NOVARTIS

**Clinical Trial Results Website**

## Sponsor

Novartis Pharmaceuticals

## Generic Drug Name

Remibrutinib

## Trial Indication

Chronic spontaneous urticaria

## Protocol Number

CLOU064A2201

## Protocol Title

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

## Clinical Trial Phase

Phase 2

## Phase of Drug Development

Phase IIb

## Study Start/End Dates

Study Start Date: June 2019
Primary Completion Date: January 2021

Study Completion Date: April 2021

## Study Design/Methodology

This was a global Phase 2b multicenter, randomized, double-blind, parallel-group, placebo-controlled study investigating the efficacy, safety and tolerability of six dosing groups of oral LOU064 in subjects with inadequately controlled CSU despite treatment with (second generation) H1-antihistamine. The study comprised of the 7 treatment arms: LOU064 10 mg q.d., LOU064 35 mg q.d., LOU064 100 mg q.d., LOU064 10 mg b.i.d, LOU064 25 mg b.i.d., LOU064 100 mg b.i.d. and placebo.

## Centers

82 centers in 17 countries: Japan(10), Hungary(6), United States(11), Czech Republic(3), Spain(6), United Kingdom(4), Belgium(2), Germany(5), Slovakia (Slovak Republic)(3), Canada(6), Poland(6), France(5), Russia(4), Argentina(4), Netherlands(2), Denmark(2), Turkey(3)

## Objectives

Primary Objective

| Objective | Endpoint |
|---|---|
| To characterize the dose-response relationship of LOU064 administered once or twice daily in subjects with chronic spontaneous urticaria (CSU) with respect to change from baseline in weekly urticaria score (UAS7) at Week 4 | Change from baseline in UAS7 at Week 4 |

Secondary Objectives

| Objectives | Endpoints |
|---|---|
| To evaluate the efficacy of LOU064 compared to placebo with respect to change from baseline in UAS7 at Week 12 | Change from baseline in UAS7 at Week 12 |
| To evaluate the efficacy of LOU064 compared to placebo with respect to change from baseline in UAS7 over time | Change from baseline in UAS7 over time |
| To evaluate the efficacy of LOU064 compared to placebo with respect to achievement of complete clinical response (UAS7= 0) over time | Complete absence of hives and itch, assessed as UAS7=0 response over time |
| To evaluate the efficacy of LOU064 compared to placebo with respect to achievement of disease control (UAS7≤6) over time | UAS7≤6 response over time |

| | |
|---|---|
| To evaluate the effect of LOU064 on angioedema (weekly angioedema score; AAS7) with respect to the number of weeks with an AAS7=0 response from baseline through Week 12 | Cumulative number of weeks with an AAS7= 0 response between baseline and Week 12 |
| To evaluate the effect of LOU064 on disease-related quality of life with respect to achievement of a dermatology life quality index (DLQI) score of 0 or 1 at Week 4 and Week 12 | DLQI score of 0 or 1 at Week 4 and Week 12 |
| To evaluate the effect of LOU064 on CSU-related quality of life with respect to change from baseline in DLQI at Week 4 and Week 12 | Change from baseline in DLQI score at Week 4 and Week 12 |
| To evaluate the pharmacokinetics of LOU064 resulting from oral dosing at Week 4 and Week 12 | Concentrations of LOU064 in blood and calculation of respective PK parameters at Week 4 and Week 12 |
| To evaluate safety and tolerability of LOU064 in subjects with CSU | Safety endpoints will include but not be limited to:<br>• Occurrence of treatment emergent adverse events during the study<br>• Occurrence of treatment emergent serious adverse events during the study |

## Test Product, Dose, and Mode of Administration

Remibrutinib (LOU064) 10 mg, LOU064 25 mg, LOU064 50 mg and placebo were supplied as hard gelatin capsules for oral administration.

## Statistical Methods

### Analysis of primary objective

The primary objective of this study was to determine a dose response signal and characterize the dose response relationship in either LOU064 q.d. and b.i.d. doses (10 mg, 35 mg, 100 mg q.d. and 10 mg, 25 mg, 100 mg b.i.d.) compared to placebo with respect to the change from baseline in UAS7 at Week 4. The consecutive steps were therefore (1) to confirm an overall dose-response signal, (2) to estimate the dose-response curve to enable selecting a dose(s) for the Phase 3 studies.

The primary endpoint for the study was the change from baseline in UAS7 at Week 4. The null hypothesis of a constant dose-response curve for the change from baseline in UAS7 score was tested at a significance level of 5% against the one-sided alternative hypothesis of a non-constant dose-response curve using the MCP-Mod methodology.

### Analysis of secondary objectives

UAS7 over time: Mean estimation and standard error for absolute value, change, and percent change from baseline in UAS7 score was presented by treatment group and visit for entire study period from the MMRM estimation in the primary analysis.

Complete clinical response (UAS7=0) and controlled disease (UAS7≤6): The number of subjects with UAS7=0 and UAS7≤6 was summarized by treatment group and visit for entire study period. For pairwise comparisons between treatment groups during treatment period (individual LOU064 arms versus placebo), odds ratios and 90% CI were derived using logistic regression with treatment group, baseline UAS7 score and prior exposure to anti-IgE biologics, geographical region as covariate. The individual rate differences of the active treatment groups to placebo and the respective 90% CI were derived using a normal approximation.

Absence of angioedema (AAS7=0): The cumulative number of weeks with an AAS7=0 response between baseline and Week 12 was summarized by treatment group. The cumulative number of weeks achieving AAS7=0 response between baseline and Week 12 was modelled using a negative binomial regression model with log link, using treatment group, prior exposure to anti-IgE biologics for the treatment of CSU, geographical region and baseline AAS7=0 status.

DLQI: Summary statistics were calculated for the absolute values as well as for the change and percentage change for DLQI total score broken down by visit and treatment group. Summary of the number of subjects with DLQI score of 0 or 1 was presented by treatment group and visit for entire study period.

### Data Sets Analyzed

All 311 subjects who were randomized were included in the Randomized set (RAN). A total of 309 (99.4%) subjects were included in the Full analysis set (FAS) and the Safety set (SAF). One subject each in the LOU064 25 mg b.i.d. and placebo arms were mis-randomized (never took any study medication) and therefore excluded from the FAS and SAF

### PK analysis

PK parameters, area under the blood concentration-time curve from time zero to the time of the last quantifiable concentration (AUClast), area under the blood concentration-time curve from time zero to the end of the dosing interval tau (AUCtau), observed maximum blood concentration following drug administration (Cmax) and time to reach the maximum concentration after drug administration (Tmax) were summarized using descriptive statistics including mean (arithmetic and geometric), standard deviation (SD), and coefficient of variation (CV) (arithmetic and geometric), median, minimum and maximum, frequency (n, %) of concentrations below the lower limit of quantification (LLOQ) and reported as zero. An exception to this was Tmax where median, minimum and maximum were presented.

## Study Population: Key Inclusion/Exclusion Criteria

Inclusion Criteria:

- Male and female subjects aged ≥18 years of age
- CSU diagnosis for ≥ 6 months prior to screening
- Presence of itch and hives for ≥6 consecutive weeks prior to screening in spite of use of non-sedating H1-antihistamines according to local Treatment guidelines during this time period
- UAS7 score (range 0-42) ≥16 and HSS7 score (range 0-21) ≥ 8 during 7 days prior to randomization (Day 1)
- Willing and able to complete an Urticaria Participant Daily eDiary (UPDD) for the duration of the study

Exclusion Criteria:

- Hypersensitivity to any of the study treatments
- Clearly defined predominant or sole trigger of their chronic urticaria (chronic inducible urticaria)
- Other diseases with symptoms of urticaria or angioedema

- Other skin disease associated with chronic itching that might influence in the investigators opinion the study evaluations and results,
- Known or suspected history of an ongoing, chronic or recurrent infectious disease including but not limited to opportunistic infections (eg tuberculosis, atypical mycobacterioses, listeriosis or aspergillosis), HIV, Hepatitis B/C.
- Pregnant or nursing (lactating) women
- Women of child-bearing potential not using highly effective methods of contraception

## Participant Flow Table

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.

### Overall Study (Randomized Set)

| | LOU064 Arm 1 | LOU064 Arm 2 | LOU064 Arm 3 | LOU064 Arm 4 | LOU064 Arm 5 | LOU064 Arm 6 | Placebo Arm | Total |
|---|---|---|---|---|---|---|---|---|
| **Arm/Group Description** | 10 mg LOU064 qd capsule once daily | 35 mg capsule qd LOU064 once daily | 100 mg capsule qd LOU064 once daily | 10 mg capsule LOU064 bid | 25 mg capsule LOU064 bid | 100 mg capsule LOU064 bid | Matching placebo twice daily | |
| **Started** | 44 | 44 | 47 | 44 | 44 | 45 | 43 | 311 |
| **Randomized set (RAN)** | 44 | 44 | 47 | 44 | 44 | 45 | 43 | 311 |
| **Full analysis set (FAS)** | 44 | 44 | 47 | 44 | 43 | 45 | 42 | 309 |
| **Safety set (SAF)** | 44 | 44 | 47 | 44 | 43 | 45 | 42 | 309 |
| **Completed** | 41 | 41 | 45 | 40 | 40 | 36 | 38 | 281 |
| **Not Completed** | 3 | 3 | 2 | 4 | 4 | 9 | 5 | 30 |
| Adverse Event | 0 | 0 | 0 | 3 | 1 | 3 | 0 | 7 |
| Lack of Efficacy | 1 | 2 | 0 | 0 | 1 | 0 | 1 | 5 |
| Physician Decision | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 1 |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Protocol Violation | 1 | 0 | 0 | 1 | 1 | 1 | 1 | 5 |
| Technical problems | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 1 |
| Withdrawal by Subject | 1 | 1 | 1 | 0 | 0 | 1 | 3 | 7 |
| Covid-19 pandemic | 0 | 0 | 1 | 0 | 1 | 2 | 0 | 4 |

## Baseline Characteristics (Randomized Set)

| | LOU064 Arm 1 | LOU064 Arm 2 | LOU064 Arm 3 | LOU064 Arm 4 | LOU064 Arm 5 | LOU064 Arm 6 | Placebo Arm | Total |
|---|---|---|---|---|---|---|---|---|
| **Arm/Group Description** | 10 mg LOU064 qd capsule once daily | 35 mg capsule qd LOU064 once daily | 100 mg capsule qd LOU064 once daily | 10 mg capsule LOU064 bid | 25 mg capsule LOU064 bid | 100 mg capsule LOU064 bid | Participants took matching placebo twice daily | |
| **Number of Participants [units: participants]** | 44 | 44 | 47 | 44 | 44 | 45 | 43 | 311 |
| **Age Continuous** (units: Years) Mean ± Standard Deviation | | | | | | | | |
| | 42.5±16.04 | 44.0±16.47 | 45.2±13.40 | 46.1±15.21 | 47.4±14.62 | 44.9±13.76 | 45.1±15.24 | 45.0±14.90 |
| **Age Categorical** (units: Participants) Count of Participants | | | | | | | | |
| <=18 years | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Between 18 and 65 years | 41 | 39 | 44 | 39 | 39 | 41 | 36 | 279 |
| >=65 years | 3 | 5 | 3 | 5 | 5 | 4 | 7 | 32 |
| **Sex: Female, Male** (units: Participants) Count of Participants | | | | | | | | |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Female | 35 | 30 | 39 | 32 | 32 | 29 | 25 | 222 |
| Male | 9 | 14 | 8 | 12 | 12 | 16 | 18 | 89 |
| **Race/Ethnicity, Customized**<br>(units: Participants )<br>Count of Participants | | | | | | | | |
| White | 36 | 37 | 40 | 36 | 36 | 36 | 35 | 256 |
| Black or African American | 1 | 0 | 0 | 0 | 0 | 0 | 1 | 2 |
| Asian | 7 | 6 | 7 | 7 | 7 | 9 | 7 | 50 |
| Native Hawaiian or Other Pacific | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 1 |
| American Indian or Alaska Native | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 1 |
| Multiple | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 1 |

## Primary Outcome Results

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

(Time Frame: Baseline, Week 4) Full Analysis Set (FAS) included all randomized subjects. Following intent-to-treat principle, subjects were analyzed according to the treatment and strata assigned to at randomization.

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.

| | LOU064 Arm 1 | LOU064 Arm 2 | LOU064 Arm 3 | LOU064 Arm 4 | LOU064 Arm 5 | LOU064 Arm 6 | Placebo Arm |
|---|---|---|---|---|---|---|---|
| **Arm/Group Description** | 10 mg LOU064 q.d. capsule once daily | 35 mg capsule q.d. LOU064 once daily | 100 mg capsule q.d. LOU064 once daily | 10 mg capsule LOU064 bid | 25 mg capsule LOU064 bid | 100 mg capsule LOU064 bid | Participants took matching placebo twice daily |
| **Number of Participants Analyzed [units: participants]** | 44 | 44 | 47 | 44 | 43 | 45 | 42 |
| **Change from baseline in weekly Urticaria Activity Score (UAS7) at Week 4** (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 | -20.02 ± 1.708 | -18.06 ± 1.691 | -5.44 ± 1.739 |

## Statistical Analysis

| **Groups** | LOU064 Arm 1, Placebo Arm | |
|---|---|---|
| Non-Inferiority/Equivalence Test | Superiority | LOU064 10 mg q.d. |
| P Value | <0.0001 | |
| Method | Mixed Models Analysis | Treatment contrast in LS mean (Change) |
| LS Mean | -13.66 | |
| Standard Error of the mean | 2.334 | |
| 90% Confidence Interval 2-Sided | -17.51 to -9.81 | |

## Statistical Analysis

| **Groups** | LOU064 Arm 2, Placebo Arm | |
|---|---|---|
| Non-Inferiority/Equivalence Test | Superiority | LOU064 35 mg q.d. |
| P Value | <0.0001 | |
| Method | Mixed Models Analysis | Treatment contrast in LS mean (Change) |
| LS Mean | -13.64 | |
| Standard Error of the mean | 2.336 | |
| 90% Confidence Interval 2-Sided | -17.49 to -9.78 | |

## Statistical Analysis

| **Groups** | LOU064 Arm 3, Placebo Arm | |
|---|---|---|
| Non-Inferiority/Equivalence Test | Superiority | LOU064 100 mg q.d. |
| P Value | <0.0001 | |
| Method | Mixed Models Analysis | Treatment contrast in LS mean (Change) |
| LS Mean | -9.21 | |
| Standard Error of the mean | 2.277 | |
| 90% Confidence Interval 2-Sided | -12.97 to -5.45 | |

## Statistical Analysis

| **Groups** | LOU064 Arm 4, Placebo Arm | |
|---|---|---|
| Non-Inferiority/Equivalence Test | Superiority | LOU064 10 mg b.i.d. |

| | | |
|---|---|---|
| P Value | <0.0001 | |
| Method | Mixed Models Analysis | Treatment contrast in LS mean (Change) |
| LS Mean | -10.55 | |
| Standard Error of the mean | 2.319 | |
| 90% Confidence Interval<br>2-Sided | -14.38 to -6.72 | |

## Statistical Analysis

| **Groups** | LOU064 Arm 5,<br>Placebo Arm | |
|---|---|---|
| Non-Inferiority/Equivalence Test | Superiority | LOU064 25 mg b.i.d. |
| P Value | <0.0001 | |
| Method | Mixed Models Analysis | Treatment contrast in LS mean (Change) |
| LS Mean | -14.58 | |
| Standard Error of the mean | 2.334 | |
| 90% Confidence Interval<br>2-Sided | -18.43 to -10.73 | |

## Statistical Analysis

| **Groups** | LOU064 Arm 6,<br>Placebo Arm | |
|---|---|---|
| Non-Inferiority/Equivalence Test | Superiority | LOU064 100 mg b.i.d. |
| P Value | <0.0001 | |
| Method | Mixed Models Analysis | Treatment contrast in LS mean (Change) |

| | |
|---|---|
| LS Mean | -12.62 |
| Standard Error of the mean | 2.327 |
| 90% Confidence Interval 2-Sided | -16.45 to -8.78 |

## Secondary Outcome Results

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

(Time Frame: Week 12) Full Analysis Set

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)

| | LOU064 Arm 1 | LOU064 Arm 2 | LOU064 Arm 3 | LOU064 Arm 4 | LOU064 Arm 5 | LOU064 Arm 6 | Placebo Arm |
|---|---|---|---|---|---|---|---|
| **Arm/Group Description** | 10 mg LOU064 q.d. capsule once daily | 35 mg capsule q.d. LOU064 once daily | 100 mg capsule q.d. LOU064 once daily | 10 mg capsule LOU064 bid | 25 mg capsule LOU064 bid | 100 mg capsule LOU064 bid | Participants took matching placebo twice daily |
| **Number of Participants Analyzed [units: participants]** | 41 | 41 | 45 | 40 | 39 | 35 | 39 |
| **Change from baseline in weekly Urticaria Activity Score (UAS7) at week 12** (units: Score) Least Squares Mean ± Standard Error | | | | | | | |
| | -18.11 ± 1.934 | -17.97 ± 1.934 | -15.27 ± 1.850 | -17.67 ± 1.939 | -20.21 ± 1.964 | -17.38 ± 1.985 | -7.87 ± 2.001 |

## Statistical Analysis

| **Groups** | LOU064 Arm 1, Placebo Arm | |
|---|---|---|
| Non-Inferiority/Equivalence Test | Superiority | LOU064 10 mg q.d. |
| P Value | <0.0001 | |
| Method | Mixed Models Analysis | Treatment contrast in LS mean (Change) |
| LS Mean | -10.24 | |
| Standard Error of the mean | 2.710 | |
| 90% Confidence Interval 2-Sided | -14.72 to -5.77 | |

## Statistical Analysis

| **Groups** | LOU064 Arm 2, Placebo Arm | |
|---|---|---|
| Non-Inferiority/Equivalence Test | Superiority | LOU064 35 mg q.d. |
| P Value | 0.0001 | |
| Method | Mixed Models Analysis | Treatment contrast in LS mean (Change) |
| LS Mean | -10.11 | |
| Standard Error of the mean | 2.711 | |
| 90% Confidence Interval 2-Sided | -14.58 to -5.63 | |

## Statistical Analysis

| **Groups** | LOU064 Arm 3, Placebo Arm |
|---|---|

| | | |
|---|---|---|
| Non-Inferiority/Equivalence Test | Superiority | LOU064 100 mg q.d. |
| P Value | 0.0027 | |
| Method | Mixed Models Analysis | Treatment contrast in LS mean (Change) |
| LS Mean | -7.40 | |
| Standard Error of the mean | 2.635 | |
| 90% Confidence Interval<br>2-Sided | -11.75 to -3.05 | |

## Statistical Analysis

| **Groups** | LOU064 Arm 4,<br>Placebo Arm | |
|---|---|---|
| Non-Inferiority/Equivalence Test | Superiority | LOU064 10 mg b.i.d. |
| P Value | 0.0002 | |
| Method | Mixed Models Analysis | Treatment contrast in LS mean (Change) |
| LS Mean | -9.80 | |
| Standard Error of the mean | 2.696 | |
| 90% Confidence Interval<br>2-Sided | -14.25 to -5.35 | |

## Statistical Analysis

| **Groups** | LOU064 Arm 5,<br>Placebo Arm | |
|---|---|---|
| Non-Inferiority/Equivalence Test | Superiority | LOU064 25 mg b.i.d. |

| | | |
|---|---|---|
| P Value | <0.0001 | |
| Method | Mixed Models Analysis | Treatment contrast in LS mean (Change) |
| LS Mean | -12.35 | |
| Standard Error of the mean | 2.714 | |
| 90% Confidence Interval<br>2-Sided | -16.82 to -7.87 | |

## Statistical Analysis

| | | |
|---|---|---|
| **Groups** | LOU064 Arm 6,<br>Placebo Arm | |
| Non-Inferiority/Equivalence Test | Superiority | LOU064 100 mg b.i.d. |
| P Value | 0.0003 | |
| Method | Mixed Models Analysis | Treatment contrast in LS mean (Change) |
| LS Mean | -9.52 | |
| Standard Error of the mean | 2.733 | |
| 90% Confidence Interval<br>2-Sided | -14.03 to -5.01 | |

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

(Time Frame: Week 12) Full Analysis Set

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.

| | LOU064 Arm 1 | LOU064 Arm 2 | LOU064 Arm 3 | LOU064 Arm 4 | LOU064 Arm 5 | LOU064 Arm 6 | Placebo Arm |
|---|---|---|---|---|---|---|---|
| **Arm/Group Description** | 10 mg | 35 mg | 100 mg | 10 mg | 25 mg | 100 mg | Participants |

| | LOU064 q.d. capsule once daily | capsule q.d. LOU064 once daily | capsule qd LOU064 once daily | capsule LOU064 bid | capsule LOU064 bid | capsule LOU064 bid | took matching placebo twice daily |
|---|---|---|---|---|---|---|---|
| **Number of Participants Analyzed [units: participants]** | 44 | 44 | 47 | 44 | 43 | 45 | 42 |
| **Percentage of participants with either complete absence of hives and itch (UAS7=0) or well-controlled disease (UAS7<=6)** (units: Percent of participants) Number (90% Confidence Interval) | | | | | | | |
| 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) | 41.9 (29.3 to 55.5) | 26.7 (16.5 to 39.8) | 14.3 (6.7 to 26.7) |
| 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) | 55.8 (42.3 to 68.6) | 42.2 (29.9 to 55.5) | 28.6 (17.7 to 42.3) |

## Cumulative number of weeks with an AAS7=0 response

(Time Frame: Baseline to Week 12) Full Analysis Set

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.

| | **LOU064 Arm 1** | **LOU064 Arm 2** | **LOU064 Arm 3** | **LOU064 Arm 4** | **LOU064 Arm 5** | **LOU064 Arm 6** | **Placebo Arm** |
|---|---|---|---|---|---|---|---|
| **Arm/Group Description** | 10 mg LOU064 qd capsule once daily | 35 mg capsule qd LOU064 once daily | 100 mg capsule qd LOU064 once daily | 10 mg capsule LOU064 bid | 25 mg capsule LOU064 bid | 100 mg capsule LOU064 bid | Participants took matching placebo twice daily |
| **Number of Participants Analyzed [units: participants]** | 44 | 44 | 47 | 44 | 43 | 45 | 42 |
| **Cumulative number of weeks with an AAS7=0 response** | | | | | | | |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| (units: Weeks)<br>Mean ± Standard Deviation | 10.2 ± 2.33 | 10.5 ± 2.59 | 10.0 ± 3.06 | 9.8 ± 3.05 | 10.3 ± 2.45 | 9.2 ± 3.38 | 8.2 ± 3.50 |

## Percentage of participants with DLQI score of 0 or 1

(Time Frame: Week 4 and Week 12) Full Analysis Set

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.

| | **LOU064 Arm 1** | **LOU064 Arm 2** | **LOU064 Arm 3** | **LOU064 Arm 4** | **LOU064 Arm 5** | **LOU064 Arm 6** | **Placebo Arm** |
|---|---|---|---|---|---|---|---|
| **Arm/Group Description** | 10 mg LOU064 qd capsule once daily | 35 mg capsule qd LOU064 once daily | 100 mg capsule qd LOU064 once daily | 10 mg capsule LOU064 bid | 25 mg capsule LOU064 bid | 100 mg capsule LOU064 bid | Participants took matching placebo twice daily |
| **Number of Participants Analyzed [units: participants]** | 44 | 44 | 47 | 44 | 43 | 45 | 42 |
| **Percentage of participants with DLQI score of 0 or 1**<br>(units: Percentage of participants)<br>Number (90% Confidence Interval) | | | | | | | |
| Week 4 | 38.6<br>(26.5 to 52.2) | 29.5<br>(18.7 to 43.0) | 29.8<br>(19.3 to 42.7) | 29.5<br>(18.7 to 43.0) | 51.2<br>(37.8 to 64.3) | 33.3<br>(22.1 to 46.7) | 16.7<br>(8.4 to 29.4) |
| Week 12 | 34.1<br>(22.6 to 47.6) | 40.9<br>(28.6 to 54.4) | 38.3<br>(26.6 to 51.4) | 40.9<br>(28.6 to 54.4) | 53.5<br>(40.0 to 66.5) | 35.6<br>(24.0 to 48.9) | 28.6<br>(17.7 to 42.3) |

## Mean change from baseline in DLQI score

(Time Frame: Baseline, Weeks 4 and 12)  FAS

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).

| | LOU064 Arm 1 | LOU064 Arm 2 | LOU064 Arm 3 | LOU064 Arm 4 | LOU064 Arm 5 | LOU064 Arm 6 | Placebo Arm |
|---|---|---|---|---|---|---|---|
| **Arm/Group Description** | 10 mg LOU064 qd capsule once daily | 35 mg capsule qd LOU064 once daily | 100 mg capsule qd LOU064 once daily | 10 mg capsule LOU064 bid | 25 mg capsule LOU064 bid | 100 mg capsule LOU064 bid | Participants took matching placebo twice daily |
| **Number of Participants Analyzed [units: participants]** | 44 | 44 | 47 | 44 | 43 | 45 | 42 |
| **Mean change from baseline in DLQI score** (units: Scores on a scale) Mean ± Standard Deviation | | | | | | | |
| Week 4 | -9.60 ± 7.214 | -8.38 ± 7.241 | -7.18 ± 7.534 | -6.20 ± 6.416 | -9.21 ± 7.994 | -6.15 ± 5.149 | -3.33 ± 8.090 |
| Week 12 | -9.03 ± 6.216 | -7.31 ± 9.392 | -6.60 ± 7.798 | -8.25 ± 6.551 | -8.97 ± 8.891 | -6.27 ± 5.513 | -4.38 ± 6.780 |

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

(Time Frame: Week 4 and Week 12)  Full Analysis Set

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

| | LOU064 Arm 1 | LOU064 Arm 2 | LOU064 Arm 3 | LOU064 Arm 4 | LOU064 Arm 5 | LOU064 Arm 6 |
|---|---|---|---|---|---|---|
| **Arm/Group Description** | 10 mg LOU064 qd capsule once daily | 35 mg capsule qd LOU064 once daily | 100 mg capsule qd LOU064 once daily | 10 mg capsule LOU064 bid | 25 mg capsule LOU064 bid | 100 mg capsule LOU064 bid |
| **Number of Participants Analyzed [units: participants]** | 44 | 44 | 47 | 44 | 43 | 45 |
| **Area under the blood concentration-time curve (AUC) of LOU064**<br>(units: hr*ng/mL)<br>Mean ± Standard Deviation | | | | | | |
| Week 4 | 45.2 ± 18.4 | 131 ± 65.4 | 427 ± 314 | 55.9 ± 32.3 | 107 ± 56.8 | 418 ± 246 |
| Week 12 | 41.8 ± 19.5 | 159 ± 151 | 441 ± 313 | 54.4 ± 29.4 | 118 ± 66.6 | 469 ± 240 |

## Observed maximum blood concentration (Cmax) of LOU064

(Time Frame: Weeks 4 and 12) Full Analysis Set

| | LOU064 Arm 1 | LOU064 Arm 2 | LOU064 Arm 3 | LOU064 Arm 4 | LOU064 Arm 5 | LOU064 Arm 6 |
|---|---|---|---|---|---|---|
| **Arm/Group Description** | 10 mg LOU064 qd capsule once daily | 35 mg capsule qd LOU064 once daily | 100 mg capsule qd LOU064 once daily | 10 mg capsule LOU064 bid | 25 mg capsule LOU064 bid | 100 mg capsule LOU064 bid |
| **Number of Participants Analyzed [units: participants]** | 44 | 44 | 47 | 44 | 43 | 45 |
| **Observed maximum blood concentration (Cmax) of LOU064**<br>(units: ng/mL)<br>Mean ± Standard Deviation | | | | | | |
| Week 4 | 27.6 ± 13.7 | 67.2 ± 32.7 | 194 ± 142 | 32.2 ± 18.7 | 55.5 ± 34.7 | 196 ± 144 |
| Week 12 | 26.1 ± 14.5 | 80.3 ± 53.9 | 199 ± 137 | 31.2 ± 16.0 | 64.9 ± 42.3 | 219 ± 125 |

## Time to reach the maximum concentration (Tmax) of LOU064

(Time Frame: Week 4 and Week 12) Full Analysis Set

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

| | LOU064 Arm 1 | LOU064 Arm 2 | LOU064 Arm 3 | LOU064 Arm 4 | LOU064 Arm 5 | LOU064 Arm 6 |
|---|---|---|---|---|---|---|
| **Arm/Group Description** | 10 mg LOU064 qd capsule once daily | 35 mg capsule qd LOU064 once daily | 100 mg capsule qd LOU064 once daily | 10 mg capsule LOU064 bid | 25 mg capsule LOU064 bid | 100 mg capsule LOU064 bid |
| **Number of Participants Analyzed [units: participants]** | 44 | 44 | 47 | 44 | 43 | 45 |
| **Time to reach the maximum concentration (Tmax) of LOU064** (units: hours) Median (Full Range) | | | | | | |
| 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) | 1.15 (0.00 to 3.02) | 1.52 (0.00 to 3.08) |
| 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) | 1.32 (0.00 to 4.00) | 1.39 (0.5000 to 4.00) |

## Safety Results

The Safety set consisted of all 309 subjects who received at least one dose of study medication whether or not being randomized. Subjects were analyzed according to treatment received

## All-Cause Mortality

| | LOU064 10mg q.d. N = 44 | LOU064 35mg q.d. N = 44 | LOU064 100mg q.d. N = 47 | LOU064 10mg b.i.d. N = 44 | LOU064 25mg b.i.d. N = 43 | LOU064 100mg b.i.d. N = 45 | Any LOU064 N = 267 | Placebo N = 42 |
|---|---|---|---|---|---|---|---|---|
| **Arm/Group Description** | 10 mg LOU064 qd capsule once daily | 35 mg capsule qd LOU064 once daily | 100 mg capsule qd LOU064 once daily | 10 mg capsule LOU064 bid | 25 mg capsule LOU064 bid | 100 mg capsule LOU064 bid | Any LOU064 | Participants took matching placebo twice daily |
| **Total participants affected** | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) |

## Serious Adverse Events by System Organ Class

| | |
|---|---|
| **Time Frame** | 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 |
| **Additional Description** | AEs and SAEs are any untoward sign or symptom that occurs during the study treatment and up to 16 weeks |
| **Source Vocabulary for Table Default** | MedDRA (24.0) |
| **Assessment Type for Table Default** | Systematic Assessment |

| | LOU064 10mg q.d. N = 44 | LOU064 35mg q.d. N = 44 | LOU064 100mg q.d. N = 47 | LOU064 10mg b.i.d. N = 44 | LOU064 25mg b.i.d. N = 43 | LOU064 100mg b.i.d. N = 45 | Any LOU064 N = 267 | Placebo N = 42 |
|---|---|---|---|---|---|---|---|---|

| Arm/Group Description | 10 mg LOU064 qd capsule once daily | 35 mg capsule qd LOU064 once daily | 100 mg capsule qd LOU064 once daily | 10 mg capsule LOU064 bid | 25 mg capsule LOU064 bid | 100 mg capsule LOU064 bid | Any LOU064 | Participants took matching placebo twice daily |
|---|---|---|---|---|---|---|---|---|
| **Total participants affected** | 1 (2.27%) | 0 (0.00%) | 0 (0.00%) | 2 (4.55%) | 2 (4.65%) | 0 (0.00%) | 5 (1.87%) | 0 (0.00%) |
| **Blood and lymphatic system disorders** | | | | | | | | |
| Lymphadenopathy | 1 (2.27%) | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 1 (0.37%) | 0 (0.00%) |
| **Infections and infestations** | | | | | | | | |
| Renal abscess | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 1 (2.33%) | 0 (0.00%) | 1 (0.37%) | 0 (0.00%) |
| **Renal and urinary disorders** | | | | | | | | |
| Ureterolithiasis | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 1 (2.27%) | 0 (0.00%) | 0 (0.00%) | 1 (0.37%) | 0 (0.00%) |
| **Skin and subcutaneous tissue disorders** | | | | | | | | |
| Chronic spontaneous urticaria | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 1 (2.27%) | 1 (2.33%) | 0 (0.00%) | 2 (0.75%) | 0 (0.00%) |

## Other Adverse Events by System Organ Class

| | |
|---|---|
| **Time Frame** | AEs were collected from first dose of study treatment until 4 weeks after last dose of study treatment, up to 16 weeks |
| **Additional Description** | Adverse Events (AEs) are any untoward sign or symptom that occurs during the study treatment and up to 16 weeks |
| **Source Vocabulary for Table Default** | MedDRA (24.0) |
| **Assessment Type for Table Default** | Systematic Assessment |
| **Frequent Event Reporting Threshold** | 5% |

| | LOU064 10mg q.d. N = 44 | LOU064 35mg q.d. N = 44 | LOU064 100mg q.d. N = 47 | LOU064 10mg b.i.d. N = 44 | LOU064 25mg b.i.d. N = 43 | LOU064 100mg b.i.d. N = 45 | Any LOU064 N = 267 | Placebo N = 42 |
|---|---|---|---|---|---|---|---|---|
| **Arm/Group Description** | 10 mg LOU064 qd capsule once daily | 35 mg capsule qd LOU064 once daily | 100 mg capsule qd LOU064 once daily | 10 mg capsule LOU064 bid | 25 mg capsule LOU064 bid | 100 mg capsule LOU064 bid | Any LOU064 | Participants took matching placebo twice daily |
| **Total participants affected** | 15 (34.09%) | 13 (29.55%) | 10 (21.28%) | 12 (27.27%) | 11 (25.58%) | 13 (28.89%) | 74 (27.72%) | 11 (26.19%) |
| **Gastrointestinal disorders** | | | | | | | | |
| Diarrhoea | 2 (4.55%) | 0 (0.00%) | 0 (0.00%) | 4 (9.09%) | 0 (0.00%) | 1 (2.22%) | 7 (2.62%) | 2 (4.76%) |
| Nausea | 2 (4.55%) | 3 (6.82%) | 1 (2.13%) | 1 (2.27%) | 1 (2.33%) | 2 (4.44%) | 10 (3.75%) | 0 (0.00%) |
| **General disorders and administration site conditions** | | | | | | | | |
| Pyrexia | 3 (6.82%) | 0 (0.00%) | 0 (0.00%) | 2 (4.55%) | 1 (2.33%) | 0 (0.00%) | 6 (2.25%) | 0 (0.00%) |
| **Infections and infestations** | | | | | | | | |
| Nasopharyngitis | 7 (15.91%) | 2 (4.55%) | 2 (4.26%) | 4 (9.09%) | 4 (9.30%) | 4 (8.89%) | 23 (8.61%) | 3 (7.14%) |
| Upper respiratory tract infection | 1 (2.27%) | 2 (4.55%) | 2 (4.26%) | 0 (0.00%) | 3 (6.98%) | 0 (0.00%) | 8 (3.00%) | 1 (2.38%) |
| **Nervous system disorders** | | | | | | | | |
| Headache | 1 (2.27%) | 7 (15.91%) | 4 (8.51%) | 3 (6.82%) | 6 (13.95%) | 5 (11.11%) | 26 (9.74%) | 6 (14.29%) |
| **Skin and subcutaneous tissue disorders** | | | | | | | | |
| Chronic spontaneous urticaria | 3 (6.82%) | 2 (4.55%) | 3 (6.38%) | 4 (9.09%) | 2 (4.65%) | 2 (4.44%) | 16 (5.99%) | 1 (2.38%) |

## Conclusion

In subjects with moderate to severe CSU, LOU064 exhibited a clear dose response in change from baseline in UAS7 score compared to placebo at Week 4, with the plateau achieved at 10 mg q.d. and 25 mg b.i.d., based on MCP-mod approach. Clinically meaningful reductions in UAS7 score were observed with LOU064 q.d. (10 mg, 35 mg and 100 mg) and b.i.d. doses (10 mg, 25 mg and 100 mg) when compared to placebo at Week 4 and Week 12 with the LOU064 25 mg b.i.d. dose showing the highest reduction. More subjects achieved UAS7=0 (complete clinical response), UAS7≤6 (well controlled disease) and AAS7=0 (absence of angioedema) with LOU064 q.d. and b.i.d. doses as compared to placebo. The LOU064 q.d. and b.i.d. doses were safe and well tolerated in the study.

## Date of Clinical Trial Report

22 December 2021