Clinical trial results:
A multicenter, randomized, double-blind, placebo- controlled Phase 2b dose-finding study to investigate the efficacy, safety and tolerability of LOU064 in adult chronic spontaneous urticaria (CSU) patients inadequately controlled by H1-antihistamines

Summary

EudraCT number	2018-000993-31
Trial protocol	DE CZ GB FR SK HU BE ES DK NL
Global end of trial date	15 April 2021

Results information

Result version number	v1 (current)
This version publication date	06 February 2022
First version publication date	06 February 2022

Trial information

Trial identification

Sponsor protocol code	CLOU064A2201

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03926611
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Novartis Pharmaceuticals
Sponsor organisation address	CH-4002, Basel, Switzerland,
Public contact	Clinical Disclosure Office, Novartis Pharma AG, 41 613241111, novartis.email@novartis.com
Scientific contact	Study Director, Novartis Pharma AG, 1 (862) 778-8300, 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	22 December 2021
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	15 April 2021
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this study was to characterize the dose-response relationship of LOU064 administered once or twice daily in subjects with CSU with respect to change from baseline in UAS7 at Week 4.

UAS7 is the sum of the HSS7 score (weekly Hives Severity Sore) and the ISS7 score (weekly Itch Severity Score). The possible range of the weekly UAS7 score is 0 – 42 (highest activity).

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	06 June 2019
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	Japan: 44
Country: Number of subjects enrolled	Hungary: 14
Country: Number of subjects enrolled	United States: 34
Country: Number of subjects enrolled	Czechia: 10
Country: Number of subjects enrolled	Spain: 21
Country: Number of subjects enrolled	United Kingdom: 7
Country: Number of subjects enrolled	Belgium: 4
Country: Number of subjects enrolled	Germany: 26
Country: Number of subjects enrolled	Slovakia: 8
Country: Number of subjects enrolled	Canada: 26
Country: Number of subjects enrolled	Poland: 43
Country: Number of subjects enrolled	France: 12
Country: Number of subjects enrolled	Russian Federation: 29
Country: Number of subjects enrolled	Argentina: 10
Country: Number of subjects enrolled	Netherlands: 9
Country: Number of subjects enrolled	Denmark: 7
Country: Number of subjects enrolled	Turkey: 7

Worldwide total number of subjects	311
EEA total number of subjects	154

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)	279
From 65 to 84 years	32
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

311 participants enrolled at 82 investigative sites in 17 countries. This Randomized Set included all randomized subjects, regardless of whether or not they actually received study medication. Subjects were analyzed according to the treatment assigned at randomization.

Pre-assignment

Screening details:

Informed consent was obtained from each subject in writing at screening before any procedure was performed. The study was explained to each subject by investigator, who answered any questions, and written information was also provided.

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, Monitor, Data analyst, Carer, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	LOU064 Arm 1

Arm description:

10 mg LOU064 qd capsule once daily

Arm type	Experimental
Investigational medicinal product name	Remibrutinib 10 mg q.d.
Investigational medicinal product code	LOU064
Other name	LOU064
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

10 mg capsule q.d. once daily

Arm title	LOU064 Arm 2

Arm description:

35 mg capsule qd LOU064 once daily

Arm type	Experimental
Investigational medicinal product name	Remibrutinib 35 mg q.d.
Investigational medicinal product code	LOU064
Other name	LOU064
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

35 mg capsule q.d. once daily

Arm title	LOU064 Arm 3

Arm description:

100 mg capsule qd LOU064 once daily

Arm type	Experimental

Investigational medicinal product name	Remibrutinib 100 mg q.d.
Investigational medicinal product code	LOU064
Other name	LOU064
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:
100 mg capsule q.d. once daily

Arm title	LOU064 Arm 4

Arm description:
10 mg capsule LOU064 bid

Arm type	Experimental
Investigational medicinal product name	Remibrutinib 10 mg bid
Investigational medicinal product code	LOU064
Other name	LOU064
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:
10 mg capsule bid

Arm title	LOU064 Arm 5

Arm description:
25 mg capsule LOU064 bid

Arm type	Experimental
Investigational medicinal product name	Remibrutinib 25 mg bid
Investigational medicinal product code	LOU064
Other name	LOU064
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:
25 mg capsule bid

Arm title	LOU064 Arm 6

Arm description:
100 mg capsule LOU064 bid

Arm type	Experimental
Investigational medicinal product name	Remibrutinib 100 mg bid
Investigational medicinal product code	LOU064
Other name	LOU064
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:
100 mg capsule bid

Arm title	Placebo Arm

Arm description:
Participants took matching placebo twice daily

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

Dosage and administration details:
matching placebo capsule twice daily

Number of subjects in period 1	LOU064 Arm 1	LOU064 Arm 2	LOU064 Arm 3
Started	44	44	47
Randomized set (RAN)	44	44	47
Full analysis set (FAS)	44	43	47
Safety set (SAF)	44	44	47
Completed	41	41	45
Not completed	3	3	2
Consent withdrawn by subject	1	1	1
Physician decision	-	-	-
Covid-19 pandemic	-	-	1
Adverse event, non-fatal	-	-	-
Technical problems	-	-	-
Protocol deviation	1	-	-
Lack of efficacy	1	2	-

Number of subjects in period 1	LOU064 Arm 4	LOU064 Arm 5	LOU064 Arm 6
Started	44	44	45
Randomized set (RAN)	44	44	45
Full analysis set (FAS)	44	43	45
Safety set (SAF)	44	43	45
Completed	40	40	36
Not completed	4	4	9
Consent withdrawn by subject	-	-	1
Physician decision	-	-	1
Covid-19 pandemic	-	1	2
Adverse event, non-fatal	3	1	3
Technical problems	-	-	1
Protocol deviation	1	1	1
Lack of efficacy	-	1	-

Number of subjects in period 1	Placebo Arm
Started	43

Randomized set (RAN)	43
Full analysis set (FAS)	42
Safety set (SAF)	42
Completed	38
Not completed	5
Consent withdrawn by subject	3
Physician decision	-
Covid-19 pandemic	-
Adverse event, non-fatal	-
Technical problems	-
Protocol deviation	1
Lack of efficacy	1

Baseline characteristics

Reporting groups	
Reporting group title	LOU064 Arm 1
Reporting group description:	
10 mg LOU064 qd capsule once daily	
Reporting group title	LOU064 Arm 2
Reporting group description:	
35 mg capsule qd LOU064 once daily	
Reporting group title	LOU064 Arm 3
Reporting group description:	
100 mg capsule qd LOU064 once daily	
Reporting group title	LOU064 Arm 4
Reporting group description:	
10 mg capsule LOU064 bid	
Reporting group title	LOU064 Arm 5
Reporting group description:	
25 mg capsule LOU064 bid	
Reporting group title	LOU064 Arm 6
Reporting group description:	
100 mg capsule LOU064 bid	
Reporting group title	Placebo Arm
Reporting group description:	
Participants took matching placebo twice daily	

Reporting group values	LOU064 Arm 1	LOU064 Arm 2	LOU064 Arm 3
Number of subjects	44	44	47
Age Categorical Units: Participants			
<=18 years	0	0	0
Between 18 and 65 years	41	39	44
>=65 years	3	5	3
Age Continuous Units: Years			
arithmetic mean	42.5	44.0	45.2
standard deviation	± 16.04	± 16.47	± 13.40
Sex: Female, Male Units: Participants			
Female	35	30	39
Male	9	14	8
Race/Ethnicity, Customized Units: Subjects			
White	36	37	40
Black or African American	1	0	0
Asian	7	6	7
Native Hawaiian or Other Pacific	0	0	0
American Indian or Alaska Native	0	0	0
Multiple	0	1	0

Reporting group values	LOU064 Arm 4	LOU064 Arm 5	LOU064 Arm 6
Number of subjects	44	44	45
Age Categorical Units: Participants			
<=18 years	0	0	0
Between 18 and 65 years	39	39	41
>=65 years	5	5	4
Age Continuous Units: Years			
arithmetic mean	46.1	47.4	44.9
standard deviation	± 15.21	± 14.62	± 13.76
Sex: Female, Male Units: Participants			
Female	32	32	29
Male	12	12	16
Race/Ethnicity, Customized Units: Subjects			
White	36	36	36
Black or African American	0	0	0
Asian	7	7	9
Native Hawaiian or Other Pacific	1	0	0
American Indian or Alaska Native	0	1	0
Multiple	0	0	0

Reporting group values	Placebo Arm	Total	
Number of subjects	43	311	
Age Categorical Units: Participants			
<=18 years	0	0	
Between 18 and 65 years	36	279	
>=65 years	7	32	
Age Continuous Units: Years			
arithmetic mean	45.1		
standard deviation	± 15.24	-	
Sex: Female, Male Units: Participants			
Female	25	222	
Male	18	89	
Race/Ethnicity, Customized Units: Subjects			
White	35	256	
Black or African American	1	2	
Asian	7	50	
Native Hawaiian or Other Pacific	0	1	
American Indian or Alaska Native	0	1	
Multiple	0	1	

Subject analysis sets

Subject analysis set title	Full Analysis Set (FAS)
Subject analysis set type	Intention-to-treat

Subject analysis set description:

The FAS included all randomized subjects. Following the intent-to-treat principle, subjects were analyzed according to the treatment and strata assigned to at randomization. The mis-randomized subjects (mis-randomized in IRT) were excluded.

Reporting group values	Full Analysis Set (FAS)		
Number of subjects	309		
Age Categorical Units: Participants			
<=18 years	0		
Between 18 and 65 years	279		
>=65 years	30		
Age Continuous Units: Years			
arithmetic mean			
standard deviation	±		
Sex: Female, Male Units: Participants			
Female			
Male			
Race/Ethnicity, Customized Units: Subjects			
White			
Black or African American			
Asian			
Native Hawaiian or Other Pacific			
American Indian or Alaska Native			
Multiple			

End points

End points reporting groups

Reporting group title	LOU064 Arm 1
Reporting group description:	
10 mg LOU064 qd capsule once daily	
Reporting group title	LOU064 Arm 2
Reporting group description:	
35 mg capsule qd LOU064 once daily	
Reporting group title	LOU064 Arm 3
Reporting group description:	
100 mg capsule qd LOU064 once daily	
Reporting group title	LOU064 Arm 4
Reporting group description:	
10 mg capsule LOU064 bid	
Reporting group title	LOU064 Arm 5
Reporting group description:	
25 mg capsule LOU064 bid	
Reporting group title	LOU064 Arm 6
Reporting group description:	
100 mg capsule LOU064 bid	
Reporting group title	Placebo Arm
Reporting group description:	
Participants took matching placebo twice daily	
Subject analysis set title	Full Analysis Set (FAS)
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
The FAS included all randomized subjects. Following the intent-to-treat principle, subjects were analyzed according to the treatment and strata assigned to at randomization. The mis-randomized subjects (mis-randomized in IRT) were excluded.	

Primary: Change from baseline in weekly Urticaria Activity Score (UAS7) at Week 4

End point title	Change from baseline in weekly Urticaria Activity Score (UAS7) at Week 4
End point description:	
UAS7 score change (LS mean Change) from baseline at Week 4 estimated with a mixed-effect repeated measurement analysis of UAS7 score change from baseline (FAS) 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. The maximum UAS7 value is 42. A higher score indicates worse disease. A negative change score (week 4 score minus Baseline score) indicates improvement.	
End point type	Primary
End point timeframe:	
Baseline, Week 4	

End point values	LOU064 Arm 1	LOU064 Arm 2	LOU064 Arm 3	LOU064 Arm 4
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	44	44	47	44
Units: Scores on a scale				
least squares mean (standard error)	-19.10 (± 1.686)	-19.08 (± 1.690)	-14.65 (± 1.624)	-15.99 (± 1.686)

End point values	LOU064 Arm 5	LOU064 Arm 6	Placebo Arm	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	43	45	42	
Units: Scores on a scale				
least squares mean (standard error)	-20.02 (± 1.708)	-18.06 (± 1.691)	-5.44 (± 1.739)	

Statistical analyses

Statistical analysis title	UAS7 score change (LS mean Change)
Comparison groups	Placebo Arm v LOU064 Arm 1
Number of subjects included in analysis	86
Analysis specification	Pre-specified
Analysis type	
P-value	< 0.0001
Method	Mixed models analysis
Parameter estimate	LS Mean
Point estimate	-13.66
Confidence interval	
level	90 %
sides	2-sided
lower limit	-17.51
upper limit	-9.81
Variability estimate	Standard error of the mean
Dispersion value	2.334

Statistical analysis title	UAS7 score change (LS mean Change)
Comparison groups	LOU064 Arm 2 v Placebo Arm
Number of subjects included in analysis	86
Analysis specification	Pre-specified
Analysis type	
P-value	< 0.0001
Method	Mixed models analysis
Parameter estimate	LS Mean
Point estimate	-13.64

Confidence interval	
level	90 %
sides	2-sided
lower limit	-17.49
upper limit	-9.78
Variability estimate	Standard error of the mean
Dispersion value	2.336

Statistical analysis title	UAS7 score change (LS mean Change)
Comparison groups	LOU064 Arm 3 v Placebo Arm
Number of subjects included in analysis	89
Analysis specification	Pre-specified
Analysis type	
P-value	< 0.0001
Method	Mixed models analysis
Parameter estimate	LS Mean
Point estimate	-9.21
Confidence interval	
level	90 %
sides	2-sided
lower limit	-12.97
upper limit	-5.45
Variability estimate	Standard error of the mean
Dispersion value	2.277

Statistical analysis title	UAS7 score change (LS mean Change)
Comparison groups	LOU064 Arm 4 v Placebo Arm
Number of subjects included in analysis	86
Analysis specification	Pre-specified
Analysis type	
P-value	< 0.0001
Method	Mixed models analysis
Parameter estimate	LS Mean
Point estimate	-10.55
Confidence interval	
level	90 %
sides	2-sided
lower limit	-14.38
upper limit	-6.72
Variability estimate	Standard error of the mean
Dispersion value	2.319

Statistical analysis title	UAS7 score change (LS mean Change)
Comparison groups	LOU064 Arm 5 v Placebo Arm

Number of subjects included in analysis	85
Analysis specification	Pre-specified
Analysis type	
P-value	< 0.0001
Method	Mixed models analysis
Parameter estimate	LS Mean
Point estimate	-14.58
Confidence interval	
level	90 %
sides	2-sided
lower limit	-18.43
upper limit	-10.73
Variability estimate	Standard error of the mean
Dispersion value	2.334

Statistical analysis title	UAS7 score change (LS mean Change)
Comparison groups	LOU064 Arm 6 v Placebo Arm
Number of subjects included in analysis	87
Analysis specification	Pre-specified
Analysis type	
P-value	< 0.0001
Method	Mixed models analysis
Parameter estimate	LS Mean
Point estimate	-12.62
Confidence interval	
level	90 %
sides	2-sided
lower limit	-16.45
upper limit	-8.78
Variability estimate	Standard error of the mean
Dispersion value	2.327

Secondary: Change from baseline in weekly Urticaria Activity Score (UAS7) at week 12

End point title	Change from baseline in weekly Urticaria Activity Score (UAS7) at week 12

End point description:

UAS7 score change (LS mean Change) from baseline at Week 12 estimated with a mixed-effect repeated measurement analysis of UAS7 score change from baseline (FAS)

End point type	Secondary

End point timeframe:

Week 12

End point values	LOU064 Arm 1	LOU064 Arm 2	LOU064 Arm 3	LOU064 Arm 4
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	41	41	45	40
Units: Score				
least squares mean (standard error)	-18.11 (± 1.934)	-17.97 (± 1.934)	-15.27 (± 1.850)	-17.67 (± 1.939)

End point values	LOU064 Arm 5	LOU064 Arm 6	Placebo Arm	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	39	35	39	
Units: Score				
least squares mean (standard error)	-20.21 (± 1.964)	-17.38 (± 1.985)	-7.87 (± 2.001)	

Statistical analyses

Statistical analysis title	UAS7 score change (LS mean Change)
Comparison groups	LOU064 Arm 1 v Placebo Arm
Number of subjects included in analysis	80
Analysis specification	Pre-specified
Analysis type	
P-value	< 0.0001
Method	Mixed models analysis
Parameter estimate	LS Mean
Point estimate	-10.24
Confidence interval	
level	90 %
sides	2-sided
lower limit	-14.72
upper limit	-5.77
Variability estimate	Standard error of the mean
Dispersion value	2.71

Statistical analysis title	UAS7 score change (LS mean Change)
Comparison groups	LOU064 Arm 2 v Placebo Arm
Number of subjects included in analysis	80
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.0001
Method	Mixed models analysis
Parameter estimate	LS Mean
Point estimate	-10.11

Confidence interval	
level	90 %
sides	2-sided
lower limit	-14.58
upper limit	-5.63
Variability estimate	Standard error of the mean
Dispersion value	2.711

Statistical analysis title	UAS7 score change (LS mean Change)
Comparison groups	LOU064 Arm 3 v Placebo Arm
Number of subjects included in analysis	84
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.0027
Method	Mixed models analysis
Parameter estimate	LS Mean
Point estimate	-7.4
Confidence interval	
level	90 %
sides	2-sided
lower limit	-11.75
upper limit	-3.05
Variability estimate	Standard error of the mean
Dispersion value	2.635

Statistical analysis title	UAS7 score change (LS mean Change)
Comparison groups	LOU064 Arm 4 v Placebo Arm
Number of subjects included in analysis	79
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.0002
Method	Mixed models analysis
Parameter estimate	LS Mean
Point estimate	-9.8
Confidence interval	
level	90 %
sides	2-sided
lower limit	-14.25
upper limit	-5.35
Variability estimate	Standard error of the mean
Dispersion value	2.696

Statistical analysis title	UAS7 score change (LS mean Change)
Comparison groups	LOU064 Arm 5 v Placebo Arm

Number of subjects included in analysis	78
Analysis specification	Pre-specified
Analysis type	
P-value	< 0.0001
Method	Mixed models analysis
Parameter estimate	LS Mean
Point estimate	-12.35
Confidence interval	
level	90 %
sides	2-sided
lower limit	-16.82
upper limit	-7.87
Variability estimate	Standard error of the mean
Dispersion value	2.714

Statistical analysis title	UAS7 score change (LS mean Change)
Comparison groups	LOU064 Arm 6 v Placebo Arm
Number of subjects included in analysis	74
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.0003
Method	Mixed models analysis
Parameter estimate	LS Mean
Point estimate	-9.52
Confidence interval	
level	90 %
sides	2-sided
lower limit	-14.03
upper limit	-5.01
Variability estimate	Standard error of the mean
Dispersion value	2.733

Secondary: Percentage of participants with either complete absence of hives and itch (UAS7=0) or well-controlled disease (UAS7<=6)

End point title	Percentage of participants with either complete absence of hives and itch (UAS7=0) or well-controlled disease (UAS7<=6)

End point description:

UAS7=0 and UAS7<=6 response rate over time by treatment group (non-responder imputation)
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. The maximum UAS7 value is 42. A higher score indicates more severe disease. A negative change score (week 4 score minus Baseline score) indicates improvement.

End point type	Secondary

End point timeframe:

Week 12

End point values	LOU064 Arm 1	LOU064 Arm 2	LOU064 Arm 3	LOU064 Arm 4
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	44	44	47	44
Units: Percent of participants				
number (confidence interval 90%)				
UAS7=0	29.5 (18.7 to 43.0)	29.5 (18.7 to 43.0)	29.8 (19.3 to 42.7)	31.8 (20.6 to 45.3)
UAS<=6	47.7 (34.8 to 61.0)	52.3 (39.0 to 65.2)	38.3 (26.6 to 51.4)	47.7 (34.8 to 61.0)

End point values	LOU064 Arm 5	LOU064 Arm 6	Placebo Arm	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	43	45	42	
Units: Percent of participants				
number (confidence interval 90%)				
UAS7=0	41.9 (29.3 to 55.5)	26.7 (16.5 to 39.8)	14.3 (6.7 to 26.7)	
UAS<=6	55.8 (42.3 to 68.6)	42.2 (29.9 to 55.5)	28.6 (17.7 to 42.3)	

Statistical analyses

No statistical analyses for this end point

Secondary: Cumulative number of weeks with an AAS7=0 response

End point title	Cumulative number of weeks with an AAS7=0 response

End point description:

The Weekly angioedema activity score
(AAS) is a validated tool to assess occurrence of episodes of angioedema. If the subject reports the occurrence of angioedema ("opening question") with “no”, AAS score for this day is 0. If “yes” is the answer to the opening question, the subject will continue to answer questions about the duration, severity and impact on daily functioning and appearance of the angioedema. The AAS7 is a weekly AAS score (AAS7). Minimum and maximum possible AAS7 scores are 0−105. Higher score means more severe disease.

End point type	Secondary

End point timeframe:

Baseline to Week 12

End point values	LOU064 Arm 1	LOU064 Arm 2	LOU064 Arm 3	LOU064 Arm 4
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	44	44	47	44
Units: Weeks				
arithmetic mean (standard deviation)	10.2 (± 2.33)	10.5 (± 2.59)	10.0 (± 3.06)	9.8 (± 3.05)

End point values	LOU064 Arm 5	LOU064 Arm 6	Placebo Arm	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	43	45	42	
Units: Weeks				
arithmetic mean (standard deviation)	10.3 (± 2.45)	9.2 (± 3.38)	8.2 (± 3.50)	

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of participants with DLQI score of 0 or 1

End point title	Percentage of participants with DLQI score of 0 or 1

End point description:

Percentage of subjects with DLQI 0/1 response by treatment group and visit (non-responder imputation)

The Dermatology Life Quality Index (DLQI) is a 10-item dermatology-specific quality of life (QoL) measure. Subjects rate 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). A DLQI score of 0 or 1 means that there is no impact of a skin disease on the patient's life.

End point type	Secondary

End point timeframe:

Week 4 and Week 12

End point values	LOU064 Arm 1	LOU064 Arm 2	LOU064 Arm 3	LOU064 Arm 4
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	44	44	47	44
Units: Percentage of participants				
number (confidence interval 90%)				
Week 4	38.6 (26.5 to 52.2)	29.5 (18.7 to 43.0)	29.8 (19.3 to 42.7)	29.5 (18.7 to 43.0)
Week 12	34.1 (22.6 to 47.6)	40.9 (28.6 to 54.4)	38.3 (26.6 to 51.4)	40.9 (28.6 to 54.4)

End point values	LOU064 Arm 5	LOU064 Arm 6	Placebo Arm	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	43	45	42	
Units: Percentage of participants				
number (confidence interval 90%)				
Week 4	51.2 (37.8 to 64.3)	33.3 (22.1 to 46.7)	16.7 (8.4 to 29.4)	

Week 12	53.5 (40.0 to 66.5)	35.6 (24.0 to 48.9)	28.6 (17.7 to 42.3)	

Statistical analyses

No statistical analyses for this end point

Secondary: Mean change from baseline in DLQI score

End point title	Mean change from baseline in DLQI score

End point description:

Summary of DLQI score and change from baseline

The Dermatology Life Quality Index (DLQI) is a 10-item dermatology-specific quality of life (QoL) measure. Subjects rate 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).

End point type	Secondary

End point timeframe:

Baseline, Week 4 and Week 12

End point values	LOU064 Arm 1	LOU064 Arm 2	LOU064 Arm 3	LOU064 Arm 4
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	44	44	47	44
Units: Scores on a scale				
arithmetic mean (standard deviation)				
Week 4	-9.60 (± 7.214)	-8.38 (± 7.241)	-7.18 (± 7.534)	-6.20 (± 6.416)
Week 12	-9.03 (± 6.216)	-7.31 (± 9.392)	-6.60 (± 7.798)	-8.25 (± 6.551)

End point values	LOU064 Arm 5	LOU064 Arm 6	Placebo Arm	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	43	45	42	
Units: Scores on a scale				
arithmetic mean (standard deviation)				
Week 4	-9.21 (± 7.994)	-6.15 (± 5.149)	-3.33 (± 8.090)	
Week 12	-8.97 (± 8.891)	-6.27 (± 5.513)	-4.38 (± 6.780)	

Statistical analyses

No statistical analyses for this end point

Secondary: Area under the blood concentration-time curve (AUC) of LOU064

End point title	Area under the blood concentration-time curve (AUC) of LOU064[1]

End point description:

Assessment of the area under the blood concentration-time curve (AUC) up to four hours following oral administration at Week 4 and Week 12 .

End point type	Secondary

End point timeframe:

Week 4 and Week 12

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: Statistical analysis was not planned

End point values	LOU064 Arm 1	LOU064 Arm 2	LOU064 Arm 3	LOU064 Arm 4
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	44	44	47	44
Units: hr*ng/mL				
arithmetic mean (standard deviation)				
Week 4	45.2 (± 18.4)	131 (± 65.4)	427 (± 314)	55.9 (± 32.3)
Week 12	41.8 (± 19.5)	159 (± 151)	441 (± 313)	54.4 (± 29.4)

End point values	LOU064 Arm 5	LOU064 Arm 6		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	43	45		
Units: hr*ng/mL				
arithmetic mean (standard deviation)				
Week 4	107 (± 56.8)	418 (± 246)		
Week 12	118 (± 66.6)	469 (± 240)		

Statistical analyses

No statistical analyses for this end point

Secondary: Observed maximum blood concentration (Cmax) of LOU064

End point title	Observed maximum blood concentration (Cmax) of LOU064[2]

End point description:

Assessment of the observed maximum blood concentration (Cmax) of LOU064 following drug administration at Week 4 and Week 12 .

End point type	Secondary

End point timeframe:

Week 4 and Week 12

Notes:

[2] - 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: Statistical analysis was not planned

End point values	LOU064 Arm 1	LOU064 Arm 2	LOU064 Arm 3	LOU064 Arm 4
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	44	44	47	44
Units: ng/mL				
arithmetic mean (standard deviation)				
Week 4	27.6 (± 13.7)	67.2 (± 32.7)	194 (± 142)	32.2 (± 18.7)
Week 12	26.1 (± 14.5)	80.3 (± 53.9)	199 (± 137)	31.2 (± 16.0)

End point values	LOU064 Arm 5	LOU064 Arm 6		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	43	45		
Units: ng/mL				
arithmetic mean (standard deviation)				
Week 4	55.5 (± 34.7)	196 (± 144)		
Week 12	64.9 (± 42.3)	219 (± 125)		

Statistical analyses

No statistical analyses for this end point

Secondary: Time to reach the maximum concentration (Tmax) of LOU064

End point title	Time to reach the maximum concentration (Tmax) of LOU064[3]

End point description:

Assessment of the time to reach the maximum concentration (Tmax) of LOU064 following drug administration at Weeks 4 and 12

End point type	Secondary

End point timeframe:

Week 4 and Week 12

Notes:

[3] - 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: Statistical analysis was not planned

End point values	LOU064 Arm 1	LOU064 Arm 2	LOU064 Arm 3	LOU064 Arm 4
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	44	44	47	44
Units: hours				
median (full range (min-max))				
Week 4	1.33 (0.00 to 4.00)	1.54 (0.00 to 4.00)	1.52 (0.500 to 3.00)	0.900 (0.00 to 2.00)
Week 12	1.17 (0.00 to 4.08)	1.48 (0.500 to 4.00)	1.61 (0.00 to 4.00)	1.17 (0.500 to 4.00)

End point values	LOU064 Arm 5	LOU064 Arm 6		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	43	45		
Units: hours				
median (full range (min-max))				
Week 4	1.15 (0.00 to 3.02)	1.52 (0.00 to 3.08)		
Week 12	1.32 (0.00 to 4.00)	1.39 (0.5000 to 4.00)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse Events (AEs) and Serious Adverse Events were collected after signature of the informed consent form until 30 days after last dose of study treatment, and up to 16 weeks

Adverse event reporting additional description:

AEs and SAEs are any untoward sign or symptom that occurs during the study treatment and up to 16 weeks

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	24.0

Reporting groups

Reporting group title	LOU064 10mg q.d.
Reporting group description: LOU064 10mg q.d.	
Reporting group title	LOU064 35mg q.d.
Reporting group description: LOU064 35mg q.d.	
Reporting group title	LOU064 100mg q.d.
Reporting group description: LOU064 100mg q.d.	
Reporting group title	LOU064 10mg b.i.d.
Reporting group description: LOU064 10mg b.i.d.	
Reporting group title	LOU064 25mg b.i.d.
Reporting group description: LOU064 25mg b.i.d.	
Reporting group title	LOU064 100mg b.i.d.
Reporting group description: LOU064 100mg b.i.d.	
Reporting group title	Any LOU064
Reporting group description: Any LOU064	
Reporting group title	Placebo
Reporting group description: Placebo	

Serious adverse events	LOU064 10mg q.d.	LOU064 35mg q.d.	LOU064 100mg q.d.
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 44 (2.27%)	0 / 44 (0.00%)	0 / 47 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Blood and lymphatic system disorders			
Lymphadenopathy			

subjects affected / exposed	1 / 44 (2.27%)	0 / 44 (0.00%)	0 / 47 (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	0 / 44 (0.00%)	0 / 44 (0.00%)	0 / 47 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Ureterolithiasis			
subjects affected / exposed	0 / 44 (0.00%)	0 / 44 (0.00%)	0 / 47 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Renal abscess			
subjects affected / exposed	0 / 44 (0.00%)	0 / 44 (0.00%)	0 / 47 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	LOU064 10mg b.i.d.	LOU064 25mg b.i.d.	LOU064 100mg b.i.d.
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 44 (4.55%)	2 / 43 (4.65%)	0 / 45 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Blood and lymphatic system disorders			
Lymphadenopathy			
subjects affected / exposed	0 / 44 (0.00%)	0 / 43 (0.00%)	0 / 45 (0.00%)
occurrences causally related to treatment / all	0 / 0	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 / 44 (2.27%)	1 / 43 (2.33%)	0 / 45 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Ureterolithiasis			

subjects affected / exposed	1 / 44 (2.27%)	0 / 43 (0.00%)	0 / 45 (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			
Renal abscess			
subjects affected / exposed	0 / 44 (0.00%)	1 / 43 (2.33%)	0 / 45 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Any LOU064	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	5 / 267 (1.87%)	0 / 42 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Blood and lymphatic system disorders			
Lymphadenopathy			
subjects affected / exposed	1 / 267 (0.37%)	0 / 42 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Chronic spontaneous urticaria			
subjects affected / exposed	2 / 267 (0.75%)	0 / 42 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Ureterolithiasis			
subjects affected / exposed	1 / 267 (0.37%)	0 / 42 (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			
Renal abscess			
subjects affected / exposed	1 / 267 (0.37%)	0 / 42 (0.00%)	
occurrences causally related to treatment / all	1 / 1	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	LOU064 10mg q.d.	LOU064 35mg q.d.	LOU064 100mg q.d.
Total subjects affected by non-serious adverse events			
subjects affected / exposed	15 / 44 (34.09%)	13 / 44 (29.55%)	10 / 47 (21.28%)
Nervous system disorders			
Headache			
subjects affected / exposed	1 / 44 (2.27%)	7 / 44 (15.91%)	4 / 47 (8.51%)
occurrences (all)	1	8	4
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	3 / 44 (6.82%)	0 / 44 (0.00%)	0 / 47 (0.00%)
occurrences (all)	3	0	0
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	2 / 44 (4.55%)	0 / 44 (0.00%)	0 / 47 (0.00%)
occurrences (all)	3	0	0
Nausea			
subjects affected / exposed	2 / 44 (4.55%)	3 / 44 (6.82%)	1 / 47 (2.13%)
occurrences (all)	2	3	1
Skin and subcutaneous tissue disorders			
Chronic spontaneous urticaria			
subjects affected / exposed	3 / 44 (6.82%)	2 / 44 (4.55%)	3 / 47 (6.38%)
occurrences (all)	3	2	3
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	7 / 44 (15.91%)	2 / 44 (4.55%)	2 / 47 (4.26%)
occurrences (all)	8	3	2
Upper respiratory tract infection			
subjects affected / exposed	1 / 44 (2.27%)	2 / 44 (4.55%)	2 / 47 (4.26%)
occurrences (all)	1	2	2

Non-serious adverse events	LOU064 10mg b.i.d.	LOU064 25mg b.i.d.	LOU064 100mg b.i.d.
Total subjects affected by non-serious adverse events			
subjects affected / exposed	12 / 44 (27.27%)	11 / 43 (25.58%)	13 / 45 (28.89%)
Nervous system disorders			

Headache			
subjects affected / exposed	3 / 44 (6.82%)	6 / 43 (13.95%)	5 / 45 (11.11%)
occurrences (all)	11	6	6
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	2 / 44 (4.55%)	1 / 43 (2.33%)	0 / 45 (0.00%)
occurrences (all)	2	1	0
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	4 / 44 (9.09%)	0 / 43 (0.00%)	1 / 45 (2.22%)
occurrences (all)	4	0	1
Nausea			
subjects affected / exposed	1 / 44 (2.27%)	1 / 43 (2.33%)	2 / 45 (4.44%)
occurrences (all)	1	1	2
Skin and subcutaneous tissue disorders			
Chronic spontaneous urticaria			
subjects affected / exposed	3 / 44 (6.82%)	1 / 43 (2.33%)	2 / 45 (4.44%)
occurrences (all)	3	1	2
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	4 / 44 (9.09%)	4 / 43 (9.30%)	4 / 45 (8.89%)
occurrences (all)	5	4	4
Upper respiratory tract infection			
subjects affected / exposed	0 / 44 (0.00%)	3 / 43 (6.98%)	0 / 45 (0.00%)
occurrences (all)	0	4	0

Non-serious adverse events	Any LOU064	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	74 / 267 (27.72%)	11 / 42 (26.19%)	
Nervous system disorders			
Headache			
subjects affected / exposed	26 / 267 (9.74%)	6 / 42 (14.29%)	
occurrences (all)	36	7	
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	6 / 267 (2.25%)	0 / 42 (0.00%)	
occurrences (all)	6	0	

Gastrointestinal disorders Diarrhoea subjects affected / exposed occurrences (all) Nausea subjects affected / exposed occurrences (all)	 7 / 267 (2.62%) 8 10 / 267 (3.75%) 10	 2 / 42 (4.76%) 2 0 / 42 (0.00%) 0	
Skin and subcutaneous tissue disorders Chronic spontaneous urticaria subjects affected / exposed occurrences (all)	 14 / 267 (5.24%) 14	 1 / 42 (2.38%) 1	
Infections and infestations Nasopharyngitis subjects affected / exposed occurrences (all) Upper respiratory tract infection subjects affected / exposed occurrences (all)	 23 / 267 (8.61%) 26 8 / 267 (3.00%) 9	 3 / 42 (7.14%) 3 1 / 42 (2.38%) 1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
28 August 2019	The primary rationale for this amendment was to align the eligibility criteria for resting heart rate (exclusion criterion 6) with a normal resting heart rate of CSU subjects. Additionally, the following clarifications were introduced: - Compliance requirements before Day 1 was clarified. - Eligibility criteria regarding INR was aligned with liver events - Fasting requirements before and during PK visits were clarified
11 May 2020	The purpose of this amendment was to address the impact of the COVID-19 pandemic on this study by: - Clarifying implications of the use of local laboratory assessments as per investigator letters "Handling of Protocol Deviations for Trials CLOU064A2201 and CLOU064A2201E1 resulting from the Coronavirus (COVID-19) outbreak" and "Coronavirus (COVID-19) outbreak: Novartis Clinical Trial Continuity for Trials CLOU064A2201 and CLOU064A2201E1" dated 02-Apr-2020. - Introducing an additional IA with a data cut-off date of 07-Apr-2020, the day recruitment for this study was temporarily paused because of the COVID-19 pandemic. The aim of this IA was to assess the benefit-risk ratio of LOU064 based on data collected prior to the recruitment pause due to the COVID-19 pandemic.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported