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Sponsor

Novartis Pharmaceuticals

Generic Drug Name

Remibrutinib/LOU064

Trial Indication(s)

Chronic spontaneous urticaria

Protocol Number

CLOU064A2302

Protocol Title

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

Clinical Trial Phase

Phase 3

Phase of Drug Development

Phase III

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Study Start/End Dates

Study Start Date: December 01, 2021 (Actual)
Primary Completion Date: December 18, 2023 (Actual)
Study Completion Date: January 05, 2024 (Actual)

Reason for Termination (If applicable)

Study Design/Methodology

This was a global Phase III multi-centered, randomized, double-blind, parallel-group, placebo-controlled study investigating the safety, tolerability, and efficacy of remibrutinib (25 mg b.i.d.) in adult patients with CSU inadequately controlled by second generation H1-AHs. The study consisted of four periods, the total study duration was up to 60 weeks: Screening period of up to 4 weeks, Double-blind placebo-controlled treatment period of 24 weeks, Open-label treatment period with remibrutinib period of 28 weeks, and treatment-free follow-up period of 4 weeks. The planned sample size was approximately 450 patients randomized in 2:1 ratio to remibrutinib or placebo arm (300 in the remibrutinib arm and 150 in placebo arm).

Centers

122 centers in 18 countries: Canada(8), United States(30), Poland(5), Slovakia (Slovak Republic)(4), Taiwan(2), Russia(5), Germany(18), China(16), Switzerland(3), Thailand(4), United Kingdom(3), Malaysia(5), Denmark(2), India(10), Austria(1), South Africa(3), Vietnam(2), Brazil(1)

Objectives:

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. This report provides all efficacy and safety results up to the end of the study with last patient last visit on 05-Jan-2024.

There are two primary objective scenarios based on regional regulatory precedent and Health Authorities' feedback. These two primary objective scenarios were tested in two distinct testing strategies (Table 2-1 and Table 2-2). Distinctions in the secondary objectives reflect the corresponding scenario: the primary objective in one scenario is presented as secondary objective(-s) in another. The other secondary and all exploratory objectives are identical in both scenarios.

Table 2-1 Objectives and related endpoints – scenario with UAS7 as the primary efficacy endpoint

Objectives	**Endpoints**
Primary objective	**Endpoint for primary objective**
To demonstrate that remibrutinib (25 mg b.i.d.) is superior to placebo in patients with CSU with respect to change from baseline in UAS7 at Week 12	Absolute change from baseline in UAS7 at Week 12
Secondary objectives	**Endpoints for secondary objectives**
To demonstrate that a greater proportion of patients achieve disease activity control (UAS7 ≤ 6) at Week 12 who are treated with remibrutinib compared to placebo-treated patients	Achievement of UAS7 ≤ 6 (yes/no) at Week 12
To demonstrate that a greater proportion of patients achieve complete absence of hives and itch (UAS7 = 0) at Week 12 who are treated with remibrutinib compared to placebo-treated patients	Achievement of UAS7 = 0 (yes/no) at Week 12
To demonstrate the superiority of remibrutinib treated patients with respect to a reduction from baseline in the weekly itch severity score at Week 12 compared to placebo-treated patients	Improvement of severity of itch, assessed as absolute change from baseline in ISS7 score at Week 12
To demonstrate the superiority of remibrutinib treated patients with respect to a reduction from baseline in the weekly hive severity score at Week 12 compared to placebo-treated patients	Improvement of severity of hives, assessed as absolute change from baseline in HSS7 score at Week 12

Objectives	Endpoints
To demonstrate that a greater proportion of patients achieve UAS7 ≤ 6 at Week 2 who are treated with remibrutinib compared to placebo-treated patients	Achieving early onset of disease activity control, as defined as achievement of UAS7 ≤ 6 (yes/no) at Week 2
To demonstrate that a greater proportion of patients who are treated with remibrutinib achieve DLQI = 0-1 at Week 12 compared to placebo-treated patients	No impact on patients' dermatology-related QoL, as defined by achievement of DLQI = 0-1 (yes/no) at Week 12
To demonstrate that remibrutinib treated patients maintain disease activity control (defined as UAS7 ≤ 6) for more weeks compared to placebo treated patients over 12 weeks	Achieving sustained disease activity control, assessed as cumulative number of weeks with an UAS7 ≤ 6 response between baseline and Week 12
To demonstrate that remibrutinib treated patients have more angioedema occurrence-free weeks over 12 weeks compared with placebo-treated patients	Number of weeks without angioedema, assessed by the cumulative number of weeks with an AAS7 = 0 response between baseline and Week 12
To demonstrate the safety and tolerability of remibrutinib	Occurrence of treatment-emergent AEs and SAEs during the study

Table 2-2 Objectives and related endpoints - scenario with ISS7 and HSS7 as the co-primary efficacy endpoints

Objectives	Endpoints
Co-primary objective	**Endpoints for co-primary objectives**
To demonstrate that remibrutinib (25 mg b.i.d.) is superior to placebo in patients with CSU with respect to change from Baseline in ISS7 and HSS7 at Week 12	• Absolute change from baseline in ISS7 at Week 12 • Absolute change from baseline in HSS7 at Week 12
Secondary objectives	**Endpoints for secondary objectives**
To demonstrate that remibrutinib is superior to placebo in patients with CSU with respect to change from baseline in UAS7 at Week 12	Absolute change from baseline in UAS7 at Week 12

Objectives	Endpoints
All the remaining secondary objectives and endpoints presented in Table 2-1 are identical in both the scenarios (except for ISS7 and HSS7 at Week 12) and therefore, are not repeated here.	

The primary estimand for the scenario with UAS7 as the primary efficacy endpoint was the difference between remibrutinib and placebo in UAS7 change from baseline after 12 weeks of treatment in adult patients with CSU who were inadequately controlled by second generation H1-AHs and receiving a stable locally label approved dose of a second generation H1-AH, regardless of discontinuation from study treatment for any reason and regardless of intake of a different second generation H1-AH as rescue medication and considering strongly confounding prohibited medication as an unfavorable outcome.

The co-primary estimand for the scenario with ISS7/HSS7 as co-primary efficacy endpoints were the difference between remibrutinib and placebo in change from baseline in ISS7 score and change from baseline in HSS7 score after treatment in adult patients with CSU who were inadequately controlled by second generation H1-AHs and receiving a stable locally label approved dose of a second generation H1-AH, regardless of discontinuation from study treatment for any reason and regardless of intake of a different second generation H1-AH as rescue medication and considering strongly confounding prohibited medication as an unfavorable outcome.

Test Product (s), Dose(s), and Mode(s) of Administration

Patients were assigned to oral treatment with either remibrutinib or placebo. At Week 24, patients in the placebo arm switched to active treatment (remibrutinib). Throughout the study, patients were required to take a second generation H1-AH at a locally label approved dose (background therapy) with a stable regimen.

Statistical Methods

The following analysis sets were used in the trial:

- **Randomized analysis set (RAS)** consisted of all randomized patients, regardless of whether or not they received a dose of study drug. Patients were analyzed according to the treatment they were assigned to.
- **Full analysis set (FAS)** comprised of all patients to whom study treatment was assigned by randomization. FAS was used for all efficacy variables, unless otherwise stated. Mis-randomized patients (mis-randomized in IRT) were included in the RAS but were excluded from FAS.
- **Safety set** included all patients who received at least one dose of study treatment, whether or not randomized. Patients were analyzed according to the study treatment received. The Safety set was used in the analysis of all safety variables. The actual treatment was defined as the treatment received over the study. In case of error in dispensation, the actual treatment corresponded to the treatment which was given most often.

The main purpose of this study was to demonstrate that remibrutinib was superior to placebo in CSU with respect to change from baseline in UAS7 at Week 12 for the Scenario 1 and ISS7/HSS7 at Week 12 for Scenario 2. A linear mixed model with repeated measures was used to estimate treatment differences for change from baseline in UAS7 (ISS7 and HSS7 for second scenario) at Week 12, based on the FAS.

The primary and secondary endpoints analyses were planned to use the multiple testing strategy to control the family-wise error at α = 0.025 (one-sided). The secondary endpoints were analyzed using logistic regression model and negative binomial regression model.

Study Population: Key Inclusion/Exclusion Criteria

Key Inclusion Criteria:

• Signed informed consent must be obtained prior to participation in the study.

• Male and female adult participants >= 18 years of age at the time of screening.

• CSU duration for >= 6 months prior to screening (defined as the onset of CSU determined by the investigator based on all available

supporting documentation).

• Diagnosis of CSU inadequately controlled by second generation H1-antihistamines at the time of randomization defined as:

~ The presence of itch and hives for >= 6 consecutive weeks prior to screening despite the use of second generation H1-antihistamines during this time period

~ UAS7 score (range 0-42) >= 16, ISS7 score (range 0-21) >= 6 and HSS7 score (range 0-21) >= 6 during the 7 days prior to randomization (Day 1)

• Documentation of hives within three months before randomization (either at screening and/or at randomization; or documented in the participants medical history).

• Willing and able to complete an Urticaria Patient Daily Diary (UPDD) for the duration of the study and adhere to the study protocol.

• Participants must not have had more than one missing UPDD entry (either morning or evening) in the 7 days prior to randomization (Day 1).

Key Exclusion Criteria:

• Participants having a clearly defined predominant or sole trigger of their chronic urticaria (CU) (chronic inducible urticaria (CINDU)) including urticaria factitia (symptomatic dermographism), cold-, heat-, solar-, pressure-, delayed pressure-, aquagenic-, cholinergic-, or contact-urticaria

• Other diseases with symptoms of urticaria or angioedema, including but not limited to urticaria vasculitis, urticaria pigmentosa, erythema multiforme, mastocytosis, hereditary urticaria, or drug-induced urticaria

• Any other skin disease associated with chronic itching that might influence in the investigator’s opinion the study evaluations and results, e.g. atopic dermatitis, bullous pemphigoid, dermatitis herpetiformis, senile pruritus or psoriasis

• Evidence of clinically significant cardiovascular (such as but not limited to myocardial infarction, unstable ischemic heart disease, New York heart association (NYHA) Class III/IV left ventricular failure, arrhythmia and uncontrolled hypertension within 12 months prior to Visit 1), neurological, psychiatric, pulmonary, renal, hepatic, endocrine, metabolic, hematological disorders, gastrointestinal

disease or immunodeficiency that, in the investigator's opinion, would compromise the safety of the participant, interfere with the interpretation of the study results or otherwise preclude participation or protocol adherence of the participant

• Significant bleeding risk or coagulation disorders

• History of gastrointestinal bleeding, e.g. in association with use of nonsteroidal anti-inflammatory drugs (NSAID), that was clinically relevant (e.g. requiring hospitalization or blood transfusion)

• Requirement for anti-platelet medication, except for acetylsalicylic acid up to 100 mg/d or clopidogrel. The use of dual anti-platelet therapy (e.g. acetylsalicylic acid + clopidogrel) is prohibited.

• Requirement for anticoagulant medication (for example, warfarin or Novel Oral Anti-Coagulants (NOAC))

• History or current hepatic disease including but not limited to acute or chronic hepatitis, cirrhosis or hepatic failure or Aspartate Aminotransferase (AST)/ Alanine Aminotransferase (ALT) levels of more than 1.5 x upper limit of normal (ULN) or International Normalized Ratio (INR) of more than 1.5 at screening

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Participant Flow Table

Overall Study

	LOU064 25 mg b.i.d.	Placebo	Total
Arm/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)	Patients initially randomized to Placebo during the Double-Blind treatment period (Up to Week 24)	
Started	300	155	455
No treatment due to mis-randomization	3	2	5
Full Analysis Set	297	153	450
Safety Set (SAF)	297	153	450
Completed	232	112	344
Not Completed	68	43	111
No treatment due to mis-randomization	3	2	5
Adverse Event	13	8	21
Pregnancy	0	2	2
Unsatisfactory therapeutic effect	4	7	11
Protocol Deviation	5	1	6
Lost to Follow-up	0	3	3
Physician Decision	7	2	9
Patient Decision	36	18	54

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Baseline Characteristics

	LOU064 25 mg b.i.d.	Placebo	Total
Arm/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)	Patients initially randomized to Placebo during the Double-Blind treatment period (Up to Week 24)	
Number of Participants [units: participants]	300	155	455
Baseline Analysis Population Description			
Age, Customized (units: Participants) Analysis Population Type: Participants Count of Participants (Not Applicable)			
>= 18 and < 65 years	276	144	420
>= 65 and < 85 years	24	11	35
Age Continuous (units: Years) Analysis Population Type: Participants Mean ± Standard Deviation			
	41.9±14.52	41.3±14.58	41.7±14.53
Sex: Female, Male (units: Participants) Analysis Population Type: Participants Count of Participants (Not Applicable)			
Female	197	100	297
Male	103	55	158
Race (NIH/OMB) (units: Participants)			

Analysis Population Type: Participants Count of Participants (Not Applicable)			
American Indian or Alaska Native	0	0	0
Asian	130	72	202
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	7	3	10
White	159	79	238
More than one race	3	1	4
Unknown or Not Reported	1	0	1

Primary Outcome Result(s)

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

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).
Time Frame	Baseline, Week 12
Analysis Population Description	Full Analysis Set (FAS)

	LOU064 25 mg b.i.d.	**Placebo**
Arm/Group Description	Patients initially randomized to Remibrutinib during the Double-blind treatment period and continued	Patients initially randomized to Placebo during the Double-Blind treatment period (Up to Week 24)

	Remibrutinib during the Open-label treatment period (Up to Week 52)	
Number of Participants Analyzed [units: participants]	297	153
Mean change from Baseline in Weekly Urticaria Activity Score (UAS7) at Week 12 (Scenario 1 with UAS7 as primary efficacy endpoint) (units: Unit on a scale)	**Least Squares Mean ± Standard Error**	**Least Squares Mean ± Standard Error**
	-19.41 ± 0.702	-11.73 ± 0.948

Statistical Analysis

Groups	LOU064 25 mg b.i.d., Placebo	UAS7 at Week 12 (Scenario 1 with UAS7 as primary efficacy endpoint)
Type of Statistical Test	Superiority	
P Value	< 0.001	
Method	Mixed Models Analysis	
Mean Difference (Final Values)	-7.68	MMRM adjusting for treatment arm, geographical region, prior exposure to anti-IgE biologics, visit week, baseline score and both interaction of treatment by visit week and interaction of baseline score by visit week.
Standard Error of the mean	1.136	
95 % Confidence Interval 2-Sided	-9.91 to -5.46	

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

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).
Time Frame	Baseline, Week 12
Analysis Population Description	Full Analysis Set (FAS)

	LOU064 25 mg b.i.d.	Placebo
Arm/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)	Patients initially randomized to Placebo during the Double-Blind treatment period (Up to Week 24)
Number of Participants Analyzed [units: participants]	297	153
Mean change from Baseline in Weekly Itch Severity Score (ISS7) at Week 12 (Scenario 2 with ISS7 and HSS7 as co-primary efficacy endpoints) (units: Unit on a scale)	**Least Squares Mean ± Standard Error**	**Least Squares Mean ± Standard Error**
	-8.95 ± 0.335	-5.72 ± 0.454

Statistical Analysis

Groups	LOU064 25 mg b.i.d., Placebo	ISS7 at Week 12 (Scenario 2 with ISS7 and HSS7 as co-primary efficacy endpoints)
Type of Statistical Test	Superiority	
P Value	<0.001	
Method	Mixed Models Analysis	
Mean Difference (Final Values)	-3.23	MMRM adjusting for treatment arm, geographical region, prior exposure to anti-IgE, biologics, visit week, baseline score, and both interaction of

	treatment by visit week and interaction of baseline score by visit week.
Standard Error of the mean	0.545
95 % Confidence Interval 2-Sided	-4.29 to -2.16

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

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).
Time Frame	Baseline, Week 12
Analysis Population Description	Full Analysis Set (FAS)

	LOU064 25 mg b.i.d.	**Placebo**
Arm/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)	Patients initially randomized to Placebo during the Double-Blind treatment period (Up to Week 24)
Number of Participants Analyzed [units: participants]	297	153
Mean change from Baseline in Weekly Hives Severity Score (HSS7) at Week 12 (Scenario 2 with ISS7 and HSS7 as co-primary efficacy endpoints) (units: Unit on a scale)	**Least Squares Mean ± Standard Error**	**Least Squares Mean ± Standard Error**
	-10.47 ± 0.394	-6.00 ± 0.531

Statistical Analysis

Groups	LOU064 25 mg b.i.d., Placebo	HSS7 at Week 12 (Scenario 2 with ISS7 and HSS7 as co-primary efficacy endpoints)
Type of Statistical Test	Superiority	
P Value	< 0.001	
Method	Mixed Models Analysis	
Mean Difference (Final Values)	-4.47	MMRM adjusting for treatment arm, geographical region, prior exposure to anti-IgE biologics, visit week, baseline score and both interaction of treatment by visit week and interaction of baseline score by visit week.
Standard Error of the mean	0.634	
95 % Confidence Interval 2-Sided	-5.71 to -3.23	

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Secondary Outcome Result(s)

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

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).
Time Frame	Week 12
Analysis Population Description	Full Analysis Set (FAS)

	LOU064 25 mg b.i.d.	**Placebo**
Arm/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)	Patients initially randomized to Placebo during the Double-Blind treatment period (Up to Week 24)
Number of Participants Analyzed [units: participants]	297	153
Number of Participants who achieved disease activity control (UAS7 =< 6) at Week 12 (units: Participants)	**Count of Participants (Not Applicable)**	**Count of Participants (Not Applicable)**
	139 (46.8%)	30 (19.61%)

Statistical Analysis

Groups	LOU064 25 mg b.i.d., Placebo	Disease activity control (UAS7 =< 6) at Week 12
Type of Statistical Test	Superiority	
P Value	< 0.001	

Method	Regression, Logistic	
Odds Ratio (OR)	3.84	Logistic regression adjusting for treatment arm, geographical region, prior exposure to anti-IgE biologics, and baseline UAS7 score.
95 % Confidence Interval 2-Sided	2.39 to 6.18	

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

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).
Time Frame	Week 12
Analysis Population Description	Full Analysis Set (FAS)

	LOU064 25 mg b.i.d.	**Placebo**
Arm/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)	Patients initially randomized to Placebo during the Double-Blind treatment period (Up to Week 24)
Number of Participants Analyzed [units: participants]	297	153
Number of Participants who achieved complete absence of hives and itch (UAS7 = 0) at Week 12 (units: Participants)	**Count of Participants (Not Applicable)**	**Count of Participants (Not Applicable)**
	83 (27.95%)	10 (6.54%)

Statistical Analysis

Groups	LOU064 25 mg b.i.d., Placebo	Complete absence of hives and itch (UAS7 = 0) at Week 12
Type of Statistical Test	Superiority	
P Value	< 0.001	
Method	Regression, Logistic	
Odds Ratio (OR)	5.78	Logistic regression adjusting for treatment arm, geographical region, prior exposure to anti-IgE biologics, and baseline UAS7 score.
95 % Confidence Interval 2-Sided	2.83 to 11.78	

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

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).
Time Frame	Week 2
Analysis Population Description	Full Analysis Set (FAS)

	LOU064 25 mg b.i.d.	Placebo
Arm/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)	Patients initially randomized to Placebo during the Double-Blind treatment period (Up to Week 24)
Number of Participants Analyzed [units: participants]	297	153

Number of Participants who achieved early onset of disease activity control (UAS7 =< 6) at Week 2 (units: Participants)	**Count of Participants (Not Applicable)**	**Count of Participants (Not Applicable)**
	89 (29.97%)	9 (5.88%)

Statistical Analysis

Groups	LOU064 25 mg b.i.d., Placebo	Early onset of disease activity control (UAS7 =< 6) at Week 2
Type of Statistical Test	Superiority	
P Value	< 0.001	
Method	Regression, Logistic	
Odds Ratio (OR)	7.92	Logistic regression adjusting for treatment arm, geographical region, prior exposure to anti-IgE biologics, and baseline UAS7 score.
95 % Confidence Interval 2-Sided	3.72 to 16.85	

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

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.
Time Frame	Week 12
Analysis Population Description	Full Analysis Set (FAS)

	LOU064 25 mg b.i.d.	Placebo
Arm/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)	Patients initially randomized to Placebo during the Double-Blind treatment period (Up to Week 24)
Number of Participants Analyzed [units: participants]	297	153
Number of Participants who achieved Dermatology Life Quality Index (DLQI) = 0-1 at Week 12 (units: Participants)	**Count of Participants (Not Applicable)**	**Count of Participants (Not Applicable)**
	106 (35.69%)	28 (18.3%)

Statistical Analysis

Groups	LOU064 25 mg b.i.d., Placebo	Dermatology Life Quality Index (DLQI) = 0-1 at Week 12
Type of Statistical Test	Superiority	
P Value	< 0.001	
Method	Regression, Logistic	
Odds Ratio (OR)	2.75	Logistic regression adjusting for treatment arm, geographical region, prior exposure to anti-IgE biologics and baseline DLQI score.
95 % Confidence Interval 2-Sided	1.65 to 4.58	

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

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).

Time Frame	Up to Week 12
Analysis Population Description	Full Analysis Set (FAS)

	LOU064 25 mg b.i.d.	Placebo
Arm/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)	Patients initially randomized to Placebo during the Double-Blind treatment period (Up to Week 24)
Number of Participants Analyzed [units: participants]	297	153
Mean cumulative number of weeks with disease activity control (UAS7 =< 6) up to Week 12 (units: Weeks)	**Least Squares Mean ± Standard Error**	**Least Squares Mean ± Standard Error**
	4.50 ± 0.464	1.38 ± 0.216

Statistical Analysis

Groups	LOU064 25 mg b.i.d., Placebo	Disease activity control (UAS7 =< 6) up to Week 12
Type of Statistical Test	Superiority	
P Value	< 0.001	
Method	Regression, Linear	
Other Rate ratio	3.26	Negative binomial regression with log link includes treatment arm as fixed effect, geographical region, prior exposure to anti-IgE biologics as covariates. A rate ratio >1 favors LOU064 25 mg b.i.d.

95 % Confidence Interval 2-Sided	2.26 to 4.71

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

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).
Time Frame	Up to Week 12
Analysis Population Description	Full Analysis Set (FAS)

	LOU064 25 mg b.i.d.	**Placebo**
Arm/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)	Patients initially randomized to Placebo during the Double-Blind treatment period (Up to Week 24)
Number of Participants Analyzed [units: participants]	297	153
Mean cumulative number of angioedema occurrence-free weeks (AAS7 = 0 response) up to Week 12 (units: Weeks)	**Least Squares Mean ± Standard Error**	**Least Squares Mean ± Standard Error**
	8.81 ± 0.308	6.68 ± 0.343

Statistical Analysis

Groups	LOU064 25 mg b.i.d., Placebo	Angioedema occurrence-free weeks (AAS7 = 0 response) up to Week 12
Type of Statistical Test	Superiority	

P Value	< 0.001	
Method	Regression, Linear	
Other Rate ratio	1.32	Negative binomial regression with log link included treatment arm as fixed effect, geographical region, prior exposure to anti-IgE biologics, baseline AAS7 = 0 response as covariates. A rate ratio > 1 favors LOU064 25 mg b.i.d.
95 % Confidence Interval 2-Sided	1.17 to 1.49	

Number of Participants with Treatment Emergent Adverse Events

Description	An adverse event (AE) is any untoward medical occurrence (e.g., any unfavorable and unintended sign [including abnormal laboratory findings], symptom or disease) in a clinical investigation participant after providing written informed consent for participation in the study. Therefore, an AE may or may not be temporally or causally associated with the use of a medicinal (investigational) product. Treatment emergent Adverse Event (TEAEs) in this study are events that started after the first dose of study treatment and until 28 after the last study treatment, or events present prior to the first dose of treatment which increased in severity based on preferred term within 28 days after the last study treatment.
Time Frame	Baseline up to 28 days after last dose of study medication, assessed up to approximately 56 weeks
Analysis Population Description	Safety Set (SAF)

	Double-blind treatment period: LOU064 25 mg b.i.d.	**Double-blind treatment period: Placebo**	**LOU064 25 mg b.i.d.**	**Transitioned to LOU064 25 mg b.i.d.**
Arm/Group Description	Patients initially randomized to Remibrutinib (Up to Week 24)	Patients initially randomized to Placebo during the Double-Blind treatment period (Up to Week 24)	Patients initially randomized to Remibrutinib during the Double-blind treatment period and continued Remibrutinib during the Open-label treatment period (Up to Week 52)	Patients initially randomized to placebo during the Double-blind treatment period and switched to Remibrutinib during the Open-label treatment period (Weeks 25-52)

Number of Participants Analyzed [units: participants]	297	153	297	129
Number of Participants with Treatment Emergent Adverse Events (units: Participants)	**Count of Participants (Not Applicable)**	**Count of Participants (Not Applicable)**	**Count of Participants (Not Applicable)**	**Count of Participants (Not Applicable)**
Patients with Adverse Events (AEs)	205 (69.02%)	112 (73.2%)	228 (76.77%)	71 (55.04%)
Patients with Treatment Emergent Adverse Events (TEAEs)	0 (%)	66 (43.14%)	157 (52.86%)	40 (31.01%)
Patients with serious or other significant events - Death	0 (%)	0 (%)	0 (%)	0 (%)
Patients with serious or other significant events - Non-fatal SAE(s)	10 (3.37%)	6 (3.92%)	12 (4.04%)	2 (1.55%)
Patients with serious or other significant events - Discontinued study treatment due to any AE(s)	6 (2.02%)	6 (3.92%)	13 (4.38%)	2 (1.55%)
Patients with serious or other significant events - Discontinued study treatment due to any SAE(s)	0 (%)	1 (.65%)	1 (.34%)	0 (%)

Other Pre-Specified Outcome Result(s)

No data identified.

Post-Hoc Outcome Result(s)

No data identified.

NOVARTIS

Safety Results

Time Frame	On-treatment adverse events and deaths were reported from first dose of study medication up to 28 days after last dose of study medication, assessed up to approximately 56 weeks
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.
Source Vocabulary for Table Default	MedDRA (26.1)
Collection Approach for Table Default	Systematic Assessment

All-Cause Mortality

	LOU064 25 mg b.i.d. N = 297	**Placebo N = 153**	**Transitioned to LOU064 25 mg b.i.d. N = 129**
Arm/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)	Patients initially randomized to Placebo during the Double-Blind treatment period (Up to Week 24)	Patients initially randomized to placebo during the Double-blind treatment period and switched to Remibrutinib during the Open-label treatment period (Weeks 25-52)
Total Number Affected	0	0	0
Total Number At Risk	297	153	129

NOVARTIS

Serious Adverse Events

Time Frame	On-treatment adverse events and deaths were reported from first dose of study medication up to 28 days after last dose of study medication, assessed up to approximately 56 weeks
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.
Source Vocabulary for Table Default	MedDRA (26.1)
Collection Approach for Table Default	Systematic Assessment

	LOU064 25 mg b.i.d. N = 297	**Placebo N = 153**	**Transitioned to LOU064 25 mg b.i.d. N = 129**
Arm/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)	Patients initially randomized to Placebo during the Double-Blind treatment period (Up to Week 24)	Patients initially randomized to placebo during the Double-blind treatment period and switched to Remibrutinib during the Open-label treatment period (Weeks 25-52)
Total # Affected by any Serious Adverse Event	12	6	2
Total # at Risk by any Serious Adverse Event	297	153	129
Cardiac disorders			
Arteriosclerosis coronary artery	1 (0.34%)	0 (0.00%)	0 (0.00%)
Ear and labyrinth disorders			

Vestibular disorder	0 (0.00%)	1 (0.65%)	0 (0.00%)
Gastrointestinal disorders			
Food poisoning	1 (0.34%)	0 (0.00%)	0 (0.00%)
Large intestine polyp	0 (0.00%)	0 (0.00%)	1 (0.78%)
Hepatobiliary disorders			
Cholecystitis acute	0 (0.00%)	0 (0.00%)	1 (0.78%)
Immune system disorders			
Drug hypersensitivity	0 (0.00%)	1 (0.65%)	0 (0.00%)
Infections and infestations			
Appendicitis	0 (0.00%)	1 (0.65%)	0 (0.00%)
Gastrointestinal infection	1 (0.34%)	0 (0.00%)	0 (0.00%)
Pneumonia	0 (0.00%)	1 (0.65%)	0 (0.00%)
Wound abscess	1 (0.34%)	0 (0.00%)	0 (0.00%)
Injury, poisoning and procedural complications			
Contusion	1 (0.34%)	0 (0.00%)	0 (0.00%)
Head injury	1 (0.34%)	0 (0.00%)	0 (0.00%)
Musculoskeletal and connective tissue disorders			
Intervertebral disc degeneration	1 (0.34%)	0 (0.00%)	0 (0.00%)
Intervertebral disc protrusion	1 (0.34%)	0 (0.00%)	0 (0.00%)
Spinal stenosis	1 (0.34%)	0 (0.00%)	0 (0.00%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Breast cancer	0 (0.00%)	1 (0.65%)	0 (0.00%)

Leiomyoma	1 (0.34%)	0 (0.00%)	0 (0.00%)
Pancreatic carcinoma	1 (0.34%)	0 (0.00%)	0 (0.00%)
Renal and urinary disorders			
Haematuria	1 (0.34%)	0 (0.00%)	0 (0.00%)
Respiratory, thoracic and mediastinal disorders			
Nasal polyps	1 (0.34%)	0 (0.00%)	0 (0.00%)
Skin and subcutaneous tissue disorders			
Angioedema	1 (0.34%)	0 (0.00%)	0 (0.00%)
Chronic spontaneous urticaria	0 (0.00%)	1 (0.65%)	0 (0.00%)

NOVARTIS

Other (Not Including Serious) Adverse Events

Time Frame	On-treatment adverse events and deaths were reported from first dose of study medication up to 28 days after last dose of study medication, assessed up to approximately 56 weeks
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.
Source Vocabulary for Table Default	MedDRA (26.1)
Collection Approach for Table Default	Systematic Assessment
Frequent Event Reporting Threshold	3%

	LOU064 25 mg b.i.d. N = 297	**Placebo N = 153**	**Transitioned to LOU064 25 mg b.i.d. N = 129**
Arm/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)	Patients initially randomized to Placebo during the Double-Blind treatment period (Up to Week 24)	Patients initially randomized to placebo during the Double-blind treatment period and switched to Remibrutinib during the Open-label treatment period (Weeks 25-52)
Total # Affected by any Other Adverse Event	157	66	40
Total # at Risk by any Other Adverse Event	297	153	129
Infections and infestations			

COVID-19	62 (20.88%)	21 (13.73%)	13 (10.08%)
Influenza	8 (2.69%)	2 (1.31%)	4 (3.10%)
Nasopharyngitis	33 (11.11%)	9 (5.88%)	3 (2.33%)
Sinusitis	5 (1.68%)	6 (3.92%)	1 (0.78%)
Suspected COVID-19	16 (5.39%)	5 (3.27%)	4 (3.10%)
Upper respiratory tract infection	22 (7.41%)	4 (2.61%)	8 (6.20%)
Urinary tract infection	11 (3.70%)	4 (2.61%)	3 (2.33%)
Investigations			
Lipase increased	9 (3.03%)	3 (1.96%)	0 (0.00%)
Metabolism and nutrition disorders			
Hyperlipidaemia	6 (2.02%)	4 (2.61%)	6 (4.65%)
Hyperuricaemia	10 (3.37%)	1 (0.65%)	2 (1.55%)
Musculoskeletal and connective tissue disorders			
Arthralgia	9 (3.03%)	2 (1.31%)	0 (0.00%)
Nervous system disorders			
Headache	22 (7.41%)	8 (5.23%)	1 (0.78%)
Skin and subcutaneous tissue disorders			
Acne	1 (0.34%)	5 (3.27%)	0 (0.00%)
Petechiae	13 (4.38%)	0 (0.00%)	5 (3.88%)
Urticaria	9 (3.03%)	7 (4.58%)	5 (3.88%)

Other Relevant Findings

None

Conclusion:

- Study CLOU064A2302 met its primary and co-primary objectives. The results demonstrated superiority of remibrutinib over placebo showing a greater reduction from baseline in weekly urticaria activity score (UAS7), and its components, the weekly itch severity score and weekly hives score (ISS7 and HSS7), in adult patients with CSU inadequately controlled with second generation H1-AHs treatment.
- Remibrutinib offered significant and durable clinical benefit up to Week 52, allowing half of the patients to achieve disease activity control (UAS7 ≤ 6) at Week 12. Furthermore, the onset of action was fast, achieved as early as Week 2, and maintained thereafter.
- At Week 12, a higher proportion of patients in the remibrutinib arm had complete absence of itch and hives when compared to the placebo arm, which was sustained up to Week 52.
- Patients treated with remibrutinib remained angioedema-free for a longer duration as compared to the placebo arm.
- Treatment with remibrutinib was associated with improvement in health-related QoL, daily activities, and the quality of sleep.
- Remibrutinib showed a favorable safety profile consistent with the prior knowledge with overall AEs balanced between treatment arms; remibrutinib was well tolerated during the double-blind treatment period with a majority of AEs being mild or moderate. No new safety concerns were noted with the long-term treatment in the entire study period.

In conclusion, the results of this study demonstrated that remibrutinib is efficacious, showing fast, clinically meaningful, and highly statistically significant improvements in CSU disease activity, in particular the severity of itch and hives, is well tolerated and has a favorable safety profile, supporting a positive benefit-risk balance in adult patients with CSU inadequately controlled with second generation H1-AHs treatment.

Date of Clinical Trial Report

21-Aug-2024