0-1 at Week 12

End point description:

The Dermatology Life Quality Index (DLQI) is a 10-item (grouped in 6 domains) dermatology-specific quality of life (QoL) measure. Participants are rating their dermatology symptoms as well as the impact of their skin condition on various aspects of their lives thinking about the previous 7 days. An overall score is calculated and ranges from 0 to 30 (higher score meaning worse disease-related QoL). Domain scores are calculated for: Symptoms and Feelings (0-6), Daily Activities (0-6), Leisure (0-6), Work and School (0-3), Personal Relationships (0-6), Treatment (0-3). The overall DLQI score range was split into score bands and validated in terms of their meaning/relevance to patients overall DLQI = 0-1 means no

effect on patient's life.

End point type	Secondary

End point timeframe:

Week 12

End point values	LOU064 25 mg b.i.d.	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	297	153		
Units: Participants	106	28		

Statistical analyses

Statistical analysis title	DLQI= 0-1 at Week 12
Comparison groups	LOU064 25 mg b.i.d. v Placebo
Number of subjects included in analysis	450
Analysis specification	Pre-specified
Analysis type	
P-value	< 0.001
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	2.75
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.65
upper limit	4.58

Secondary: Mean cumulative number of weeks with disease activity control (UAS7 =< 6) up to Week 12

End point title	Mean cumulative number of weeks with disease activity control (UAS7 =< 6) up to Week 12

End point description:

Maintaining disease activity control was assessed as cumulative number of weeks with an UAS7 =< 6 response between baseline and Week 12. The UAS7 is the sum of the Weekly Hives Severity Score (HSS7) and the Weekly Itch Severity Score (ISS7). The possible range of the UAS7 score is 0 – 42 (highest hives and itch severity).

End point type	Secondary

End point timeframe:

Up to Week 12

End point values	LOU064 25 mg b.i.d.	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	297	153		
Units: Weeks				
least squares mean (standard error)	4.50 (± 0.464)	1.38 (± 0.216)		

Statistical analyses

Statistical analysis title	Disease activity control (UAS7 =< 6) up to Week 12
Comparison groups	LOU064 25 mg b.i.d. v Placebo
Number of subjects included in analysis	450
Analysis specification	Pre-specified
Analysis type	
P-value	< 0.001
Method	Regression, Linear
Parameter estimate	Rate ratio
Point estimate	3.26
Confidence interval	
level	95 %
sides	2-sided
lower limit	2.26
upper limit	4.71

Secondary: Number of Participants with Treatment Emergent Adverse Events

End point title	Number of Participants with Treatment Emergent Adverse Events[1]

End point description:

An adverse event (AE) is any untoward medical occurrence (e.g., any unfavorable and unintended sign [including abnormal laboratory findings], symptom or disease) in a clinical investigation participant after providing written informed consent for participation in the study. Therefore, an AE may or may not be temporally or causally associated with the use of a medicinal (investigational) product.

Treatment emergent Adverse Event (TEAEs) in this study are events that started after the first dose of study treatment and until 28 days after the last dose of study treatment, or events present prior to the first dose of treatment which increased in severity based on preferred term within 28 days after the last study treatment.

End point type	Secondary

End point timeframe:

Baseline up to 28 days after last dose of study medication, assessed up to approximately 56 weeks

Notes:

[1] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Only descriptive statistics performed

End point values	LOU064 25 mg b.i.d.	Double-blind treatment period: LOU064 25 mg b.i.d.	Double-blind treatment period: Placebo	Transitioned to LOU064 25 mg b.i.d.
Subject group type	Reporting group	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	297	297	153	129
Units: Participants				
Patients with at least one Adverse Event (AE)	228	205	112	71
Death	0	0	0	0
Non-fatal SAE(s)	12	10	6	2
Discontinued study treatment due to any AE(s)	13	6	6	2
Discontinued study treatment due to any SAE(s)	1	0	1	0

Statistical analyses

No statistical analyses for this end point

Secondary: Mean cumulative number of angioedema occurrence-free weeks (AAS7 = 0 response) up to Week 12

End point title	Mean cumulative number of angioedema occurrence-free weeks (AAS7 = 0 response) up to Week 12

End point description:

Angioedema occurrence was recorded once daily in the evening in the electronic Diary by the participant. Reporting the occurrence of angioedema was used as opening question for the assessment of the Angioedema Activity Score (AAS). The AAS consists of 5 questions with 4 answer options (scored 0-3) for each item, with a minimum score of 0 and a maximum score of 15 per day. The AAS score over 7 days (AAS7) ranges from 0 (no angioedema episodes) to 105 (highest angioedema severity).

End point type	Secondary

End point timeframe:

Up to Week 12

End point values	LOU064 25 mg b.i.d.	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	297	153		
Units: Weeks				
least squares mean (standard error)	8.81 (± 0.308)	6.68 (± 0.343)		

Statistical analyses

Statistical analysis title	AAS7= 0 response up to Week 12
Comparison groups	LOU064 25 mg b.i.d. v Placebo

Number of subjects included in analysis	450
Analysis specification	Pre-specified
Analysis type	
P-value	< 0.001
Method	Regression, Linear
Parameter estimate	Rate ratio
Point estimate	1.32
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.17
upper limit	1.49

Adverse events

Adverse events information

Timeframe for reporting adverse events:

On-treatment adverse events and deaths were reported from first dose of study medication up to 28 days after last dose of study medication, assessed up to approximately 56 weeks

Adverse event reporting additional description:

Any sign or symptom that occurred during the conduct of the trial and safety follow-up. The safety analysis were done on the safety population, which included all randomized subjects who received at least one dose of study medication.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	26.1

Reporting groups

Reporting group title	LOU064 25mg b.i.d.

Reporting group description:

LOU064 25mg b.i.d.

Reporting group title	Transitioned to LOU064 25mg b.i.d.

Reporting group description:

Transitioned to LOU064 25mg b.i.d.

Reporting group title	Placebo

Reporting group description:

Placebo

Serious adverse events	LOU064 25mg b.i.d.	Transitioned to LOU064 25mg b.i.d.	Placebo
Total subjects affected by serious adverse events			
subjects affected / exposed	12 / 297 (4.04%)	2 / 129 (1.55%)	6 / 153 (3.92%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Pancreatic carcinoma			
subjects affected / exposed	1 / 297 (0.34%)	0 / 129 (0.00%)	0 / 153 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Breast cancer			
subjects affected / exposed	0 / 297 (0.00%)	0 / 129 (0.00%)	1 / 153 (0.65%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Leiomyoma			

subjects affected / exposed	1 / 297 (0.34%)	0 / 129 (0.00%)	0 / 153 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	1 / 297 (0.34%)	0 / 129 (0.00%)	0 / 153 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Head injury			
subjects affected / exposed	1 / 297 (0.34%)	0 / 129 (0.00%)	0 / 153 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Arteriosclerosis coronary artery			
subjects affected / exposed	1 / 297 (0.34%)	0 / 129 (0.00%)	0 / 153 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ear and labyrinth disorders			
Vestibular disorder			
subjects affected / exposed	0 / 297 (0.00%)	0 / 129 (0.00%)	1 / 153 (0.65%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Immune system disorders			
Drug hypersensitivity			
subjects affected / exposed	0 / 297 (0.00%)	0 / 129 (0.00%)	1 / 153 (0.65%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Large intestine polyp			
subjects affected / exposed	0 / 297 (0.00%)	1 / 129 (0.78%)	0 / 153 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Food poisoning			

subjects affected / exposed	1 / 297 (0.34%)	0 / 129 (0.00%)	0 / 153 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Cholecystitis acute			
subjects affected / exposed	0 / 297 (0.00%)	1 / 129 (0.78%)	0 / 153 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Nasal polyps			
subjects affected / exposed	1 / 297 (0.34%)	0 / 129 (0.00%)	0 / 153 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
Angioedema			
subjects affected / exposed	1 / 297 (0.34%)	0 / 129 (0.00%)	0 / 153 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chronic spontaneous urticaria			
subjects affected / exposed	0 / 297 (0.00%)	0 / 129 (0.00%)	1 / 153 (0.65%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Haematuria			
subjects affected / exposed	1 / 297 (0.34%)	0 / 129 (0.00%)	0 / 153 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Intervertebral disc degeneration			
subjects affected / exposed	1 / 297 (0.34%)	0 / 129 (0.00%)	0 / 153 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intervertebral disc protrusion			

subjects affected / exposed	1 / 297 (0.34%)	0 / 129 (0.00%)	0 / 153 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Spinal stenosis			
subjects affected / exposed	1 / 297 (0.34%)	0 / 129 (0.00%)	0 / 153 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Wound abscess			
subjects affected / exposed	1 / 297 (0.34%)	0 / 129 (0.00%)	0 / 153 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	0 / 297 (0.00%)	0 / 129 (0.00%)	1 / 153 (0.65%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal infection			
subjects affected / exposed	1 / 297 (0.34%)	0 / 129 (0.00%)	0 / 153 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Appendicitis			
subjects affected / exposed	0 / 297 (0.00%)	0 / 129 (0.00%)	1 / 153 (0.65%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Frequency threshold for reporting non-serious adverse events: 3 %

Non-serious adverse events	LOU064 25mg b.i.d.	Transitioned to LOU064 25mg b.i.d.	Placebo
Total subjects affected by non-serious adverse events			
subjects affected / exposed	157 / 297 (52.86%)	40 / 129 (31.01%)	66 / 153 (43.14%)
Investigations			
Lipase increased			
subjects affected / exposed	9 / 297 (3.03%)	0 / 129 (0.00%)	3 / 153 (1.96%)
occurrences (all)	10	0	3

Nervous system disorders			
Headache			
subjects affected / exposed	22 / 297 (7.41%)	1 / 129 (0.78%)	8 / 153 (5.23%)
occurrences (all)	26	1	8
Skin and subcutaneous tissue disorders			
Acne			
subjects affected / exposed	1 / 297 (0.34%)	0 / 129 (0.00%)	5 / 153 (3.27%)
occurrences (all)	1	0	5
Petechiae			
subjects affected / exposed	13 / 297 (4.38%)	5 / 129 (3.88%)	0 / 153 (0.00%)
occurrences (all)	28	5	0
Urticaria			
subjects affected / exposed	9 / 297 (3.03%)	5 / 129 (3.88%)	7 / 153 (4.58%)
occurrences (all)	10	6	9
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	9 / 297 (3.03%)	0 / 129 (0.00%)	2 / 153 (1.31%)
occurrences (all)	11	0	2
Infections and infestations			
Influenza			
subjects affected / exposed	8 / 297 (2.69%)	4 / 129 (3.10%)	2 / 153 (1.31%)
occurrences (all)	8	4	2
COVID-19			
subjects affected / exposed	62 / 297 (20.88%)	13 / 129 (10.08%)	21 / 153 (13.73%)
occurrences (all)	62	13	21
Upper respiratory tract infection			
subjects affected / exposed	22 / 297 (7.41%)	8 / 129 (6.20%)	4 / 153 (2.61%)
occurrences (all)	25	9	5
Suspected COVID-19			
subjects affected / exposed	16 / 297 (5.39%)	4 / 129 (3.10%)	5 / 153 (3.27%)
occurrences (all)	16	4	5
Sinusitis			
subjects affected / exposed	5 / 297 (1.68%)	1 / 129 (0.78%)	6 / 153 (3.92%)
occurrences (all)	5	1	6
Nasopharyngitis			

subjects affected / exposed	33 / 297 (11.11%)	3 / 129 (2.33%)	9 / 153 (5.88%)
occurrences (all)	42	3	14
Urinary tract infection			
subjects affected / exposed	11 / 297 (3.70%)	3 / 129 (2.33%)	4 / 153 (2.61%)
occurrences (all)	13	3	6
Metabolism and nutrition disorders			
Hyperuricaemia			
subjects affected / exposed	10 / 297 (3.37%)	2 / 129 (1.55%)	1 / 153 (0.65%)
occurrences (all)	16	2	1
Hyperlipidaemia			
subjects affected / exposed	6 / 297 (2.02%)	6 / 129 (4.65%)	4 / 153 (2.61%)
occurrences (all)	8	6	4

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
23 May 2022	The key rationale for this amendment was to implement recommendations from the US FDA regarding statistical analysis covering intercurrent event handling for COVID-19 related reasons for treatment discontinuation and the use of the same covariates in both primary and secondary endpoints. The other key aspect was to ensure consistency across the program involving both pivotal studies (CLOU064A2301 and CLOU064A2302).

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported