Sponsor: Sanofi **Drug substance(s):** rilzabrutinib	**Study Identifiers:** Not applicable **Study code:** PRN1008-004/PKM17285

Title of the study:

A Phase 1, Single-Center, Open-label Study to Evaluate the Pharmacokinetics of PRN1008 in Healthy Male and Female Volunteers

Study center(s):

This study was conducted at 1 center in Australia

Study period:

Study initiation date: 03 June 2015 (signed informed consent)

Study completion date: 01 July 2015 (last participant last visit)

Study Status: Completed

Phase of development: Phase 1

Objectives:

Primary:

To evaluate the relative bioavailability of a single oral dose of PRN1008 when administered as a liquid formulation and a capsule formulation in the fasted state.

Secondary:

To assess the safety and tolerability of single oral doses of PRN1008 when administered as a liquid and a capsule formulation in healthy subjects.

Methodology:

This clinical study was a single-centre, two-period, open-label study to investigate the single dose pharmacokinetics (PK) of PRN1008 300 mg when administered as a liquid formulation compared to a capsule formulation under fasted conditions.

Participants were screened for participation in the study within 28 days before dosing. Participants were admitted to the study unit the day before dosing (Day -1), then dosed in the mornings of Days 1 and 3, and were to remain in the clinic up to Day 4, after collection of the final PK sample.

Participants were randomized to one of the two possible orders in which the following treatments were completed. Doses were to be approximately 48 hours apart:

- Treatment A:

Immediately prior to and following a single oral 300 mg dose of PRN1008 liquid formulation, blood samples were to be obtained over a period of 24 hours for determination of the PRN1008 PK profile

- Treatment B:

Immediately prior to and following a single oral 300 mg dose of PRN1008 capsule formulation, blood samples were to be obtained over a period of 24 hours for determination of the PRN1008 PK profile

Note that Treatment A and Treatment B are denoted Treatment 1 and Treatment 2 in the Study Protocol. 'Treatment A' and 'Treatment B' are used in this Study Report for clarity with Treatment Order AB and Treatment Order BA used hereinafter.

Following discharge from the study unit, subjects were to return for a follow-up assessment 7 ± 2 days after final study drug administration.

Number of study participants:

Number planned: 12 healthy participants

Number analysed: 12 (Safety Population)

12 (PK Population, Capsule formulation)

11 (PK Population, Liquid formulation)

Diagnosis and criteria for inclusion:

To be eligible for this study, participants must have been healthy males or healthy nonpregnant non-lactating females, aged between 40 and 75 (inclusive), with a body mass index (BMI) of ≥18.0 and ≤35.0 kg/m^2 (inclusive) and a minimum body weight of 45 kg. All participants must have been willing to comply with the study procedures and restrictions.

Study products

Treatment A: single oral 300 mg dose of PRN1008 liquid formulation

Treatment B: single oral 300 mg dose of PRN1008 capsule formulation

Duration of study intervention:

Single administration on Day 1 and single administration on Day 3

Criteria for evaluation:

Safety:

Specific assessments to evaluate treatment safety included the following: the frequency, severity and type of adverse events (AEs), clinical laboratory testing, physical examination, 12-lead electrocardiograms (ECGs), vital signs and review of concomitant medications.

Pharmacokinetics:

Primary PK outcome measures included the following: relative oral bioavailability (area under the plasma concentration-time curve [AUC], maximum observed plasma concentration [C_{max}]) of PRN1008 when administered as a capsule (test formulations) compared to a liquid (reference formulation), and single dose PK of PRN1008, including C_{max}, time of observed maximum plasma concentration (T_{max}), AUC and plasma terminal elimination half-life ($t½$).

Statistical methods:

Safety and Tolerability

Quantitative safety data were to be summarised by descriptive statistics (simple counts, arithmetic mean, standard deviation, median, minimum, and maximum) by treatment group. Summaries were also to be presented for the change from baseline, when appropriate.

Pharmacokinetics:

Plasma concentrations and the computed PK parameters were to be listed for PRN1008. Individual and mean concentration versus time data were to be plotted on linear and semi-logarithmic scales. Summary statistics of PK parameters (primary and secondary) were to be presented for each treatment period including means, geometric means, standard deviations, coefficient of variation (CV), medians and ranges, as appropriate. Plasma PK parameters were to be estimated using standard non-compartmental methods using validated software.

Geometric mean ratios and 90% confidence limits of plasma AUC and C_{max} by formulation were to be computed. Analysis of variance (ANOVA) was to be applied to the log-transformed primary PK parameters. Additional summaries or analyses could be applied to the data as appropriate.

Plasma PK parameters to be determined were C_{max}, AUC from time zero to infinity ($AUC_{0-\infty}$), AUC from time zero to the time of the last measurable concentration (AUC_{0-last}), T_{max}, $t½$ and other PK parameters as needed.

Summary Results:

Pharmacokinetics Results:

The median PRN1008 T_{max} was less than 2 hours for both liquid and capsule formulations. The arithmetic mean PRN1008 C_{max} and AUC0-∞ were approximately 16% and 15% lower for the capsule formulation as compared to the liquid formulation. The PRN1008 geometric mean ratios for $AUC_{0-\infty}$, AUC_{0-last} and C_{max} were less than 70% for the capsule formulation relative to the liquid formulation, respectively.

Safety results:

All 12 participants who enrolled into the study were included in the Safety Population. All participants received at least one dose of PRN1008 300 mg: 11 participants received one dose of PRN1008 liquid formulation, and all 12 participants received one dose of PRN1008 capsule formulation.

A total of 38 treatment-emergent AEs (TEAEs) were reported by 12 (100%) of the 12 participants during the study. Ten (10) participants reported 22 TEAEs that were judged to be related to study medication. There were no deaths, Serious Adverse Events (SAEs) or withdrawals due to AEs in the study.

Occurrence of TEAEs and drug-related TEAEs were greater in participants following administration of PRN1008 300 mg liquid formulation (91% and 64% of study population, respectively), compared with PRN1008 300 mg capsule formulation (67% and 42%, respectively). Eight TEAEs were classified as moderate TEAEs, three following PRN1008 300 mg liquid formulation administration and five following PRN1008 300 mg capsule administration. Only one of the moderate TEAEs (nausea) was reported as related to study drug, which occurred following administration of the capsule formulation and resolved without intervention. All other TEAEs were assessed as mild.

Following PRN1008 300 mg liquid formulation administration, seven (64%) participants reported throat irritation, three (27%) participants reported headache, two (18%) participants reported diarrhoea and two (18%) participants reported nausea. Of these, the seven reports of throat irritation, one headache and two reports of nausea were considered to be related to study drug. All other TEAEs were reported in one participant only.

Following PRN1008 300 mg capsule administration, three (25%) participants reported headache, three (25%) participants reported diarrhoea and two (17%) participants reported nausea. Of these, one case of diarrhoea and both reports of nausea were considered to be related to study drug. All other TEAEs were reported in one participant only.

Haematology, biochemistry and coagulation parameters were measured throughout the study. There were no clinically significant abnormal laboratory findings. The number of participants whose laboratory results were flagged as lower or higher than normal range for any laboratory parameter, and the mean change from Baseline in each parameter, was low following administration of either PRN1008 formulation.

No noteworthy change in heart rate was observed within the 3 hours following PRN1008 liquid or capsule formulation administration (PRN1008 liquid formulation pooled population: mean change from baseline of -0.7, -2.3 and -3.5 bpm at 1.5, 2 and 3 hours post-dose, respectively; PRN1008 capsule formulation pooled population:+0.1, +2.0 and -0.8 bpm, respectively). Both PRN1008 300 mg formulations induced a mild increase in heart rate by 24 hours after dose, at which point PRN1008 plasma concentration is negligible. Both treatment formulations led to an increase in RR interval by 2 hours post-dose compared with pre-dose (+37.4 ms [PRN1008 liquid formulation]; +24.7 ms [PRN1008 capsules]). All other vital signs, ECG or physical examination abnormalities were negligible and there were no clinically significant vital signs, ECG or physical examinations findings for either study formulation.

Overall, PRN1008 300 mg liquid formulation and capsule formulation were safe and well tolerated in this healthy population. Given that there were seven instances of throat irritation and TEAEs affecting 91% of the study population following PRN1008 liquid formulation administration, compared with no instances of throat irritation and TEAEs affecting 64% of the study population following PRN1008 capsule formulation, in general, PRN1008 300 mg was better tolerated in capsule formulation.

Issue date: 01-Dec-2025