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| **Sponsor:** Sanofi<br>**Drug substance(s):** rilzabrutinib | **Study Identifiers:** NCT04748926, U1111-1260-4526<br>**Study code:** PRN1008-025/PKM17098 |

**Title of the study:**

A randomized, open-label, Phase I study to assess the effects of food and formulation on the pharmacokinetics of a single dose of rilzabrutinib (SAR444671 [formerly PRN1008]) in healthy male and female participants

**Study center(s):**

This study was conducted at 1 center in Australia

**Study period:**

Study initiation date: 07-APR-2021 (first participant enrolled)

Study completion date: 20-MAY-2021 (last participant last visit)

Study Status: Completed

**Phase of development:** Phase 1

**Objectives:**

**Primary**

- To evaluate the impact of food on the pharmacokinetics (PK) of rilzabrutinib following a single oral 400 mg dose to healthy participants.
- To evaluate the impact of formulation on the PK of rilzabrutinib following a single oral 400 mg dose to healthy participants.

**Secondary**

- To assess the safety and tolerability of a single oral 400 mg dose of rilzabrutinib administered under fasted and fed conditions.

**Methodology:**

This was an open-label, randomized, two-part (Parts 1 and 2) Phase I study conducted in healthy adult male and female participants at one or more sites. Part 1 was a 2-period crossover design in which participants received a single 400 mg dose of the reference formulation of rilzabrutinib in the fed and fasted states, and Part 2 consisted of a 1-period parallel design in which participants received a single 400 mg dose of one of two test formulations of rilzabrutinib in the fasted state. Up to 24 healthy adult male and female participants aged 18 to 65 years, were to be enrolled.

In Part 1, participants were randomized to receive single oral 400 mg doses of the reference formulation of rilzabrutinib in the fasted (A) and fed (B) states in a crossover design. For the fasted treatment (A), participants received a single oral 400 mg dose of rilzabrutinib with 240 mL of water following an overnight (approximately 10 hr) fast. For the fed treatment (B), participants fasted overnight (approximately 10 hr), then began eating a high-fat breakfast 30 minutes prior to study drug administration. Participants completed the breakfast in 30 minutes or less. Participants then received a single oral 400 mg dose of rilzabrutinib with 240 mL of water.

In Part 2, participants completing Part 1 were stratified by the treatment sequence (AB or BA) in Part 1 and randomized to receive a single oral 400 mg dose of one of two test formulations (Treatments C and D) following an overnight (approximately 10 hr) fast.

Administration of each treatment were separated by a washout period of 4 days.

Blood samples were collected for the determination of plasma rilzabrutinib (PRN1008) and metabolites PK for Treatments A, B, C, and D and for PBMC BTK occupancy for Treatments A, C, and D were drawn at the timepoints indicated in the Schedule of Assessments.

Participants were screened for participation in this study within 28 days prior to the first dose of study drug.

Screening procedures were performed, and eligibility was confirmed within 28 days of randomization. All eligible participants were randomized to receive a single dose of the investigational product on Day 1, Day 6, and Day 11. Participants were admitted to the Clinical Study Unit the day before dosing (Day -1) and remained confined until the last study assessment was completed for Part 2 on Day 12. Participants were confined in the study unit for approximately 12 days. Following discharge from the study unit, study personnel contacted participants by telephone for a follow-up assessment on Day 15 ±1 day to determine if any AE(s) had occurred since the last visit.

**Number of study participants:**

Planned: 24 (12 per treatment sequence)

Randomized: 25

Treated: 24

**Evaluated:**

Pharmacokinetics: 24 for rilzabrutinib (PRN1008) and Metabolite for both treatments and 10 for SCN for treatment A and 11 for Treatment B

Safety: 24

**Diagnosis and criteria for inclusion:**

Participants were healthy male or non-pregnant non-lactating females, 18 to 65 years of age (inclusive), body mass index (BMI) within the range ≥18 and ≤31 kg/m$^2$ (inclusive) and a minimum body weight of 45 kg who provided informed consent.

**Study products**

**Investigational medicinal product(s):**

**Treatment A**: Rilzabrutinib (PRN1008) 400 mg caplet in fasted state, and Treatment B: Rilzabrutinib 400 mg caplet after highfat meal

Formulation: Caplet

Route(s) of administration: Oral

Dose regimen: Single dose

**Treatment C**: Rilzabrutinib (PRN1008) 400mg film-coated (FC) tablets, in fasted state

Formulation: FC Tablet

Route(s) of administration; Oral

Dose regimen: Single dose

**Treatment D**: Rilzabrutinib (PRN1008) 400 mg (as 2x 200 mg) spray-dried dispersion (SDD) tablets, in fasted state

Formulation: SDD Tablet

Route(s) of administration; Oral

Dose regimen: Single dose

Lot number(s): 20N09

**Duration of treatment:** In Part 1, Two single oral doses of rilzbrutinib 400 mg were administered on Day 1 and Day 6, followed by single oral dose of rilzabrutinib 400mg FC tablet or SDD tablet on Day 11 in Part 2.

**Duration of observation:** Participants were admitted to the Clinical Study Unit the day before dosing (Day -1) and remained confined until the last study assessment was completed for Part 2 on Day 12. Participants were confined in the study unit for approximately 12 days. Following discharge from the study unit, study personnel contacted participants by telephone for a follow-up assessment on Day 15 ±1 day to determine if any AE(s) had occurred since the last visit.

**Criteria for evaluation:**

Pharmacokinetics: The following plasma PK parameters were derived separately for plasma concentrations of rilzabrutinib and metabolites: $AUC_{0\text{-}last}$, $AUC_{0\text{-}inf}$, $C_{max}$, $T_{max}$, $t_{1/2}$, $K_{el}$, CL/F, $V_z$/F.

Safety: Physical examinations, vital signs, 12-lead Electrocardiograms (ECGs), clinical laboratory tests (clinical chemistry, hematology, coagulation, and urinalysis), and adverse events (AEs) or serious AEs (SAEs).

Efficacy/pharmacodynamics: BTK occupancy in PBMCs following a single oral 400 mg dose of rilzabrutinib in the fasted state in healthy participants.

**Statistical methods:**

The following analysis sets were used:

Screened Population: Screened population was defined as all participants who signed the ICF.

Randomized Population: Randomized population was defined as all participants from screened population who were allocated to an intervention, regardless of whether the intervention was received.

Intent-to-treat (ITT) Population: ITT population was defined as all randomized participants. Participants were analyzed according to the intervention allocated by randomization.

Safety Population: The safety population was defined as all participants who took at least one dose of study intervention.

Participants were analyzed according to the intervention they actually received. Pharmacokinetic (PK) Population: The PK population included all randomized and treated participants (safety population) with at least one post-baseline PK sample with adequate documentation of dosing and sampling dates and times. Participants were analyzed according to the intervention they actually received.

Pharmacodynamic (PD) Population: The PD population included all randomized and treated participants (safety population) with at least one post-baseline PD sample with adequate documentation of dosing and sampling dates and times. Participants were analyzed according to the intervention they actually received.

Study results were described using summary statistics by treatment and time point.

Safety data, including physical examinations, vital signs, 12-lead Electrocardiograms (ECGs), clinical laboratory tests (clinical chemistry, hematology, coagulation, and urinalysis), and adverse events (AEs) or serious AEs (SAEs) are listed individually and summarized for treatment.

Plasma PK parameters are listed and summarized descriptively by treatment group. Descriptive statistics (arithmetic and geometric means, SD, CV%, Min, Max, and median) of the plasma PK parameters are presented based on the PK Population.

The PK parameters $AUC_{0\text{-last}}$, $AUC_{0\text{-inf}}$, and $C_{max}$ were statistically compared between fed (B) and fasted (A) states, Treatment C and Treatment A, Treatment D and Treatment A, Treatment C and Treatment D, and metabolites, as data permitted. For rilzabrutinib, an analysis using linear mixed model in SAS, ANOVA was performed on ln-transformed $AUC_{0\text{-last}}$, $AUC_{0\text{-inf}}$, and $C_{max}$, at the alpha level of 0.05. The ratio of geometric means (B/A, C/A, D/A, C/D) and the 90% confidence interval for the ratio of geometric means, based on least-squares means from the ANOVA of the ln-transformed data were also calculated for $AUC_{0\text{-last}}$, $AUC_{0\text{-inf}}$ and $C_{max}$.

Individual and average % BTK occupancy data are summarized descriptively by treatment group. Descriptive statistics (arithmetic and geometric means, SD, coefficient of variation [CV%], Min, Max, and median) of Individual and average % BTK occupancy data are presented based on the PD Population. Individual BTK occupancy data are listed separately for Part 1 and Part 2.

**Summary Results:**

**Population characteristics:**

Part 1 and Part 2

The population consisted of 24 healthy male and female volunteers aged between 18 and 66 years. The majority (66.7%) were of white race and were of non-Hispanic or Latino ethnicity (70.8%).

**Pharmacokinetics Results:**

Part 1

For single dose of 400 mg rilzabrutinib (PRN1008) caplet formulation administered under fasted and fed conditions, the ratio of geometric LSM (Fed/Fasted [B/A]) and 90% CI were 81.75% (69.40% to 96.29%), 78.70% (67.27% to 92.06%) and 69.04% (55.36% to 86.11%) for AUC0-last, AUC0-inf, and Cmax, respectively. The median Tmax appeared to be delayed by 1.5 hours under fed conditions (1.5 hours under fasting and 3.0 hours under fed state).

For metabolite, the mean exposure (AUC0-last, and AUC0-inf) and maximal plasma concentration (Cmax) were higher by

approximately 36%, 36%, and 35%, respectively, and median Tmax was delayed by 3 hours, when rilzabrutinib was administered under fed conditions compared to fasting conditions.

For metabolite SCN, PK parameters appeared similar between fed and fasted conditions.

Part 2

A summary of the findings of the main ANOVA performed on ln-transformed PK parameters, displaying the geometric LSM ratio and 90% CI for AUC0-last, AUC0-inf and Cmax for rilzabrutinib (PRN1008) and metabolites is provided below for Treatment C (Rilzabrutinib FC tablet) versus Treatment A (reference caplet formulation) and treatment D (Rilzabrutinib SDD tablet) versus Treatment A, under fasted conditions. Post-hoc sensitivity analysis with participant included in the ANOVA model as a random effect is also displayed.

| | | Main ANOVA | Sensitivity ANOVA |
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| | Parameter (unit) | Geometric LSM Ratio (90% CI) (%) | Geometric LSM Ratio (90% CI) (%) |
| **Treatment C vs. Treatment A** | | | |
| Analyte: PRN1008 | $AUC_{0\text{-last}}$ (h*ng/mL) | 144.62 (97.14, 215.32) | 142.96 (114.95, 177.80) |
| | $AUC_{0\text{-inf}}$ (h*ng/mL) | 182.67 (127.14, 262.45) | 152.82 (120.94, 193.11) |
| | $C_{max}$ (ng/mL) | 148.91 (97.97, 226.32) | 148.45 (117.97, 186.79) |
| Analyte: Metabolite | $AUC_{0\text{-last}}$ (h*ng/mL) | 93.59 (72.23, 121.28) | 90.34 (73.53, 111.00) |
| | $AUC_{0\text{-inf}}$ (h*ng/mL) | 94.49 (73.22, 121.95) | 91.06 (74.98, 110.58) |
| | $C_{max}$ (ng/mL) | 98.52 (75.41, 128.71) | 92.27 (74.40, 114.43) |
| Analyte: SCN | $AUC_{0\text{-last}}$ (h*ng/mL) | 75.23 (59.15, 95.68) | 88.10 (77.68, 99.93) |
| | $C_{max}$ (ng/mL) | 69.12 (54.55, 87.58) | 77.07 (62.23, 95.46) |
| **Treatment D vs. Treatment A** | | | |
| Analyte: PRN1008 | $AUC_{0\text{-last}}$ (h*ng/mL) | 112.19 (79.18, 158.97) | 113.50 (79.49, 162.05) |
| | $AUC_{0\text{-inf}}$ (h*ng/mL) | 109.48 (77.91, 153.85) | 110.26 (76.25, 159.43) |
| | $C_{max}$ (ng/mL) | 110.72 (77.27, 158.64) | 111.06 (82.91, 148.76) |
| Analyte: Metabolite | $AUC_{0\text{-last}}$ (h*ng/mL) | 73.29 (56.16, 95.64) | 75.92 (55.96, 103.00) |
| | $AUC_{0\text{-inf}}$ (h*ng/mL) | 74.04 (57.04, 96.10) | 76.83 (57.56, 102.55) |
| | $C_{max}$ (ng/mL) | 72.03 (53.79, 96.45) | 76.91 (54.60, 108.33) |
| Analyte: SCN | $AUC_{0\text{-last}}$ (h*ng/mL) | 94.37 (74.01, 120.33) | 84.33 (74.16, 95.90) |
| | $C_{max}$ (ng/mL) | 93.78 (74.73, 117.69) | 86.94 (69.76, 108.35) |

**Safety Results:**

Part 1

Overall, the administration of a single dose of 400 mg rilzabrutinib caplet was safe and well tolerated. There were no deaths, serious or life-threatening AEs during Part 1 of the study. None of the participants were discontinued due to TEAEs. No AESIs were reported during Part 1 of the study. All of the TEAEs were recovered/resolved at the end of the study and concomitant medications were used for only 2 TEAEs during Part 1 of the study.

More TEAEs were reported by a nominally higher proportion of participants following administration of rilzabrutinib in fasted compared to fed state.

The most commonly reported TEAEs during this study were related to the SOC gastrointestinal disorders, and the most commonly reported TEAE was diarrhea, The incidence of these events was higher in the fasted state compared to in the fed state.

The majority (58) of TEAEs were mild in severity, with 5 TEAEs of moderate severity all reported following rilzabrutinib administration in the fasted state.

Overall, 60.3% of TEAEs were judged as possibly, probably, or definitely related to the study drug by the PI and the incidence of treatment-related TEAEs was higher when the drug was administered in fasted state compared to when taken after a high-fat meal (58.3% versus 29.2%).

There were no TEAEs related to ECGs, and physical examination during the study. One participant had some abnormal laboratory and vital signs results which were reported in conjunction with other TEAEs including abdominal pain, diarrhea, viral infection, headache, and catheter site irritation. The participant experienced similar events after both fasted and fed dosing.

Part 2

Overall, the administration of a single dose of 400 mg rilzabrutinib FC and SDD tablets was safe and well tolerated. There were no deaths, serious or life-threatening AEs during Part 2 of the study. None of the participants were discontinued due to TEAEs. No AESIs were reported during Part 2 of the study. All of the TEAEs except 3 TEAEs (1 TEAE of “vessel puncture site bruise” was recovering/resolving, 1 TEAE of “catheter site pain” was not recovered/not resolved, and 1 TEAE of “vessel puncture site pain” outcome was unknown at the end of study) were recovered/resolved at the end of the study and concomitant medications were used for only 2 TEAEs during Part 2 of the study.

More TEAEs were reported by a higher proportion of participants following administration of rilzabrutinib FC tablets compared to SDD tablets formulation.

The most commonly reported TEAEs during this study were related to the SOC gastrointestinal disorders, and the most commonly reported TEAE was diarrhea, The incidence of these events was higher in participants who received rilzabrutinib FC tablets (25.0%) compared to those who received rilzabrutinib SDD tablets (8.3%).

The majority (28) of TEAEs were mild in severity, with 3 TEAEs of moderate severity all reported following administration rilzabrutinib FC tablets.

Overall, 67.7% of TEAEs were judged as possibly, probably, or definitely related to the study drug by the PI and the incidence of treatment-related TEAEs was nominally higher following administration of rilzabrutinib FC tablets than rilzabrutinib SDD tablets (66.7% versus 41.7%).

There were no TEAEs related to ECGs, vital signs, and physical examination during the study. One participant had some abnormal laboratory results which were deemed clinically significant.

**Issue date:** 01-Dec-2025