Sponsor: Sanofi **Drug substance(s):** rilzabrutinib	**Study Identifiers:** Not applicable **Study code:** PRN1008-015/POP17292

Title of the study:

A Two Part Phase 1, Open-Label Study of the Absorption, Metabolism, Excretion and Absolute Bioavailability of [^{14}C]-PRN1008 in Healthy Male Subjects

Study center(s):

This study was conducted at 1 center in United States

Study period:

Study initiation date: 31 December 2019 (signed informed consent)

Study completion date: 12 March 2020 (last participant last visit)

Study Status: Completed

Phase of development: Phase 1

Objectives:

Primary:

- To determine the absolute oral bioavailability of PRN1008 in healthy male subjects (Part 1)
- To characterize the intravenous (IV) pharmacokinetics (PK) of [^{14}C]-PRN1008 in healthy male subjects (Part 1)
- To assess the mass balance recovery from excreta after a single oral dose of [14C]-PRN1008 in healthy male subjects (Part 2)
- To determine the routes and rates of elimination of [^{14}C]-PRN1008 in healthy male subjects (Part 2)
- To characterize the PK of PRN1008 and total radioactivity following oral administration of [^{14}C]-PRN1008 in healthy male subjects (Part 2)

Secondary:

- To evaluate the safety and tolerability of PRN1008 in healthy male subjects (Parts 1 and 2)
- To investigate the metabolic profile of [^{14}C]-PRN1008 in plasma, urine, and feces following oral administration in healthy male subjects (Part 2 only)
- To characterize the PK of metabolites (PRN618, metabolite, PRN1186, and others, if applicable) following oral administration of PRN1008 in healthy male subjects (Part 2 only).

Methodology:

This was a single-center, open-label, non-randomized, 2-part study. Part 1 of the study aimed to evaluate the absolute oral bioavailability of a single oral dose of PRN1008 using an IV microtracer dose. Part 2 of the study aimed to characterize the absorption, metabolism, and excretion of a single oral dose of 300 mg [^{14}C]-PRN1008.

Number of study participants: It was planned to enroll 2 groups of healthy male subjects (Part 1, N = 8 and Part 2, N = 10). In total, 18 subjects entered and completed the study as planned. Data for all subjects entered into the study were included in the PK and safety analyses.
Diagnosis and criteria for inclusion: Healthy male subjects of any ethnic origin, aged between 18 and 60 years, inclusive, and with a body mass index between 18 and 35 kg/m^2, inclusive.
Study products Part 1 On the morning of Day 1, subjects were administered a single oral dose of 400 mg PRN1008 tablet, plus an IV microtracer dose of [^{14}C]-PRN1008 (100 µg in approximately 2 mL) containing ~37.0 kBq (~1 µCi) [^{14}C], administered as an IV push over an approximately 2-minute period, after an overnight 10-hour fast. Part 2 On the morning of Day 1, all subjects received a single oral dose of approximately 300 mg in 100 mL [^{14}C]-PRN1008 liquid formulation, containing ~37.0 MBq (~1000 µCi) [^{14}C], after an overnight 10-hour fast.
Duration of study intervention: Single oral doses were administered in both parts of the study. The IV microtracer dose was administered at 120 minutes post-administration of the single oral dose.

Criteria for evaluation:

Pharmacokinetics:

Parts 1 and 2

For Part 1, plasma samples were collected for the analysis of concentrations of PRN1008 and [^{14}C]-PRN1008. For Part 2, plasma samples were collected for the determination of concentrations of PRN1008 (and metabolites if applicable), total radioactivity (plasma and whole blood), and metabolite profiling and identification.

In Part 1, the following PK parameters were calculated based on plasma concentrations of oral PRN1008 and IV [^{14}C]-PRN1008: maximum observed plasma concentration (C_{max}), time of the maximum observed plasma concentration (T_{max}), area under the plasma concentration-time curve from time 0 to the last quantifiable concentration ($AUC_{0\text{-}last}$), area under the plasma concentration-time curve from time zero extrapolated to infinity ($AUC_{0\text{-}inf}$), apparent terminal elimination half-life ($t_{1/2}$; whenever possible), absolute bioavailability (F), total clearance (CL; [^{14}C]-PRN1008 only), and volume of distribution (Vz; [^{14}C]-PRN1008 only).

Part 2 only

Bile samples (N=2) were collected for the analysis of total radioactivity, metabolite profiling and identification, and [^{14}C]-PRN1008. Continuous urine and fecal samples were collected for analysis of total radioactivity, metabolite profiling and identification, and determination of concentrations of PRN1008 (urine only). Other accidental sources of elimination (e.g., emesis) were collected for the analysis of total radioactivity.

In Part 2, the following PK parameters were determined from the plasma concentrations of PRN1008 and whole blood and plasma concentrations of total radioactivity; C_{max}, T_{max}, $AUC_{0\text{-}last}$, $AUC_{0\text{-}inf}$, $t_{1/2}$, apparent total plasma clearance (CL/F; PRN1008 only), apparent volume of distribution during the terminal elimination phase (V_z/F; PRN1008 only), $AUC_{0\text{-}inf}$ Blood/Plasma Ratio, and $AUC_{0\text{-}inf}$ Plasma PRN1008/Total Radioactivity Ratio. The following PK parameters were calculated based on the concentration of PRN1008 and metabolites, if available, in urine: amount excreted in urine per sampling interval (A_{eu}), cumulative A_{eu}, renal clearance (CL_R; PRN1008 only), percentage of dose excreted in urine (f_{eu}), cumulative f_{eu}.

The following metabolite profiling and identification parameters were also determined for Part 2: f_{eu}, percentage of dose excreted in feces (f_{ef}), and percentage of dose excreted in bile (f_{eb}; where applicable).

Safety:

Adverse events (AEs), vital signs, 12-lead electrocardiogram (ECG), clinical laboratory evaluations, and physical examination.

Statistical methods:

All PK concentrations and parameters were listed and summarized. Plasma PK concentrations were graphically represented with an arithmetic mean (+ standard deviation) plot and a concentration-time profile by subject (linear and semi-logarithmic scales). Summary tables are provided for all PK parameters, with the exception of regression-related PK parameters. Separate summary tables by part and time interval are provided for excretion parameters and cumulative excretion parameters.

In Part 1, a mixed-effect analysis of variance model was applied to the log-transformed dose-normalized (DN) $AUC_{0\text{-}last}$ and $AUC_{0\text{-}inf}$ of PRN1008 obtained after oral dosing and that of the IV administered [^{14}C]-PRN1008. The model contained formulation (oral or IV) as a fixed effect and subject as a random effect. The absolute bioavailability was expressed as the geometric least squares mean ratio of the formulations (oral:IV) along with its corresponding 90% confidence interval (CI).

No formal statistical analyses were performed in Part 2 of the study. All PK parameters and concentrations for PRN1008, [^{14}C]-PRN1008, and total radioactivity in plasma and whole blood were summarized and listed.

No inferential statistical analyses were performed for safety and tolerability data.

Summary Results:

Pharmacokinetics Results:

In Part 1, PRN1008 was rapidly absorbed and eliminated following oral administration of a single dose of 400 mg PRN1008, with a median T_{max} of 2.03 hours and a geometric mean (coefficient of variation [CV%]) $t_{1/2}$ of 3.20 (51.0%) hours. Following IV administration of a single microtracer dose of ~100 µg [^{14}C]-PRN1008 (~1 µCi), the Cmax of [^{14}C]-PRN1008 was observed within 5 minutes after the start of the IV push, after which plasma concentrations of [^{14}C]-PRN1008 rapidly declined with a geometric mean (CV%) $t_{1/2}$ value of 1.78 (37.6%) hours. As expected, PRN1008 absorption, based on the DN AUC parameters, was lower for the tablet formulation than for the IV formulation; GLSM ratios (90% CI) for DN $AUC_{0\text{-last}}$ and DN $AUC_{0\text{-inf}}$ between the tablet and IV formulations were 0.0473 (0.0315, 0.0713) and 0.0471 (0.0314, 0.0707), respectively. Within-subject variability was moderate (45.3% and 45% for DN $AUC_{0\text{-last}}$ and DN $AUC_{0\text{-inf}}$, respectively).

Geometric mean (CV%) V_z was 149 L (28.4%).

In Part 2, PRN1008 was characterized by rapid absorption in the systemic circulation following a single oral dose of 300 mg [^{14}C]-PRN1008, with a median T_{max} of 1.00 hour in plasma, followed by a rapid elimination phase, with a geometric mean $t_{1/2}$ of 2.45 hours in plasma. Maximal levels of total radioactivity in plasma and blood peaked after PRN1008 T_{max} and elimination was far slower; geometric mean $t_{1/2}$ values of total radioactivity in plasma and blood were 182 hours and 176 hours, respectively. For radioactivity in blood and plasma, all subjects had a $t_{1/2}$ calculated over a span of time less than 2 times the resulting $t_{1/2}$; thus, data should be interpreted with caution.

The mean whole blood/plasma ratio for total radioactivity was 0.786 for $AUC_{0\text{-last}}$, indicating low association of radioactivity with red blood cells. The mean $AUC_{0\text{-last}}$ for PRN1008 in plasma was approximately 0.3% of that for total radioactivity in plasma, suggesting that metabolites play a major role in contributing towards the circulating total radioactivity in plasma.

In the mass balance and excretion portion of Part 2, following oral dosing, the primary route of elimination of total radioactivity was in the feces; for non-bile collection subjects, a mean of 87.0% of the administered radioactivity was recovered in feces and 5.25% was recovered in urine. Most of the administered radioactivity was recovered in the first 168 hours postdose (92.1%). For bile collection subjects, a mean of 72.7% of the administered radioactivity was recovered in feces, 5.42% was recovered in urine, and 6.29% was recovered in bile. Most of the administered radioactivity was recovered in the first 192 hours postdose (87.1%). The overall mean recoveries of radioactivity in urine, bile (as applicable), feces, and vomitus samples were 92.9% (non-bile subjects) and 87.6% (bile collection subjects) over the 312-hour study (28 days for 2 subjects), with recovery in individual non-bile collection subjects that ranged from 89.8% to 94.2%. Overall individual recoveries from bile collection subjects were 94.8% and 80.4%.

PRN1008 underwent extensive metabolism in human subjects after an oral dose of [^{14}C]-PRN1008. This metabolism produced 46 radiolabeled components, of which, 25 metabolites were identified or characterized. PRN1008 was a trace radiolabeled component in plasma and accounted for 0.760% of total plasma radioactivity exposure. M1 was the most abundant radiolabeled component in plasma and accounted for 94.2% of total plasma radioactivity exposure. M was a minor plasma metabolite that accounted for 1.09% of total plasma radioactivity exposure. Cumulatively, metabolites of PRN1008 accounted for approximately 95% of total plasma radioactivity exposure.

[^{14}C]-PRN1008-derived radioactivity was excreted primarily in feces (approximately 86% of dose) and to a lesser extent in urine (approximately 5% of dose) and bile (approximately 6% of dose). PRN1008 was a minor component for non-bile collection subjects in feces (9.02% of dose) and a trace component in bile (0.239% of dose); PRN1008 was not detected in urine. In comparison, metabolites of PRN1008 accounted for approximately 3.8% of dose in urine, approximately 4.2% of dose in bile, and approximately 63.0% of dose in feces.

Safety results:

PRN1008 was well tolerated in both parts of the study. Overall in Part 1 of the study, 2 of 8 subjects (25%) experienced a total of 3 treatment-related treatment-emergent adverse events (TEAEs), and in Part 2 of the study, 6 of 10 subjects (70%) reported a total of 13 treatment-related TEAEs. The most frequently reported class of treatment-related TEAEs was gastrointestinal disorders, reported by 2 subjects (25%) in Part 1 of the study, and 6 subjects (60%) in Part 2 of the study.

Across the entire study, all TEAEs were mild in severity, with the exception of 1 moderate TEAE (viral infection) that was assessed as not related. No subject discontinued treatment or withdrew from the study because of an AE. There were no clinically significant

findings from clinical laboratory evaluations, vital signs measurements, 12-lead ECG assessments, or physical examinations noted during the study.
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