Sponsor: Sanofi **Drug substance(s):** rilzabrutinib	**Study Identifiers:** U1111-1260-4355 **Study code:** PRN1008-022/PKM17088

Title of the study:

A Phase 1, Single-center, Open-label Study to Evaluate the Pharmacokinetics, Safety and Tolerability of Rilzabrutinib (PRN1008/ SAR444671) in Chinese Healthy Male and Female Subjects

Study center(s):

This study was conducted at 1 center that enrolled participants in China.

Study period:

Study initiation date: 23 March 2023 (signed informed consent)

Study completion date: 06 April 2023 (last participant last visit)

Study Status: Completed

Phase of development: Phase 1

Objectives:

Primary

• To evaluate the pharmacokinetics (PK) of a single dose of rilzabrutinib in healthy Chinese subjects

Secondary

• To assess the safety and tolerability of a single dose of rilzabrutinib in healthy Chinese subjects

Methodology:

This is a single-center, open-label study to investigate the PK, safety, and tolerability of a single dose of rilzabrutinib in Chinese healthy participants.

Approximately 10 healthy participants were planned for this study.

Participants were screened for this study within 28 days prior to the administration of study drug. Each enrolled participant was admitted to the study unit the day before dosing (Day -1) and dosed on the morning of Day 1 following overnight (≥10 hours) fast. Participants remained in the study unit until assessments for Day 2 had been completed. Following discharge from the study unit, study personnel contacted study participants by telephone for a follow-up assessment on Day 5 ±1 to determine if any adverse events (AEs) have occurred or if any concomitant medications have been taken since the last visit.

Blood samples for plasma PK analysis were drawn at prespecified timepoints prior to and after dosing rilzabrutinib.

Safety was evaluated by the occurrence of AEs or serious adverse events (SAEs), as well as clinical laboratory tests (serum chemistry, hematology, coagulation, urinalysis), vital signs measurements, 12-lead electrocardiograms (ECGs), and findings from physical examinations.

Number of study participants:

Number of planned participants: 10

Number of enrolled participants: 10

Safety analysis set: 10

Pharmacokinetic analysis set: 10

Diagnosis and criteria for inclusion:

Healthy Chinese male and/or female participants, between 18 and 45 years of age, inclusive, body mass index (BMI) ≥19.0 and ≤26.0 (kg/m^2), inclusive, and a minimum body weight of 45 kg for female, and 50 kg for male.

Study products

All enrolled participants were administered a single dose of 400 mg rilzabrutinib in the morning on Day 1 following overnight (≥10 hours) fast.

Investigational Product: Rilzabrutinib: 400 mg, modified-capsule shaped tablets.

Duration of study intervention:

The study treatment period was 2 days, and each participant administered a single dose of 400 mg of rilzabrutinib on Day 1. A Follow-up phone call was performed on Day 5 ±1 day.

Criteria for evaluation:

Primary

The following PK parameters will be calculated for rilzabrutinib following a single dose:

• maximum plasma concentration (C_{max})

• time to maximum plasma concentration (t_{max})

• area under the plasma concentration-time curve from zero to the last measurable concentration (AUC_{last})

• area under the plasma concentration-time curve from zero to infinity (AUC)

• terminal elimination phase half-life ($t_{1/2}$)

• apparent total clearance of drug from plasma after oral administration (CL/F)

Secondary

• 12-lead electrocardiograms (ECGs), vital signs, clinical laboratory tests (hematology, serum chemistry, coagulation, and urinalysis), adverse events (AEs) or serious adverse events (SAEs), and physical examination

Statistical methods:

Safety and Tolerability

Clinical safety analysis focused on the treatment-emergent (TE) period, defined as the time from first administration of study intervention up to the end of study (EOS) (inclusive). The number (%) of participants experiencing treatment-emergent adverse events (TEAEs) as well as the number of occurrences were summarized. Potentially clinically significant abnormalities (PCSAs) in clinical laboratory test results, vital signs, and ECGs were flagged and summarized.

Pharmacokinetics

Pharmacokinetic parameters were calculated from plasma rilzabrutinib concentrations using standard noncompartmental methods and included, but not limited to, C_{max}, t_{max}, AUC_{last}, AUC, $t_{1/2}$, and CL/F.

Pharmacokinetic parameters were summarized using descriptive statistics. Mean plasma concentration versus time data were presented graphically.

Summary Results:

Demographic and other baseline characteristics:

Overall, the majority of Chinese participants were male (8/10, 80.0%) aging from 22 to 40 years old. The mean BMI (SD) in the Chinese participants was 22.35 (1.73) kg/m^2 with a mean body weight (SD) of 66.510 (9.205) kg.

Exposure:

All participants received a single dose of 400 mg of rilzabrutinib on Day 1 of the study.

Safety results:

Overall, the incidence of TEAEs was low in the study. Two out of 10 participants (20.0%) reported 4 TEAEs during the study. No participants reported any grade ≥3 TEAEs (Table 1).

Table 1 - Overview of adverse event profile: Treatment Emergent Adverse Events - Safety Analysis Set

	Rilzabrutinib 400 mg (N=10) n (%) m
Participants with any TEAE	2 (20.0%) 4
Participants with any grade>=3 TEAE	0
Participants with any treatment emergent SAE	0
Participants with any TEAE leading to death	0
Participants with any TEAE leading to permanent study discontinuation	0
Participants with any treatment emergent AESI	0

An adverse event is considered as treatment emergent if it occurred from the time of the first investigational medicinal product administration up to the end of study(included).

SAE: Serious adverse event, AESI: Adverse event of special interest

If a participant has multiple occurrences of a TEAE, the participant is presented only once in the Participant count (n) column.

Occurrences are counted each time in the mentions/Occurrence (m) column.

Percentages are calculated (the denominator used for the calculation) based on the number of participants in the Safety Analysis Set.

Medical Dictionary for Regulatory Activities (MedDRA) Version 26.0.

Program: D01T006.sas, Output Name: D01T006.rtf, Creation Date/Time: 2023-06-06/14:35

The 4 TEAEs by preferred term (PT) reported in the study were alanine aminotransferase increased, basophil count increased, blood albumin decreased, and blood uric acid increased. These 4 AEs were evenly reported by 2 participants. All TEAEs were of grade 1 intensity.

One participant reported the AE of alanine aminotransferase increased on an unscheduled visit on Day 6. The elevated ALT value of this participant was 53 U/L with a ULN at 50 U/L. There was no increase of AST or albumin accompanied with this ALT increase. The follow up of this case was not obtained.

Overall, there were no clinically meaningful findings in the hematology measurements, clinical chemistry measurements, urinalysis measurements, vital signs measurements, ECG assessments, or other observations related to safety in this study.

Pharmacokinetic results:

Twelve blood samples from Day 1 up to Day 2 (24 hours) were collected for the quantification of plasma rilzabrutinib using validated LC-MS/MS bioanalysis methods with a lower limit of qualification (LLOQ) of 0.100 ng/mL.

Mean (±SD) plasma concentration-time profiles of rilzabrutinib following a single oral administration of 400 mg rilzabrutinib in Chinese participants are presented in Figure 1 and Figure 2 with liner scale and semi-log scale, respectively.

Descriptive statistics of plasma PK parameters for rilzabrutinib are summarized in Table 2.

Figure 1 - Mean (±SD) rilzabrutinib plasma concentration - time profiles following a single oral administration of rilzabrutinib (400 mg) in Chinese participants - Linear scale

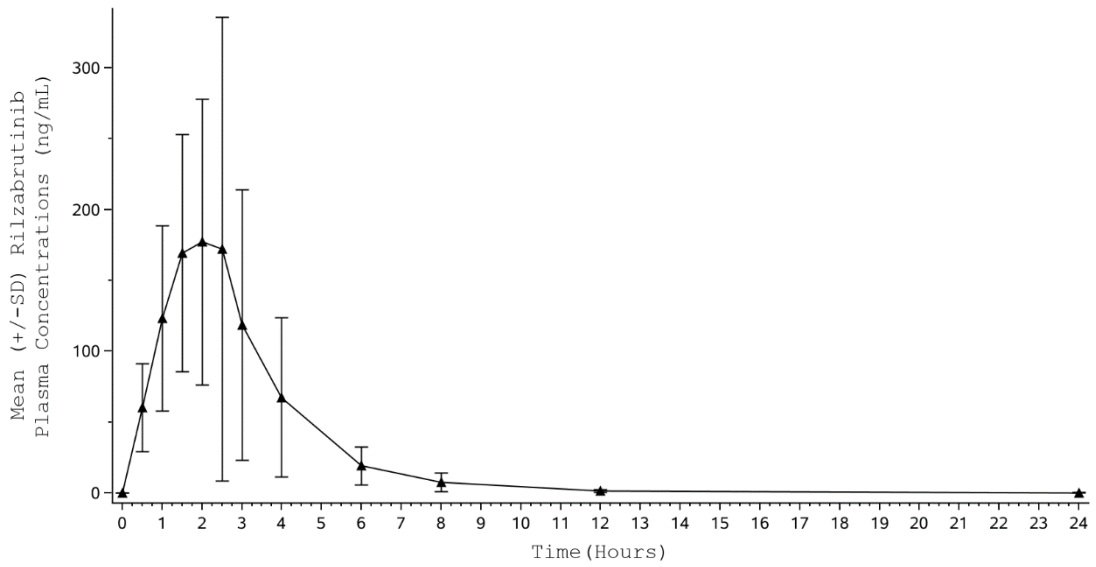
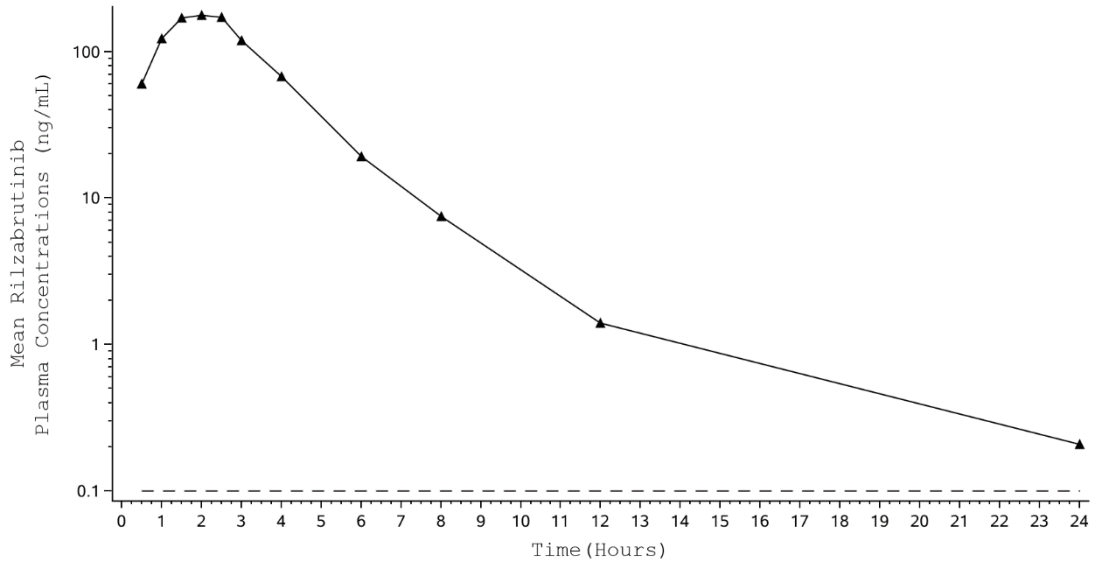


Figure 2 - Mean (± SD) rilzabrutinib plasma concentration - time profiles following a single oral administration of rilzabrutinib (400 mg) in Chinese participants - semi-log scale



Note: LLOQ of rilzabrutinib is 0.100 ng/mL.

Table 2 - Descriptive statistics of plasma PK parameters for rilzabrutinib following a single oral administration 400 mg rilzabrutinib in healthy Chinese participants

PK Parameter	N, Mean ± SD (Geometric Mean) [CV%]
	Rilzabrutinib
C_{max} (ng/mL)	10 221±143 (192) [64.6]
T_{max} (h)[a]	10 1.50 (1.00, 3.00)
AUC_{last} (h*ng/mL)	10 613±388 (532) [63.4]
AUC (h*ng/mL)	10 614±388 (533) [63.2]
$t_{1/2}$ (h)	10 3.10±1.07 (2.92) [34.6]
CL/F (L/h)	10 836±364 (749) [43.6]

NA = Not Applicable; NC = Not Calculable; SD = Standard Deviation; CV% = Coefficient of Variation.

a Median (Minimum - Maximum)

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