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

Summary

EudraCT number	2022-001034-11
Trial protocol	FR ES SK DE AT HU IT BG DK CZ
Global end of trial date	19 January 2024

Results information

Result version number	v1 (current)
This version publication date	06 November 2024
First version publication date	06 November 2024

Trial information

Trial identification

Sponsor protocol code	CLOU064A2301

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT05030311
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)	
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	19 January 2024
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	19 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	30 November 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	Argentina: 47
Country: Number of subjects enrolled	Australia: 5
Country: Number of subjects enrolled	Bulgaria: 11
Country: Number of subjects enrolled	Colombia: 14
Country: Number of subjects enrolled	Czechia: 16
Country: Number of subjects enrolled	France: 33
Country: Number of subjects enrolled	Hungary: 9
Country: Number of subjects enrolled	India: 58
Country: Number of subjects enrolled	Italy: 6
Country: Number of subjects enrolled	Japan: 27
Country: Number of subjects enrolled	Korea, Republic of: 37
Country: Number of subjects enrolled	Mexico: 17
Country: Number of subjects enrolled	Russian Federation: 1
Country: Number of subjects enrolled	Singapore: 1
Country: Number of subjects enrolled	Spain: 19
Country: Number of subjects enrolled	Taiwan: 13
Country: Number of subjects enrolled	Türkiye: 35
Country: Number of subjects enrolled	United States: 121

Worldwide total number of subjects	470
EEA total number of subjects	94

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)	425
From 65 to 84 years	45
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

The study was conducted globally across 18 countries. 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	Investigator, Monitor, Carer, Subject

Arms

Are arms mutually exclusive?	Yes
Arm title	LOU064 25mg 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	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	Coated tablet
Routes of administration	Oral use

Dosage and administration details:

Placebo

Number of subjects in period 1	LOU064 25mg b.i.d.	Placebo
Started	313	157
Safety Set	309	153
Full Analysis Set (FAS)	309	153
Completed	251	124
Not completed	62	33
Consent withdrawn by subject	31	17
Physician decision	5	2
Adverse event, non-fatal	13	5
Technical problems	-	1
Unsatisfactory therapeutic effect	4	3
Lost to follow-up	5	1
Protocol deviation	4	4

Baseline characteristics

Reporting groups	
Reporting group title	LOU064 25mg 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 25mg b.i.d.	Placebo	Total
Number of subjects	313	157	470
Age Categorical Units: Participants			
>= 18 - < 65 years	282	143	425
>= 65 - < 85 years	31	14	45
>= 85 years	0	0	0
Age Continuous Units: Years			
arithmetic mean	44.6	45.9	
standard deviation	± 14.27	± 13.44	-
Sex: Female, Male Units: Participants			
Female	212	109	321
Male	101	48	149
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	12	14	26
Asian	94	46	140
Native Hawaiian or Other Pacific Islander	0	1	1
Black or African American	12	3	15
White	188	89	277
More than one race	6	2	8
Unknown or Not Reported	1	2	3
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	76	44	120
Not Hispanic or Latino	237	113	350
Unknown or Not Reported	0	0	0

End points

End points reporting groups

Reporting group title	LOU064 25mg 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	Per protocol
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	Per protocol
Subject analysis set description:	
Patients initially randomized to Placebo (Up to Week 24)	
Subject analysis set title	Entire Study period: LOU064 25mg b.i.d.
Subject analysis set type	Per protocol
Subject analysis set 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)	
Subject analysis set title	Open-label period: Transitioned to LOU064 25 mg b.i.d.
Subject analysis set type	Per protocol
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)	
Subject analysis set title	LOU064 25mg b.i.d.
Subject analysis set type	Per protocol
Subject analysis set description:	
LOU064 25mg b.i.d.	
Subject analysis set title	Placebo
Subject analysis set type	Per protocol
Subject analysis set description:	
Placebo	

Primary: Change from baseline in Weekly Urticaria Score (UAS7) at Week 12 (Scenario 1 with UAS7 as primary efficacy endpoint)

End point title	Change from baseline in Weekly Urticaria 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 25mg b.i.d.	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	309	153		
Units: Scores on a scale				
least squares mean (standard error)	-20.02 (± 0.716)	-13.79 (± 0.980)		

Statistical analyses

Statistical analysis title	LOU064 25mg b.i.d. v Placebo
Comparison groups	LOU064 25mg b.i.d. v Placebo
Number of subjects included in analysis	462
Analysis specification	Pre-specified
Analysis type	
P-value	< 0.001
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-6.22
Confidence interval	
level	95 %
sides	2-sided
lower limit	-8.45
upper limit	-4
Variability estimate	Standard error of the mean
Dispersion value	1.136

Primary: 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	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 25mg b.i.d.	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	309	153		
Units: Scores on a scale				
least squares mean (standard error)	-9.52 (± 0.343)	-6.89 (± 0.470)		

Statistical analyses

Statistical analysis title	LOU064 25mg b.i.d. v Placebo
Statistical analysis description:	
ISS7 at Week 12 (Scenario 2 with ISS7 and HSS7 as co-primary efficacy endpoints)	
Comparison groups	LOU064 25mg b.i.d. v Placebo
Number of subjects included in analysis	462
Analysis specification	Pre-specified
Analysis type	
P-value	< 0.001
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-2.63
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.7
upper limit	-1.56
Variability estimate	Standard error of the mean
Dispersion value	0.544

Primary: 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	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 25mg b.i.d.	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	309	153		
Units: Scores on a scale				
least squares mean (standard error)	-10.47 (± 0.401)	-6.86 (± 0.548)		

Statistical analyses

Statistical analysis title	LOU064 25mg b.i.d. v Placebo
Statistical analysis description:	
HSS7 at Week 12 (Scenario 2 with ISS7 and HSS7 as co-primary efficacy endpoints)	
Comparison groups	LOU064 25mg b.i.d. v Placebo
Number of subjects included in analysis	462
Analysis specification	Pre-specified
Analysis type	
P-value	< 0.001
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-3.61
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.85
upper limit	-2.36
Variability estimate	Standard error of the mean
Dispersion value	0.635

Secondary: Number of patients who achieved disease activity control (UAS7 ≤6)

End point title	Number of patients who achieved disease activity control (UAS7 ≤6)
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 25mg b.i.d.	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	309	153		
Units: Participants	154	38		

Statistical analyses

Statistical analysis title	LOU064 25mg b.i.d. v Placebo
Statistical analysis description:	
Disease activity control (UAS7 =< 6) at Week 12	
Comparison groups	LOU064 25mg b.i.d. v Placebo
Number of subjects included in analysis	462
Analysis specification	Pre-specified
Analysis type	
P-value	< 0.001
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	3.11
Confidence interval	
level	95 %
sides	2-sided
lower limit	2
upper limit	4.84

Secondary: Number of patients who achieved complete absence of hives and itch (UAS7 = 0

End point title	Number of patients who achieved complete absence of hives and itch (UAS7 = 0

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 25mg b.i.d.	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	309	153		
Units: Participants	96	16		

Statistical analyses

Statistical analysis title	LOU064 25mg b.i.d. v Placebo
Statistical analysis description:	
Complete absence of hives and itch (UAS7 = 0) at Week 12	
Comparison groups	LOU064 25mg b.i.d. v Placebo
Number of subjects included in analysis	462
Analysis specification	Pre-specified
Analysis type	
P-value	< 0.001
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	3.83
Confidence interval	
level	95 %
sides	2-sided
lower limit	2.16
upper limit	6.82

Secondary: Number of patients who achieved DLQI = 0 - 1

End point title	Number of patients who achieved DLQI = 0 - 1
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 25mg b.i.d.	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	308	153		
Units: Participants	120	34		

Statistical analyses

Statistical analysis title	LOU064 25mg b.i.d. v Placebo
Comparison groups	LOU064 25mg b.i.d. v Placebo
Number of subjects included in analysis	461
Analysis specification	Pre-specified
Analysis type	
P-value	< 0.001
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	2.44
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.53
upper limit	3.9

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

End point title	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 25mg b.i.d.	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	309	153		
Units: weeks				
least squares mean (standard error)	5.17 (± 0.414)	1.92 (± 0.241)		

Statistical analyses

Statistical analysis title	LOU064 25mg b.i.d. v Placebo
Comparison groups	LOU064 25mg b.i.d. v Placebo
Number of subjects included in analysis	462
Analysis specification	Pre-specified
Analysis type	
P-value	< 0.001
Method	Regression, Logistic
Parameter estimate	Rate ratio
Point estimate	2.69
Confidence interval	
level	95 %
sides	2-sided
lower limit	2.01
upper limit	3.61

Secondary: Number of patients with early onset of disease control (UAS7 ≤ 6 at week 2)

End point title	Number of patients with early onset of disease 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 25mg b.i.d.	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	309	153		
Units: Participants	104	5		

Statistical analyses

Statistical analysis title	LOU064 25mg b.i.d. v Placebo
Comparison groups	LOU064 25mg b.i.d. v Placebo
Number of subjects included in analysis	462
Analysis specification	Pre-specified
Analysis type	
P-value	< 0.001
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	15.67

Confidence interval	
level	95 %
sides	2-sided
lower limit	6.18
upper limit	39.77

Secondary: Number of participants with Adverse Events

End point title	Number of participants with Adverse Events

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.

Pts = patients
w/ = with
sign. = significant

End point type	Secondary

End point timeframe:

On-treatment adverse events are reported from first dose of study medication up to 28 days after last dose of study medication, for a timeframe up to approximately 56 weeks

End point values	Double-blind treatment period: LOU064 25 mg b.i.d.	Double-blind treatment period: Placebo	Entire Study period: LOU064 25mg b.i.d.	Open-label period: Transitioned to LOU064 25 mg b.i.d.
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	309	153	309	133
Units: Participants				
Patients with at least one AE	188	86	218	62
Pts w/ serious or other sign. events - Death	0	0	0	0
Pts w/ serious or other significant events - SAEs	10	1	13	1
Discontinued study treatment due to any AEs	11	3	15	2
Discontinued study treatment due to any SAEs	2	0	3	1
Treatment interruption due to AEs	17	9	18	3
Treatment interruption due to SAEs	5	1	5	0

Statistical analyses

No statistical analyses for this end point

Secondary: Cumulative number of weeks without angioedema (AAS7 = 0)

End point title	Cumulative number of weeks without angioedema (AAS7 = 0)

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 25mg b.i.d.	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	309	153		
Units: Weeks				
least squares mean (standard error)	8.43 (± 0.274)	6.72 (± 0.330)		

Statistical analyses

Statistical analysis title	LOU064 25mg b.i.d. v Placebo

Statistical analysis description:

Angioedema occurrence-free weeks (AAS7 = 0 response) up to Week 12

Comparison groups	LOU064 25mg b.i.d. v Placebo
Number of subjects included in analysis	462
Analysis specification	Pre-specified
Analysis type	
P-value	< 0.001
Method	Regression, Linear
Parameter estimate	Rate ratio
Point estimate	1.25
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.12
upper limit	1.41

Adverse events

Adverse events information

Timeframe for reporting adverse events:

On-treatment adverse events are reported from first dose of study medication up to 28 days after last dose of study medication, for a timeframe 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	13 / 309 (4.21%)	1 / 133 (0.75%)	1 / 153 (0.65%)
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)			
Small intestine adenocarcinoma			
subjects affected / exposed	1 / 309 (0.32%)	0 / 133 (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
Mucinous adenocarcinoma of appendix			
subjects affected / exposed	1 / 309 (0.32%)	0 / 133 (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
Benign renal neoplasm			

subjects affected / exposed	1 / 309 (0.32%)	0 / 133 (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			
Face injury			
subjects affected / exposed	1 / 309 (0.32%)	0 / 133 (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			
Angina pectoris			
subjects affected / exposed	1 / 309 (0.32%)	0 / 133 (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 failure congestive			
subjects affected / exposed	1 / 309 (0.32%)	0 / 133 (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
Pregnancy, puerperium and perinatal conditions			
Abortion spontaneous			
subjects affected / exposed	0 / 309 (0.00%)	1 / 133 (0.75%)	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
Gastrointestinal disorders			
Gastrointestinal wall thickening			
subjects affected / exposed	1 / 309 (0.32%)	0 / 133 (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			
subjects affected / exposed	0 / 309 (0.00%)	0 / 133 (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
Respiratory, thoracic and mediastinal disorders			

Pleuritic pain			
subjects affected / exposed	1 / 309 (0.32%)	0 / 133 (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			
Chronic spontaneous urticaria			
subjects affected / exposed	1 / 309 (0.32%)	0 / 133 (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			
Back pain			
subjects affected / exposed	1 / 309 (0.32%)	0 / 133 (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
Spondylolisthesis			
subjects affected / exposed	1 / 309 (0.32%)	0 / 133 (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			
COVID-19			
subjects affected / exposed	1 / 309 (0.32%)	0 / 133 (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	1 / 309 (0.32%)	0 / 133 (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
Metabolism and nutrition disorders			
Hypokalaemia			
subjects affected / exposed	1 / 309 (0.32%)	0 / 133 (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
Diabetic ketoacidosis			

subjects affected / exposed	1 / 309 (0.32%)	0 / 133 (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

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	139 / 309 (44.98%)	26 / 133 (19.55%)	53 / 153 (34.64%)
Nervous system disorders			
Headache			
subjects affected / exposed	25 / 309 (8.09%)	3 / 133 (2.26%)	11 / 153 (7.19%)
occurrences (all)	30	3	11
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	10 / 309 (3.24%)	1 / 133 (0.75%)	3 / 153 (1.96%)
occurrences (all)	15	2	4
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	11 / 309 (3.56%)	2 / 133 (1.50%)	7 / 153 (4.58%)
occurrences (all)	11	2	7
Nausea			
subjects affected / exposed	11 / 309 (3.56%)	0 / 133 (0.00%)	3 / 153 (1.96%)
occurrences (all)	11	0	4
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	12 / 309 (3.88%)	0 / 133 (0.00%)	2 / 153 (1.31%)
occurrences (all)	14	0	2
Skin and subcutaneous tissue disorders			
Urticaria			
subjects affected / exposed	11 / 309 (3.56%)	2 / 133 (1.50%)	8 / 153 (5.23%)
occurrences (all)	26	2	12
Petechiae			
subjects affected / exposed	11 / 309 (3.56%)	2 / 133 (1.50%)	1 / 153 (0.65%)
occurrences (all)	13	2	1
Musculoskeletal and connective tissue			

disorders			
Arthralgia			
subjects affected / exposed	9 / 309 (2.91%)	2 / 133 (1.50%)	5 / 153 (3.27%)
occurrences (all)	10	2	5
Infections and infestations			
COVID-19			
subjects affected / exposed	31 / 309 (10.03%)	6 / 133 (4.51%)	14 / 153 (9.15%)
occurrences (all)	31	6	14
Influenza			
subjects affected / exposed	10 / 309 (3.24%)	4 / 133 (3.01%)	2 / 153 (1.31%)
occurrences (all)	13	4	2
Nasopharyngitis			
subjects affected / exposed	22 / 309 (7.12%)	6 / 133 (4.51%)	5 / 153 (3.27%)
occurrences (all)	27	6	7
Urinary tract infection			
subjects affected / exposed	17 / 309 (5.50%)	1 / 133 (0.75%)	4 / 153 (2.61%)
occurrences (all)	20	1	4
Upper respiratory tract infection			
subjects affected / exposed	12 / 309 (3.88%)	3 / 133 (2.26%)	2 / 153 (1.31%)
occurrences (all)	18	3	3

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