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Sponsor

Novartis Pharmaceuticals

Generic Drug Name

Remibrutinib

Trial Indication(s)

Chronic Spontaneous Urticaria (CSU)

Protocol Number

CLOU064A2305

Protocol Title

A multicenter, open-label Phase 3 study: ambulatory blood pressure monitoring in adult patients with chronic spontaneous urticaria inadequately controlled by H1-antihistamines treated with remibrutinib up to 12 weeks.

Clinical Trial Phase

Phase 3

Phase of Drug Development

Phase III

Study Start/End Dates

Study Start Date: April 05, 2023 (Actual)
Primary Completion Date: April 25, 2024 (Actual)

Study Completion Date: April 25, 2024 (Actual)

Reason for Termination (If applicable)

Not applicable

Study Design/Methodology

This was a global, open-label Phase 3 study assessing the safety of remibrutinib 25 mg twice a day (b.i.d.), in adult participants with CSU inadequately controlled by second generation HI antihistamines (H1-AH) in regards to a change in 24-hour weighted average Systolic Blood Pressure (SBP) at Week 4 measured by Ambulator Blood Pressure Monitoring (ABPM) at baseline and Week 4 and overall efficacy, safety, and tolerability over 12 weeks. This study consisted of a screening period of up to 4 weeks, a 12-week open-label treatment period and a treatment-free follow-up period of 4 weeks, with a total study duration of up to 20 weeks. The planned sample size was approximately 136 participants.

At the end of the treatment phase, participants had the option to continue in an extension study (CLOU064A2303B) if approved in the country and at the site.

Centers

45 centers in 10 countries: United States(11), France(8), Spain(4), Germany(6), Republic of Korea(3), Singapore(1), Canada(2), Slovakia (3), Argentina(4), Turkey(3)

Objectives

The primary objective of the study was to rule out an increase of > 3 mmHg in 24-hour average SBP at steady state (Week 4) compared to baseline using an endpoint of the change in the ABPM-measured 24-hour weighted average SBP at Week 4 compared to baseline. The primary clinical question of interest was: Does remibrutinib treatment increase on average the 24-hour weighted average SBP at a steady state (Week 4) compared to baseline, by more than 3 mmHg, in adult participants without ongoing or past history of hypertension and with 90 < SBP < 140 mmHg, 60 < DBP < 90 mmHg at screening, with CSU who are inadequately controlled by H1-

AH and receiving a stable local label-approved standard dose of a second generation H1-AH, excluding participants who discontinue from study treatment for any reason before Week 4 and considering intake of prohibited antihypertensive treatment as an unfavorable outcome?

The secondary objectives (endpoints) were as follows:

- To evaluate changes in 24-hour average SBP at steady state (Week 4) compared to baseline (the change in the ABPM-measured 24 hour weighted average SBP at Week 4 compared to baseline)
- To evaluate changes in 24-hour average DBP at steady state (Week 4) compared to baseline (the change in the ABPM-measured 24 hour weighted average DBP at Week 4 compared to baseline)
- To evaluate changes in daytime and nighttime average SBP at 4 weeks (the change in the measured ABPM daytime and nighttime weighted average SBP at Week 4)
- To evaluate changes in daytime and nighttime average DBP at 4 weeks (the change in the measured ABPM daytime and nighttime weighted average DBP at Week 4)
- To evaluate the safety and tolerability of remibrutinib 25 mg b.i.d. (occurrence of treatment-emergent AEs and SAEs during the study, evaluation of laboratory and vital signs data)

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

One film-coated tablet (25 mg) of remibrutunib was to be orally taken in the morning and evening, respectively, with a 12-hour interval at approximately the same time everyday.

Statistical Methods

The following analysis sets were used:

- **Safety analysis set (SAF)** included all patients who received at least 1 dose of study treatment.

- **Full analysis set (FAS)** all participants who were assigned study treatment and received at least 1 dose of treatment. FAS was used for all efficacy variables, unless otherwise stated.

The primary endpoint tested was that the change from baseline of 24-hour weighted average SBP at Week 4 measured by ABPM using the FAS.

A linear regression model was used to estimate the 24-hour weighted average SBP mean change from baseline with baseline SBP as a covariate to analyze the primary efficacy endpoint. The upper limit of the 95% CI was prespecified as 3 mmHg, as based on FDA guidance. For secondary endpoints related to ABPM estimands, the same analyses as described for the primary estimand were conducted.

For all safety analyses, the Safety set was used. Summary statistics for safety variables were presented and included only data from the on-treatment period (from first dose until up to 28 days after last dose of the study drug).

There were no changes to the planned analyses.

Study Population: Key Inclusion/Exclusion Criteria

Key Inclusion Criteria:

• Signed informed consent obtained prior to participation in the study

• Male and female adult participants >= 18 years of age

• 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-AH at the time of baseline (Day 1)

• Documentation of hives within three months before baseline (either at screening and/or at baseline (Day 1); 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 protocol

• Participants had no more than 2 missing UPDD entries (either morning or evening) in the 7 days prior to baseline (Day 1).

Key Exclusion Criteria:

• Participants unable to tolerate 24-hour ambulatory blood pressure measurement using automatic ABPM device

• Ongoing or past history of hypertension and/or SBP >= 140 or =< 90 OR DBP >= 90 or =< 60 mmHg at screening

• Participants working night shifts

• Participants taking/requiring medications prohibited by the protocol (including those known to interfere with blood pressure assessments in the study)

• Evidence of clinically significant cardiovascular, 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.

Participant Flow Table

Overall Study

	LOU064 (remibrutinib)	Total
Arm/Group Description	All participants were assigned to remibrutinib 25 mg b.i.d. for 12 weeks.	
Started	144	144
Completed	137	137
Not Completed	7	7
Adverse Event	2	2
Unsatisfactory therapeutic effect	2	2

Lost to Follow-up	1	1
Subject decision	2	2

Baseline Characteristics

	LOU064 (remibrutinib)	Total
Arm/Group Description	All participants were assigned to remibrutinib 25 mg b.i.d. for 12 weeks.	
Number of Participants [units: participants]	144	144
Baseline Analysis Population Description		
Age Continuous (units: Years) Analysis Population Type: Participants Mean ± Standard Deviation		
	42.2±14.52	
Sex: Female, Male (units: Participants) Analysis Population Type: Participants Count of Participants (Not Applicable)		
Female	105	105
Male	39	39
Race (NIH/OMB) (units: Participants) Analysis Population Type: Participants Count of Participants (Not Applicable)		
American Indian or Alaska Native	1	1
Asian	19	19

Native Hawaiian or Other Pacific Islander	0	0
Black or African American	3	3
White	89	89
More than one race	0	0
Unknown or Not Reported	32	32

Study Specific Characteristic **Baseline Systolic Blood Pressure (SBP)** (units: millimeter of mercury (mmHg)) Analysis Population Type: Participants Mean ± Standard Deviation	
	117.1±13.11

Study Specific Characteristic **Baseline Diastolic Blood Pressure (DBP)** (units: millimeter of mercury (mmHg)) Analysis Population Type: Participants Mean ± Standard Deviation	
	75.0±8.98

Primary Outcome Result(s)

Estimated Mean Change from Baseline at Week 4 in 24-hour Systolic Blood Pressure (SBP) measured by Ambulatory Blood Pressure Monitoring (ABPM)

Description: A linear regression with SBP as a covariate was employed. The change in SBP from baseline to Week 4 was predicted at the median baseline level. The change from baseline in the 24-hour weighted average SBP was calculated using the time weighted average of the area under the curve (AUC) of SBP obtained over a 24-hour period as measured by ABPM. That is, the time weighted average of AUC of 24-hour SBP obtained at baseline was subtracted from corresponding time weighted average of AUC of SBP at Week 4. In the analysis, if participants took prohibited antihypertensive treatment before Week 4, their subsequent measurements were excluded. In such cases, the excluded measurements were imputed by increasing the 24-hour SBP by 3 mmHg from the baseline value at Week 4. Moreover, participants who discontinued of study treatment due to any reason prior to the Week 4 were excluded from the analysis. The Mixed Models for Repeated Measures (MMRM) approach was used.

Time Frame	Baseline, Week 4
Analysis Population Description	Full Analysis Set (FAS): all participants to whom study treatment was assigned and received at least one dose of treatment. Participants who discontinued treatment prior to Week 4 were excluded from the analysis.

	LOU064 (remibrutinib)
Arm/Group Description	All participants were assigned to remibrutinib 25 mg b.i.d. for 12 weeks.
Number of Participants Analyzed [units: participants]	143
Estimated Mean Change from Baseline at Week 4 in 24-hour Systolic Blood Pressure (SBP) measured by Ambulatory Blood Pressure Monitoring (ABPM) (units: millimeter of mercury (mmHg))	**Mean (95% Confidence Interval)**
	-1.3 (-2.3 to -0.3)

Secondary Outcome Result(s)

Observed Mean Change from Baseline to Week 4 in 24-hour weighted average Systolic Blood Pressure (SBP) measured by ABPM

Description	The change from baseline in the 24-hour weighted average systolic blood pressure (SBP) was calculated using the time weighted average of the area under the curve (AUC) of SBP obtained over a 24-hour period as measured by ABPM. This analysis was conducted using the observed data. Data was computed taking weighted averages over time and discarding time intervals of more than 1 hour without measurements.
Time Frame	Baseline, Week 4
Analysis Population Description	Full Analysis Set (FAS): all participants to whom study treatment was assigned and received at least one dose of treatment. Only participants with a value at both baseline and Week 4 were included.

	LOU064 (remibrutinib)
Arm/Group Description	All participants were assigned to remibrutinib 25 mg b.i.d. for 12 weeks.
Number of Participants Analyzed [units: participants]	142
Observed Mean Change from Baseline to Week 4 in 24-hour weighted average Systolic Blood Pressure (SBP) measured by ABPM (units: millimeter of mercury (mmHg))	**Mean ± Standard Deviation**
	-1.65 ± 6.905

Estimated Mean Change from Baseline at Week 4 in 24-hour Diastolic Blood Pressure (DBP) measured by ABPM

Description	A linear regression with DBP as a covariate was employed. The change in DBP from baseline to Week 4 was predicted at the median baseline level. The change from baseline in the 24-hour weighted average DBP was calculated using the time weighted average of the area under the curve (AUC) of DBP obtained over a 24-hour period as measured by ABPM. That is, the time weighted average of AUC of 24-hour DBP obtained at baseline was subtracted from corresponding time weighted average of AUC of DBP at Week 4. In the analysis, if participants took prohibited antihypertensive treatment before Week 4, their subsequent measurements were excluded. In such cases, the excluded measurements were imputed by increasing the 24-hour DBP by 3 mmHg from the baseline value at Week 4. Moreover, participants who discontinued of study treatment due to any reason prior to the Week 4 were excluded from the analysis. The Mixed Models for Repeated Measures (MMRM) approach was used.
Time Frame	Baseline, Week 4
Analysis Population Description	FAS: all participants to whom study treatment was assigned and received at least one dose of treatment. Participants who discontinued treatment prior to Week 4 were excluded from the analysis.

	LOU064 (remibrutinib)
Arm/Group Description	All participants were assigned to remibrutinib 25 mg b.i.d. for 12 weeks.
Number of Participants Analyzed [units: participants]	143

Estimated Mean Change from Baseline at Week 4 in 24-hour Diastolic Blood Pressure (DBP) measured by ABPM (units: millimeter of mercury (mmHg))	**Mean** **(95% Confidence Interval)**
	-0.1 (-0.8 to 0.6)

Estimated Mean Change from Baseline at Week 4 in daytime and nighttime average SBP measured by ABPM

Description	The change in daytime (respectively nighttime) weighted average SBP was analyzed using linear regression model with baseline weighted average daytime SBP (respectively nighttime) as a covariate. The change in daytime (respectively nighttime) SBP from baseline to Week 4 was predicted at the median baseline level. The change from baseline of daytime (respectively nighttime) SBP was calculated using the time weighted average of the AUC of DBP obtained over daytime (respectively nighttime) In the analysis, if participants took prohibited antihypertensive treatment before Week 4, their subsequent measurements were excluded. In such cases, the excluded measurements were imputed by increasing the 24-hour SBP by 3 mmHg from the baseline value at Week 4. Moreover, participants who discontinued of study treatment due to any reason prior to the Week 4 were excluded from the analysis. The multiple imputation approach was used. Daytime: from 7am until 10 pm. Nighttime: from 10pm until 7 am.
Time Frame	Baseline, Week 4
Analysis Population Description	FAS: all participants to whom study treatment was assigned and received at least one dose of treatment. Participants who discontinued treatment prior to Week 4 were excluded from the analysis.

	LOU064 (remibrutinib)
Arm/Group Description	All participants were assigned to remibrutinib 25 mg b.i.d. for 12 weeks.
Number of Participants Analyzed [units: participants]	143
Estimated Mean Change from Baseline at Week 4 in daytime and nighttime average SBP measured by ABPM (units: millimeter of mercury (mmHg))	**Mean** **(95% Confidence Interval)**
daytime average SBP	-1.2 (-2.3 to -0.0)

nighttime average SBP	-0.9 (-2.2 to 0.5)

Estimated Mean Change from Baseline at Week 4 in daytime and nighttime average DBP measured by ABPM

Description	The change in daytime (respectively nighttime) weighted average DBP was analyzed using linear regression model with baseline weighted average daytime DBP (respectively nighttime) as a covariate. The change in daytime (respectively nighttime) DBP from baseline to Week 4 was predicted at the median baseline level. The change from baseline of daytime (respectively nighttime) DBP was calculated using the time weighted average of the AUC of DBP obtained over daytime (respectively nighttime) In the analysis, if participants took prohibited antihypertensive treatment before Week 4, their subsequent measurements were excluded. In such cases, the excluded measurements were imputed by increasing the 24-hour DBP by 3 mmHg from the baseline value at Week 4. Moreover, participants who discontinued of study treatment due to any reason prior to the Week 4 were excluded from the analysis. The multiple imputation approach was used. Daytime: from 7am until 10 pm. Nighttime: from 10pm until 7 am.
Time Frame	Baseline, Week 4
Analysis Population Description	FAS: all participants to whom study treatment was assigned and received at least one dose of treatment. Participants who discontinued treatment prior to Week 4 were excluded from the analysis.

	LOU064 (remibrutinib)
Arm/Group Description	All participants were assigned to remibrutinib 25 mg b.i.d. for 12 weeks.
Number of Participants Analyzed [units: participants]	143
Estimated Mean Change from Baseline at Week 4 in daytime and nighttime average DBP measured by ABPM (units: millimeter of mercury (mmHg))	**Mean** **(95% Confidence Interval)**
daytime average DBP	-0.6 (-1.3 to 0.2)
nighttime average DBP	0.2 (-0.8 to 1.1)

Other Pre-Specified Outcome Result(s)

No data identified.

Post-Hoc Outcome Result(s)

No data identified.

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 18 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 enrolled subjects who received at least one dose of study medication.
Source Vocabulary for Table Default	MedDRA (27.0)
Collection Approach for Table Default	Systematic Assessment

All-Cause Mortality

	LOU064 (remibrutinib) N = 144
Arm/Group Description	All participants were assigned to remibrutinib 25 mg b.i.d. for 12 weeks
Total Number Affected	0
Total Number At Risk	144

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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 18 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 enrolled subjects who received at least one dose of study medication.
Source Vocabulary for Table Default	MedDRA (27.0)
Collection Approach for Table Default	Systematic Assessment

	LOU064 (remibrutinib) N = 144
Arm/Group Description	All participants were assigned to remibrutinib 25 mg b.i.d. for 12 weeks
Total # Affected by any Serious Adverse Event	4
Total # at Risk by any Serious Adverse Event	144
Hepatobiliary disorders	
Cholecystitis acute	1 (0.69%)
Nervous system disorders	
Dizziness	1 (0.69%)
Skin and subcutaneous tissue disorders	
Chronic spontaneous urticaria	1 (0.69%)

Vascular disorders	
Aortic dissection	1 (0.69%)

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 18 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 enrolled subjects who received at least one dose of study medication.
Source Vocabulary for Table Default	MedDRA (27.0)
Collection Approach for Table Default	Systematic Assessment

Frequent Event Reporting Threshold 5%

	LOU064 (remibrutinib) N = 144
Arm/Group Description	All participants were assigned to remibrutinib 25 mg b.i.d. for 12 weeks
Total # Affected by any Other Adverse Event	32
Total # at Risk by any Other Adverse Event	144

Infections and infestations	
Nasopharyngitis	12 (8.33%)
Nervous system disorders	
Headache	13 (9.03%)
Skin and subcutaneous tissue disorders	
Chronic spontaneous urticaria	8 (5.56%)

Other Relevant Findings

None

Conclusion

- This study met its primary objective and showed that the effect of remibrutinib 25 mg twice a day on Ambulator Blood Pressure Monitoring (ABPM) -measured 24 hour weighted average Systolic Blood Pressure (SBP) at Week 4 is less than 3 mmHg. The results were similar when considering a different assumption for the missing data as well as a different estimand.
- Secondary efficacy results at Week 4 showed no changes to 24-hour weighted average SBP or diastolic Blood Pressure (SBP) DBP or daytime or nighttime average SBP or DBP, as measured by ABPM.
- The safety profile of remibrutinib in this study up to Week 12 was consistent with the known safety profile and showed no new or unexpected safety signals.

Date of Clinical Trial Report

15-Oct-2024