Sponsor: Sanofi **Drug substance(s):** rilzabrutinib	**Study Identifiers:** Not applicable **Study code:** PRN1008-023/PKM17089

Title of the study:

A Phase 1, Single-Center, Open-Label Study to Evaluate the Pharmacokinetics and Tolerability of Rilzabrutinib (PRN1008) in Japanese and Caucasian Healthy Male and Female Subjects

Study center(s):

This study was conducted at 2 centers in United States

Study period:

Study initiation date: 04-Jan-2021 (signed informed consent)

Study completion date: 12-Apr-2021 (last participant last visit)

Study Status: Completed

Phase of development: Phase 1

Objectives:

Primary:

- To evaluate the pharmacokinetics (PK) of rilzabrutinib in Japanese and Caucasian healthy participants following single and multiple doses

Secondary:

- To assess the safety and tolerability of rilzabrutinib in Japanese and Caucasian healthy participants following single and multiple doses
- To evaluate Bruton's agammaglobulinemia tyrosine kinase (BTK) occupancy following single and multiple doses of rilzabrutinib
- To evaluate the PK of rilzabrutinib metabolites following rilzabrutinib administration

Methodology:

This was a single-center, open-label study to investigate the PK, pharmacodynamic (PD), safety, and tolerability of single and multiple doses of rilzabrutinib in Japanese and Caucasian healthy participants. A total of 23 healthy participants were enrolled into one of two cohorts (11 in Japanese cohort [Cohort 1] and 12 in Caucasian cohort [Cohort 2]) in a single center in the United States. Cohort 1 had three sequential treatment periods separated by 4-day washout periods and enrolled participants of Japanese ancestry. Cohort 2 had one treatment period and enrolled participants of Caucasian ancestry. Participants were screened for enrollment in this study within 28 days prior to the first dose of rilzabrutinib.

Study participants in both cohorts were admitted to the clinical study unit the day before dosing (Day -1). Participants remained in the clinical study unit until end of study assessments had been completed (Day 15 for Cohort 1, and Day 7 for Cohort 2). Following discharge from the clinical study unit, study personnel contacted study participants by telephone for a follow-up assessment on Day 18 (±1 day) for Cohort 1 and on Day 10 (±1 day) for Cohort 2 to determine if any adverse events (AEs) occurred since the last visit.

Blood samples for plasma PK analysis, peripheral blood mononuclear cell (PBMC) Bruton's agammaglobulinemia tyrosine kinase (BTK) occupancy characterization were drawn prior to and/or following doses at prespecified timepoints.

Safety was evaluated by means of occurrence of AEs, clinical laboratory tests (serum chemistry, hematology, coagulation, urinalysis), vital signs measurements, 12-lead electrocardiograms (ECGs), and physical examinations.

Number of study participants:

A total of 24 healthy participants (12 participants of Japanese ancestry in Cohort 1 and 12 Caucasian participants in Cohort 2) were planned to be enrolled at a single center in the United States. A total of 23 healthy participants (11 participants of Japanese ancestry and 12 Caucasian participants) were enrolled.

Diagnosis and criteria for inclusion:

Enrolled in this study were participants with Japanese ancestry and Caucasians (including Hispanics) aged 18 to 75 years of age (inclusive) at the time of screening.

Study products

Rilzabrutinib were supplied as 100 mg tablets and 400 mg caplets in white plastic bottles with child-resistant induction-sealed caps.

Duration of study intervention:

Cohort 1 (Japanese healthy participants) treatments:

・Period 1 (100 mg single dose on Day 1).

・Period 2 (200 mg single dose on Day 5).

・Period 3 (400 mg twice daily [BID] × 4 days [beginning on Day 9] plus the morning dose on Day 13).

Cohort 2 (Caucasian healthy participants) treatments:

・Period 1 (400 mg BID × 4 days [beginning on Day 1] plus the morning dose on Day 5).

Criteria for evaluation:

Pharmacokinetics:

Plasma PK parameters, including the following, were calculated for total rilzabrutinib after a single dose or multiple doses, as appropriate:

- maximum plasma concentration (Cmax)
- time to maximum plasma concentration (tmax)
- area under the plasma concentration-time curve from zero to the last measurable concentration (AUC0-last)
- area under the plasma concentration-time curve from zero to infinity (AUC0-inf)
- area under the plasma concentration-time curve from zero during the dosage interval (AUC0-τ)
- terminal elimination phase half-life (t1/2)
- apparent total clearance of drug from plasma after oral administration (CL/F)
- apparent volume of distribution after oral administration (Vd/F)
- dose proportionality
- accumulation ratio (Rac)

Safety:

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 examinations

Pharmacodynamics (PD): rilzabrutinib BTK occupancy in peripheral blood mononuclear cells (PBMCs) at specified timepoints **Plasma PK parameters**, including Cmax, tmax, AUC0-last, AUC0-inf, AUC0-τ, and t½
Statistical methods: **Pharmacokinetics:** Pharmacokinetic parameters were calculated from plasma rilzabrutinib concentrations using standard noncompartmental methods and included Cmax, tmax, AUC0-last, AUC0-inf, AUC0-τ, t½, CL/F, Vd/F, dose proportionality, and accumulation ratio Rac as appropriate. Plasma concentrations of rilzabrutinib were listed and computed. PK parameters were listed and summarized using descriptive statistics by dosing group and cohort. Individual and mean plasma concentration versus time data were presented graphically. Clinical safety data were summarized using descriptive statistics. Safety data were tabulated by dosing group and cohort, and individual participant data were provided in listings. No formal hypothesis testing was planned. Change from baseline for quantitative safety data were summarized using appropriate descriptive statistics. In addition, shift tables were provided for clinical laboratory tests, vital signs measurements, and 12-lead ECGs. Treatment-emergent adverse events (TEAEs) were coded using the most current version of Medical Dictionary for Regulatory Activities (MedDRA) version 23.1 and summarized by cohort for the number of participants reporting the TEAE and the number of TEAEs reported. A by-participant AE data listing including verbatim term, coded term, treatment, severity, and relationship to intervention were provided.

Summary Results:

Demographic and other baseline characteristics:

Overall, the majority of Japanese participants were males (8 participants [72.7%]), and the majority of Caucasian participants were females (7 participants [58.3%]). In Caucasian participants, the majority were of Hispanic or Latino ethnicity (8 participants [66.7%]). The mean BMI in Japanese participants was 24.55 kg/m2 while in Caucasian participants it was 27.58 kg/m2. The demographic characteristics were well balanced between the two cohorts.

Safety results:

The incidence of all TEAEs reported during the study was higher in Caucasian participants as compared to Japanese participants. Gastrointestinal (GI) disorders were the most common TEAEs occurring in 2 (18.2%) of 11 participants (Period 2) and 4 (36.4%) of 11 participants (Period 3) in Japanese cohort and in 10 (83.3%) of 12 participants in the Caucasian cohort. Of the GI disorders, diarrhoea was the most common, 1 event occurring in 1 (9.1%) of 11 participants (Period 2) and 5 events occurring in 4 (36.4%) of 11 participants (Period 3) in the Japanese cohort. The occurrence of diarrhoea was higher in the Caucasian cohort with 10 events occurring in 9 (75%) of 12 participants. No TEAEs were reported during Period 1 in Cohort 1 participants. One of 2 TEAEs (Period 2) and 8 of 9 TEAEs (Period 3) reported by participants in Cohort 1 and 24 out of 26 TEAEs reported by 11 participants in Cohort 2, were considered related to rilzabrutinib. All TEAEs were considered mild in severity except for 1 TEAE of moderate gout reported by 1 participant in the Japanese cohort in Period 2.

No deaths, serious adverse events (SAEs) or AEs leading to discontinuation of rilzabrutinib occurred during the study.

Pharmacokinetic results:

Single Dose

Following single doses of 100, 200, and 400 mg rilzabrutinib in Japanese participants, exposure (C_{max} and AUC) increased slightly greater than dose proportionally. Variability was relatively high with geometric percent coefficient of variation CV% ranging from 67 to 136%. Geometric mean $t_{½}$ of rilzabrutinib ranged from 2 to 3 hours across the dose range and was similar. The geometric mean CL/F and V_d/F were similar with all three doses of rilzabrutinib.

Following single doses of 100, 200 and 400 mg rilzabrutinib in Japanese participants, metabolite exposure (C_{max} and AUC) increased approximately dose proportionally. The variability was high with geometric CV% ranged from 53% to 121% for the 100, 200 and 400 mg dose levels. Geometric mean $t_{½}$ of metabolite was approximately 5 to 6 hours for the 100 and 200 mg dose levels, respectively. The geometric mean metabolite ratio for $AUC_{0\text{-}inf}$ (Rmet_AUC_{inf}) was 3.11 and 2.51 for the 100 and 200 mg dose levels, respectively.

Metabolite SCN formation was much higher following single doses of 100, 200 and 400 mg in Japanese participants than metabolite and the parent rilzabrutinib. Metabolite SCN exposure parameters were reported; however, they do not reflect a true measurement from a typical monotonic patterned PK profile. Terminal phase (λz) estimates were not obtained for metabolite SCN; therefore, $AUC_{0\text{-}inf}$ and $t_{½}$ were not estimated.

Multiple Dose

Following administration of 400 mg rilzabrutinib BID in Japanese and Caucasian participants, rilzabrutinib peak plasma concentrations occurred at a median tmax of 1.5 to 2.3 hours when administered as a single dose or following multiple doses. The rilzabrutinib geometric mean Cmax and AUC parameters were slightly higher for Japanese participants compared to Caucasian participants following single dose. Multiple dose rilzabrutinib Cmax and AUC parameters were approximately 14% to 30% lower for Japanese participants compared to Caucasian participants. Rilzabrutinib variability for exposure parameters for both Japanese and Caucasian participants was high at 68% to 136% following single and multiple dose administration. Geometric mean $t_{½}$ estimated after the last dose was 8.28 hours and 7.01 hours for Japanese and Caucasian participants, respectively. Geometric mean CL/F and V_d/F values were approximately 50% higher for Japanese participants compared to Caucasian participants, after the last dose. Accumulation of rilzabrutinib was observed for both cohorts over time. Geometric mean RacCmax and RacAUCtau were 1.60 and 1.74 for Japanese participants and 2.28 and 2.42 for Caucasian participants.

Following administration of 400 mg rilzabrutinib BID in Japanese and Caucasian participants, metabolite peak plasma concentrations occurred at a median t_{max} of 2.5 to 3.0 hours when administered as a single dose or following multiple doses. Metabolite geometric mean C_{max} and AUC parameters were comparable for Japanese and Caucasian participants following single dose. Multiple dose metabolite C_{max} and AUC parameters were higher for Caucasian participants compared to Japanese participants. The geometric CV% for exposure parameters ranged from 32% to 121%. Metabolite geometric mean $t_{½}$ estimated after the last dose was approximately 8 hours for Japanese and Caucasian participants, and was similar to the parent, rilzabrutinib. Metabolite to parent ratios for AUC values were approximately 1.5- to 2.7-fold of rilzabrutinib for Japanesevand Caucasian participants following single and multiple doses respectively.

Following administration of 400 mg rilzabrutinib BID in Japanese and Caucasian participants, metabolite SCN peak plasma concentrations occurred at a median t_{max} of 0.57 to 2.5 hours when administered as a single dose or following multiple doses. Geometric mean C_{max} values were comparable for the first and last doses to Japanese and Caucasian participants, but again, the PK profiles were a series of multiple peaks rather than a true C_{max}. The geometric CV% for C_{max} ranged from 15% to 29% across visit and ethnicity. While the AUC appeared comparable between Japanese and Caucasian participants following single and multiple dose administration, the variability ranged from 4% to 176%. Lambda z (λz) estimates were not obtained for metabolite SCN; therefore, $AUC_{0\text{-}inf}$ and $t_{½}$ were not estimated. The geometric mean metabolite to parent ratios were high ranging from 143 to 662 for AUC parameters.

Pharmacodynamic results:

Overall, the results from the BTK occupancy analysis in PBMCs suggested after 400 mg BID first dose, Caucasian participants have 15% higher BTK occupancy than Japanese participants at 1.5 hours and 12 hours. Large variability was observed in Japanese participants (%CV >80%). At 400 mg BID last dose (steady state), BTK occupancies were comparable for the Japanese and Caucasian participants. The BTK occupancy in PBMCs initially increased after each dose and then gradually decreased in both the cohorts.

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