Sponsor: Sanofi **Drug substance(s):** rilzabrutinib	**Study Identifiers:** Not applicable **Study code:** PRN1008-006/PKM17286
Title of the study: Relative Bioavailability and Effect of Food and Esomeprazole on the Pharmacokinetics of PRN1008 in Healthy Volunteers	
Study center(s): This study was conducted at 1 center in Australia	
Study period: Study initiation date: 24 August 2015 (signed informed consent) Study completion date: 22 Sept 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 compared to a tablet formulation in the fasted state • To compare the impact of food on the pharmacokinetics of a tablet formulation of PRN1008 • To evaluate the effect of a Proton Pump Inhibitor (esomeprazole) on the pharmacokinetics of PRN1008 tablet formulation **Secondary:** To assess the safety and tolerability of single oral doses of PRN1008 when administered orally as a liquid and a tablet formulation, and in combination with a Proton Pump Inhibitor in healthy participants	

Methodology:

This clinical study was a single-centre, four-period, open-label, complete crossover study to investigate the single dose pharmacokinetics (PK) of PRN1008 300 mg when administered as a liquid formulation compared to a tablet formulation under fasted conditions. In addition, the study investigated the effect of a meal on the single dose pharmacokinetics of PRN1008 when administered as a tablet formulation, and the effect of prior administration of a proton pump inhibitor (esomeprazole) on the single dose pharmacokinetics of PRN1008 when administered as a tablet formulation.

Participants were screened for participation in the study within 28 days prior to dosing. Participants were admitted to the study unit the day before dosing (Day -1), then dosed in the mornings of Days 1, 3, 5 and 10, and were to remain in the clinic up to Day 11, after collection of the final PK sample.

Participants were randomized to one of six possible sequences in which there were one of three possible orders of treatment (1, 2 and 3) for the first three periods. All participants were then to receive Treatment 4 as the final treatment, such that the final period would be identical for all participants. Doses were to be administered approximately 48 hours apart, and treatments are listed below:

- Treatment 1:
  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. Participants were to be in a fasted state.
- Treatment 2:
  Immediately prior to and following a single oral 300 mg dose of PRN1008 tablet formulation, blood samples were to be obtained over a period of 24 hours for determination of the PRN1008 PK profile. Participants were to be in a fasted state.
- Treatment 3:
  Immediately prior to and following a single oral 300 mg dose of PRN1008 tablet formulation, blood samples were to be obtained over a period of 24 hours for determination of the PRN1008 PK profile. Participants were to be in a fed state.
- Treatment 4:
  Following collection of the final PK sample from Period 3, participants were to begin dosing esomeprazole 40 mg once daily in the morning, on Days 6 - 10. On Day 10, immediately prior to and following a single oral 300 mg dose of PRN1008 tablet formulation, blood samples were to be obtained over a period of 24 hours for determination of the PRN1008 PK profile. The Day 10 PRN1008 dose was to be administered in a fasted state.

There were 6 possible sequences in which treatments were to be completed:

- 1234
- 1324
- 2134
- 2314
- 3124
- 3214

Following discharge from the study unit, participants 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, Liquid formulation)

12 (PK Population, Tablet formulation, fasted)

12 (PK Population, Tablet formulation, fed)

12 (PK Population, Tablet formulation, fasted, with once daily 40 mg esomeprazole pre-dosing for 5 days)

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 18 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 1: single oral 300 mg dose of PRN1008 liquid formulation
- Treatment 2: single oral 300 mg dose of PRN1008 tablet formulation
- Treatment 3: single oral 300 mg dose of PRN1008 tablet formulation
- Treatment 4: multiple oral 40 mg doses of esomeprazole, administered once daily on days 6 – 10 (5 doses); single oral 300 mg dose of PRN1008 tablet formulation, on day 10Treatment A: single oral 300 mg dose of PRN1008 liquid formulation

Duration of study intervention:

Single administration of PRN1008 on Day 1, 3, 5 and 10. Single administration of esomeprazole on Day 6, 7, 8, 9, and 10.

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:

The primary PK study parameters were Area under the plasma concentration-time curve (AUC) from time zero extrapolated to infinity ($AUC_{0-\infty}$), AUC from time zero to the last measureable concentration (AUC_{0-last}) and maximum observed plasma concentration (C_{max}) of PRN1008 by formulation, and geometric mean ratios (90% confidence interval) were to be computed to determine the relative bioavailability of the tablet (test) compared to the liquid (reference) formulation. Other PK parameters were to be regarded as secondary variables. The secondary outcome measures of the study were safety and tolerability, including the assessment of physical examinations, ECGs, vital signs, clinical laboratory results and AEs.

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.

Plasma PK parameters to be determined were C_{max}, $AUC_{0-\infty}$, AUC_{0-last}, T_{max}, $t_{½}$ and other PK parameters as needed.

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.

Summary Results:

Pharmacokinetics Results:

Bioavailability of PRN1008 from the tablet formulation was decreased relative to the liquid formulation. The PRN1008 geometric mean ratios for $AUC_{0-\infty}$, $AUC_{0\text{-last}}$ and C_{max} were 70.8%, 70.5%, and 69.6% for the tablet formulation relative to the liquid formulation, respectively, under fasted conditions.

The median PRN1008 T_{max} was approximately 1.5 hours for all fasted treatments but 2.25 hours following PRN1008 tablet formulation administration under fed conditions. However, administration of the PRN1008 tablet in the presence of food had minimal impact on PRN1008 exposure relative to the fasted condition. The PRN1008 geometric mean ratios for $AUC_{0-\infty}$, $AUC_{0\text{-last}}$, and C_{max} were 97.2%, 97.1% and 98.8% for the tablet formulation under fed conditions relative to the tablet under fasted conditions, respectively.

Co-administration of PRN1008 with esomeprazole decreased PRN1008 exposures. PRN1008 geometric mean ratios for $AUC_{0-\infty}$, $AUC_{0\text{-last}}$, and C_{max} were 49.1%, 47.9%, and 45.4%, respectively, for PRN1008 administered with esomeprazole compared to the PRN1008 tablet administered alone under fasted conditions.

Safety results:

All 12 participants who enrolled into the study were included in the Safety Population. All participants received Treatment 1, Treatment 2, Treatment 3 and Treatment 4, thereby receiving a total of 1200 mg PRN1008, and 200 mg esomeprazole.

A total of 43 treatment-emergent adverse events (TEAEs) were reported by 12 (100%) of the 12 participants within 48 hours of drug administration, and 48 TEAEs were reported by 12 participants for the duration of the study. Within 48 hours of dosing, 9 participants reported 19 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.

Under fasting conditions, occurrence of TEAEs and drug-related TEAEs within 48 hours of dosing was greater in participants following administration of PRN1008 300 mg liquid formulation (Treatment 1; 83% and 75% of study population, respectively), compared with PRN1008 300 mg tablet formulation (Treatment 2; 67% and 25%, respectively). By contrast, occurrence of TEAEs and drug-related TEAEs within 48 hours of dosing following administration of PRN1008 300 mg tablet formulation under fed conditions (Treatment 3) was 17% and 0%, respectively, and following administration of PRN1008 300 mg tablet formulation under fasting conditions following pre-dosing with 40 mg esomeprazole once daily for 5 days (Treatment 4) was 33% and 0%, respectively.

One TEAE was classified as of moderate severity (elevated ALT). This TEAE occurred at Follow-up after all treatments, and was reported as related to study drug. The TEAE resolved without intervention. All other TEAEs were assessed as mild.

Following Treatment 1 (liquid formulation), five (42%) participants reported throat irritation, four (33%) participants reported nausea, two (17%) participants reported diarrhoea, two (17%) participants had vomiting and two (17%) participants reported catheter site pain. Of these, only catheter site pain was considered to be unrelated to study drug. Following Treatment 2 (tablet formulation), there were no reports of throat irritation. Three (25%) participants reported nausea and two (17%) participants reported catheter site pain. Of these, only the nausea TEAEs were considered to be related to study drug. No drug-related TEAEs were reported after administration of Treatment 3 or Treatment 4.

There were no SAEs or deaths during the study.

Haematology, serum chemistry, coagulation and urinalysis parameters were measured throughout the study. There were no clinically significant abnormal haematology, coagulation or urinalysis laboratory findings. One clinically significant serum chemistry finding was reported (elevated ALT at Follow-up, drug related, resolved without intervention).

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 throughout the study.

Minimal individual variations in vital signs were recorded throughout the study, and none of these changes were deemed to be clinically significant. No noteworthy change in heart rate was observed within the 3 hours following PRN1008 liquid or tablet formulation administration under fasting conditions (Treatment 1: mean change from baseline of 0.4, - 0.6, -0.8 and 12.4 bpm at

1.5, 2 and 3 hours post-dose, respectively; Treatment 2: +2.3, +1.5 and +0.4 bpm, respectively). By comparison, Treatment 3 was associated with an increase in heart rate of +6.5, +6.9 and +4.2 bpm at 1.5, 2 and 3 hours post-dose, respectively; whereas Treatment 4 was associated with a decrease in heart rate of -2.8, -4.3 and -5.4 bpm at 1.5, 2 and 3 hours post-dose, respectively. All treatments were associated with an increase in heart rate compared with Baseline by 24 hours post dose (+12.4, +6.0, +12.4 and +8.9 bpm for Treatments 1, 2, 3 and 4, respectively). No noteworthy mean changes from Baseline were detected following study drug administration and at 24 hours post-dose for either formulation in the pooled population for systolic or diastolic blood pressure, respiratory rate or body temperature.

Only one ECG finding was considered to be abnormal (Participant T561, prolonged PR interval at 2 hours post Treatment 1 administration), but did not represent a change from pre-dose. Mean RR interval and QT interval decreased at all time points after first receipt of study drug up to -156.4 ms and -22.2 ms by Follow-up compared to Baseline, respectively, and negligible changes in heart rate and QTcB were recorded throughout the dosing period but increased to +11.1 bpm and +12.0 ms, respectively, by Follow-up. Minimal treatment-specific effects on ECG readings were observed.

There were no abnormal physical examination findings.

Overall, PRN1008 300 mg liquid and tablet formulations were safe and well tolerated under fasting and fed conditions in this healthy population, and PRN1008 300 mg tablet formulation was well tolerated under fasting conditions following pre-dosing with 40 mg esomeprazole once daily for 5 days. Given that there were five instances of throat irritation, TEAEs affecting 83% of the study population and an increased number of participants with out of normal range haematology parameters following PRN1008 liquid formulation administration under fasting conditions (Treatment 1), compared with no instances of throat irritation and TEAEs affecting 67% of the study population following PRN1008 tablet formulation under fasting conditions (Treatment 2), in general, PRN1008 300 mg was better tolerated in tablet formulation. The safety profile of PRN1008 further improved when PRN1008 tablet formulation was administered with food. Given no drug-related TEAEs were recorded within 48 hours following Treatment 4, no safety concern with co-administration of esomeprazole is inferred.

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