Study Results Synopsis for Public Disclosure

Name of product: Remibrutinib/LOU064, 100 mg film-coated tablet

Protocol identification number: CLOU064A2105, IND 154120, ClinicalTrials.gov: NCT07032272

Title of study: A Phase 1, open-label study to investigate the pharmacokinetics and safety of remibrutinib (LOU064) in participants with severe renal impairment compared to matched healthy participants with normal renal function

Study center(s): 4 sites in the USA

Publication (reference): None

Study period:

Study initiation date: 23-Jul-2025 (first participant first visit)

Study completion date: 14-Oct-2025 (last participant last visit)

Phase of development (phase of this clinical study): I

Objectives:

Objective(s)	Endpoint(s)
Primary Objective(s)	**Endpoint(s) for primary objective(s)**
• To assess the PK of remibrutinib in blood and urine at steady state following oral doses of remibrutinib (Days 1 and 2: 100 mg b.i.d. and Day 3: morning dose of 100 mg) in participants with severe RI, compared to matched healthy control participants with normal renal function.	• Primary PK parameters of remibrutinib in **blood**: Cmax,ss, AUCtau,ss • Additional PK parameters of remibrutinib in **blood**: Tmax,ss, AUClast,ss, T1/2, CL/F,ss • Primary PK parameters of remibrutinib in urine: Ae0-12h,ss and CLr,ss
Secondary Objective(s)	**Endpoint(s) for secondary objective(s)**
• To assess the safety and tolerability of remibrutinib following 5 consecutive oral doses of remibrutinib (Days 1 and 2: 100 mg b.i.d and Day 3: morning dose of 100 mg) in participants with severe RI, compared to matched healthy control participants with normal renal function.	• All safety endpoints (including vital signs, ECGs, clinical laboratory evaluations, and AEs).
• To assess the plasma protein binding (unbound fraction, fu) of remibrutinib in participants with severe RI and matched healthy control participants with normal renal function.	• Fraction unbound and remibrutinib PK parameters in plasma (e.g., Cmax,ss,u, AUCtau,ss,u, as appropriate). • Additional PK parameters of remibrutinib in plasma: AUClast,ss,u

Study design and methodology: This was a Phase 1, open-label, non-randomized study to evaluate the pharmacokinetics (PK) after 5 administrations of remibrutinib in participants with severe renal impairment (RI) compared to matched healthy control participants with normal renal function.

A total of 16 participants (8 participants with severe RI and 8 healthy control participants), aged 18-75 years inclusive, completed the study.

Healthy control participants were matched 1:1 by age (±10 years), body weight (±20%), race, ethnicity and sex of an individual participant with severe RI. Each participant in the healthy control group (Group 2) could only be matched to 1 participant from the severe RI group (Group 1).

Diagnosis and main criteria for inclusion:

The key inclusion criteria were:

All participants (Group 1 and 2)

- Male and non-childbearing potential female participants 18 to 75 years of age, inclusive, at Screening.
- Non-smokers or light smokers who smoked no more than 10 cigarettes (or equivalent, including use of nicotine products) per day at Screening. Smokers agreed to smoke no more than 5 cigarettes (or equivalent) per day from check-in until after Study completion evaluations.

Participants with severe RI (Group 1)

- Weighed at least 50 kg to participate in the study and had a body mass index (BMI) within the range of 18.0 to 35.0 kg/m^2, inclusive, at Screening.
- Seated vital signs were within the following ranges at Screening and Baseline:
  1. body temperature, 35.0 to 37.5°C, inclusive.
  2. systolic blood pressure, 90 to 159 mmHg, inclusive.
  3. diastolic blood pressure, 60 to 99 mmHg, inclusive.
  4. pulse rate, 50 to 99 bpm, inclusive.
- Had impaired renal function as determined by eGFR using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) Creatinine – Cystatin C equation (2021), in the following group at Screening
  - severe RI; eGFR <30 mL/min, not requiring dialysis.
- Had stable renal function with no clinically significant change in renal status prior to first dosing of study treatment as determined by the Investigator and was not or had not been previously on hemodialysis for at least 1 year. Participants with other stable medical disorders such as controlled diabetes, hyperlipidemia, hypothyroidism, arterial hypertension etc., were eligible as long as they were considered appropriate for enrollment as determined by the Investigator by past medical history, physical examination, ECG, and clinical laboratory tests at Screening.

Healthy control participants (Group 2)

- Each healthy participant matched the age (±10 years), body weight (±20%), race, ethnicity and sex of an individual participant in Group 1.

- Weighed at least 50 kg to participate in the study and had a BMI within the range of 18.0 to 35.0 kg/m^2 inclusive, at Screening.
- Was in good health as determined by medical history, physical examination, ECG, vital signs and clinical laboratory tests at Screening.
- Had normal renal function with eGFR ≥90 mL/min, determined using the CKD-EPI Creatinine - Cystatin C equation (2021) at Screening. Actual creatinine clearance computed over a 24-hour urine collection could be used in place of or in conjunction with the CKD-EPI Creatinine – Cystatin C equation (2021), at the Investigator's discretion.

The key exclusion criteria were:

All participants (Groups 1 and 2)

- Use of other investigational drugs within 5 half-lives or 30 days prior to first dosing of study treatment, whichever was longer, as far as known.
- History of hypersensitivity to the study treatment or its excipients or to drugs of similar chemical classes.
- Use of prescription drugs, over-the counter medications, or herbal supplements (within the last 2 weeks prior to first dosing (unless permitted by the protocol)), or use of cannabis/marijuana, within the last 4 weeks prior to initial dosing.
- Note: Paracetamol could be allowed at the discretion of the Investigator but had to be documented in the Concomitant medications/Significant nondrug therapies page of the electronic case report form (eCRF)
- Participants not willing to abstain from food and beverages known to inhibit or induce Cytochrome P450 (CYP)3A4 from 7 days prior to first dosing and until their respective end-of-study (EoS) visit.
- History or presence of malignancy of any organ system (other than treated localized basal cell or squamous cell carcinoma of the skin or in-situ cervical cancer), treated or untreated, within the past 5 years of Screening, regardless of whether there was evidence of local recurrence or metastases.
- History or presence of any ongoing, chronic or recurrent infectious disease (including tuberculosis, atypical mycobacterioses, listeriosis, and aspergillosis).
- Participants with a history of bone marrow failure or cytopenia were excluded from the study.
- Was on immunosuppressant therapy or immunomodulator therapy ≤ 4 weeks prior to first dosing.
- Any single parameter of alanine aminotransferase (ALT), aspartate aminotransferase (AST), gamma-glutamyl transferase (GGT) or alkaline phosphatase (ALP) exceeded 1.2 x upper limit of normal (ULN) or ≥ 1.5 x ULN total bilirubin (TBL) OR any elevation above ULN of more than 1 parameter of ALT, AST, GGT, ALP, or TBL.

- Known or suspected diagnosis of Gilbert's syndrome.

Participants with severe RI (Group 1)

- Clinically significant abnormal findings in physical examination, ECG, or clinical laboratory evaluations, extended over findings related to the known renal disease.
- Participants who had myocardial infarction < 2 years before Screening were not eligible to participate; participants who had myocardial infarction ≥ 2 years before Screening could be eligible to participate.
- Clinically significant illness within 2 weeks prior to first dosing that might have jeopardized safety of the study participant and/or altered the study results as judged by the Investigator.
- Participants with end-stage renal disease requiring dialysis.

Healthy control participants (Group 2)

- Any clinical laboratory parameters (e.g., hemoglobin, platelets, leukocytes, neutrophils) outside of local laboratory ranges at Screening unless judged not clinically significant by the Investigator.
- Significant illness that had not resolved within 2 weeks prior to first dosing of study treatment.

Test and reference therapies, dose and mode of administration

All 16 participants received oral doses of remibrutinib as a film-coated tablet on Day 1 and Day 2 (100 mg remibrutinib B.I.D. [bis in die/twice a day], 12 hours apart), and Day 3 (100 mg remibrutinib, single morning dose only).

Protocol amendments and other changes to study conduct:

The study protocol was amended 1 time. This report describes the conduct of the study as amended.

Criteria for evaluation

Pharmacokinetics: Blood and urine remibrutinib concentrations were determined by validated liquid chromatography with tandem mass spectrometry methods. The plasma protein binding of remibrutinib in clinical samples was determined using ultrafiltration. Radiolabeled [14C] remibrutinib was added ex-vivo to clinical samples and the concentrations were determined by liquid scintillation counting. Based on remibrutinib blood concentrations, remibrutinib blood to plasma ratio, and remibrutinib protein binding in plasma, unbound remibrutinib concentrations and PK parameters in plasma were calculated.

Safety: Adverse events (AEs) including severity, relationship to the study treatment, duration, and whether it constituted a serious adverse event (SAE), as well as clinical laboratory, vital signs, and ECGs, were assessed, and C-SSRS and physical examinations were performed.

Statistical methods: Remibrutinib concentrations in blood and urine were listed by participant and visit/sampling time point/collection interval, including time deviations and comments for

the PK analysis set. Descriptive summary statistics of these concentrations were provided by visit/sampling time point/collection interval.

PK parameters for remibrutinib in blood and urine were listed by participant, and descriptive summary statistics of the PK parameters were provided. A statistical analysis was performed for the primary PK parameters (Cmax,ss, AUCtau,ss, Ae0-12h,ss, and CLr,ss) separately to assess the effect of RI on the PK of remibrutinib by comparing the severe RI group with the control group with normal renal function.

Summary - Results

Demographic and background characteristics: A total of 16 participants, whom 14 were male and 2 were female, participated in the study. Participants were between the age of 34 and 75 years. BMI ranged from 18 to 34 kg/m^2. Twelve (12) participants were White and 4 participants were Black or African American. Twelve (12) participants were of Hispanic or Latino ethnicity and 4 participants were not of Hispanic or Latino ethnicity. The matching of participants with severe RI to healthy controls was successful.

Exposure: All 16 participants received an oral tablet of 100 mg remibrutinib twice a day (b.i.d.) on Day 1 and Day 2, and once in the morning of Day 3.

Pharmacokinetic results:

Table 0-1 Statistical analysis of primary PK parameters for remibrutinib (PK analysis set)

Parameter (unit)**	Group	n*	Adjusted geo-mean	Comparisons	Geo-mean ratio	90% CI
Cmax,ss (ng/mL)	Healthy Control Group (reference)	8	131			
	Severe RI Group (test)	8	276	test/reference	2.11	(1.17, 3.79)
AUCtau,ss (h x ng/mL)	Healthy Control Group (reference)	8	304			
	Severe RI Group (test)	8	510	test/reference	1.68	(0.94, 2.98)
Ae0-12,ss (mg)	Healthy Control Group (reference)	8	0.382			
	Severe RI Group (test)	7	0.150	test/reference	0.393	(0.201, 0.768)
CLr,ss (L/h)	Healthy Control Group (reference)	8	1.232			
	Severe RI Group (test)	7	0.336	test/reference	0.273	(0.171, 0.437)

CI = confidence interval; PK = pharmacokinetics
The model is a linear model including group, sex, age (<65 years, >=65 years), and body weight as fixed factors. Sex and age were considered as categorical covariates, while body weight was considered a continuous covariate. The log-transformed PK parameters were used for the analysis. Results were back transformed to get adjusted geometric mean, geometric mean ratio, and 90% CI.
n* = number of observations used for analysis.
**=remibrutinib PK parameters in blood: Cmax,ss and AUCtau,ss; and remibrutinib PK parameters in urine: Ae0-12,ss and CLr,ss.
Note: For 1 participant in the severe RI group, the Day 3 urine PK collection weight and volume were not captured in the source/logs for the following time points: predose, 0-4 hours, 4 8 hours, 8-12 hours. Therefore, the urine data for this participant were excluded.

Table 0-2 Statistical analysis of secondary unbound PK parameters for remibrutinib (PK analysis set)

Parameter (unit)	Group	n*	Adjusted geo-mean	Comparisons	Geo-mean ratio	90% CI
Cmax,ss,u (ng/mL)	Healthy Control Group (reference)	8	7.30			
	Severe RI Group (test)	8	16.6	test/reference	2.27	(1.27,4.08)
AUCtau,ss,u (h x ng/mL)	Healthy Control Group (reference)	8	16.9			
	Severe RI Group (test)	8	30.7	test/reference	1.81	(1.02,3.22)

CI = confidence interval; n = number of participants; PK = pharmacokinetics; RI = renal impairment
The model is a linear model including group, sex, age (<65 years, >=65 years), and body weight as fixed factors. Sex and age were considered as categorical covariates while body weight was considered a continuous covariate.
The log-transformed PK parameters were used for the analysis. Results were back transformed to get adjusted geometric mean, geometric mean ratio, and 90% CI.

The total remibrutinib exposure in whole blood was higher in participants with severe RI compared to matched healthy controls (geometric-mean ratio [GMR] of 2.11 for Cmax,ss and 1.68 for AUCtau,ss). The variability in the whole blood PK parameters was moderate to high, both in participants with severe RI as well as in the matched healthy controls. The reduction in renal function is unlikely to account for the observed increase in blood PK parameters but is likely based on reduced metabolic activity in participants with severe RI. Impaired hepatic metabolic function in patients with severe RI would be expected to reduce metabolic CYP450 activity due to abundance of uremic toxins.

Unbound remibrutinib exposure in plasma was higher in participants with severe RI compared to healthy controls (GMR of 2.27 for Cmax,ss,u and 1.81 for AUCtau,ss,u); and the extent of exposure increase with RI was comparable to total remibrutinib. The geometric mean fraction unbound for remibrutinib was 0.0479 in the severe RI group and 0.0441 in the healthy controls (4.8% and 4.4%, respectively), indicating that RI did not have any appreciably impact on protein binding.

Safety results: A total of 2 participants (12.5%) reported at least 1 treatment-emergent adverse event (TEAE). Of these, 1 participant was in the severe RI group and 1 participant was in the healthy control group. In total, 7 TEAEs were reported, of which 1 TEAE was observed in 1 participant in the severe RI group and 6 TEAEs in 1 participant in the healthy control group. No differences were observed in the percentage of participants experiencing TEAEs between the severe RI and healthy control groups. All reported TEAEs were mild (non were moderate or severe), and there were no SAEs. All TEAEs were resolved by the end of the study.

No TEAE led to a discontinuation from the study.

Conclusions:

Pharmacokinetics

- On average, the exposure was higher for both total remibrutinib (2.11-fold for Cmax,ss and 1.68-fold for AUCtau,ss) in blood and unbound remibrutinib (2.27-fold for Cmax,ss and 1.81-fold for AUCtau,ss) in plasma in participants with severe RI compared to matched healthy controls.

- RI did not have any appreciable impact on protein binding, and the geometric mean fraction unbound was similar in participants with severe RI (0.0479) compared to matched healthy controls (0.0441), or 4.8% and 4.4%, respectively.

Safety

- Multiple oral doses of 100 mg remibrutinib b.i.d. for 2 days and a 100 mg morning dose on the third day were safe and well tolerated by all 16 participants (8 with severe RI and 8 healthy controls).
- There were no SAEs or deaths in this study, and no TEAE that led to a discontinuation from the study.
- All reported TEAEs were mild. Five (5) TEAEs reported by 1 participant in the healthy control group were considered related to study drug by the Investigator (pyrexia, C-reactive protein increased, haematuria, nasal congestion, and blepharitis).
- There were no clinically relevant changes in 12-lead ECGs, AEs, or vital signs and no clinically important trends were seen in any of the clinical laboratory parameters.