Sponsor: Sanofi **Drug substance(s):** rilzabrutinib	**Study Identifiers:** Not applicable **Study code:** PRN1008-011/INT17290
Title of the study: A Phase I Study of the Relative Bioavailability of Two PRN1008 Tablet Formulations, Effect of PRN1008 on Midazolam Pharmacokinetics, and Impact of Famotidine on PRN1008 Pharmacokinetics in Healthy Subjects	
Study center(s): This study was conducted at 1 center in Australia	
Study period: Study initiation date: 22 February 2018 (signed informed consent) Study completion date: 19 April 2018 (last participant last visit) Study Status: Completed	
Phase of development: Phase 1	
Objectives: **Primary:** • To evaluate the relative oral bioavailability of single oral doses of two novel tablet formulations of PRN1008 compared to a Reference Formulation in the fasted state • To evaluate the impact of PRN1008 on the pharmacokinetics (PK) of oral midazolam, a CYP3A probe substrate • To explore the impact of famotidine, an H2-receptor antagonist, on the PK of PRN1008 **Secondary:** • To assess the safety and tolerability of single oral doses of two novel tablet formulations and one reference tablet formulation of PRN1008 when administered to healthy participants • To assess the safety and tolerability of co-administering PRN1008 with midazolam and famotidine • To explore the potential impact of formulation on Bruton's tyrosine kinase (BTK) occupancy	

Methodology:

This was a single center, four-period, open-label, randomized, complete cross-over study in healthy adult participants to compare the relative bioavailability of single oral doses of two novel formulations of PRN1008 (Test Formulation #1 and Test Formulation #2) to that of an existing tablet formulation (PRN1008 Reference Formulation) administered to participants in the fasted state. The study also aimed to evaluate any potential impact of PRN1008 on the PK of oral midazolam and to explore the impact of famotidine on the PK of PRN1008. The safety and tolerability of Test Formulation #1 and Test Formulation #2 compared to the PRN1008 Reference Formulation was assessed. Additionally, the safety and tolerability of co-administration of PRN1008 with midazolam and famotidine was assessed. Evaluation of a potential formulation effect on BTK occupancy was also investigated.

Consenting participants were screened for up to 29 days prior to dosing and those that met the eligibility criteria were enrolled and randomized on Day -1 to one of six sequences, each containing four treatments over four dosing periods. Participants were admitted to the clinical research unit (CRU) on Day -2, and remained in the CRU until the last PK sample draw on Day 8. A final end of study (EOS) follow-up visit occurred on Day 15 (±2 days).

All participants received a single 2 mg oral dose of midazolam (1 mg/mL solution) on Day -1. PRN1008 (Test Formulation #1, Test Formulation #2 or Reference Formulation) treatment administration occurred as per the assigned sequence on days 1, 3, 5 and 7 involving administration of one of the following treatments:

Treatment 1: Single 400 mg oral dose of PRN1008 (Reference Formulation) with simultaneous administration of a single 2 mg oral dose of midazolam

Treatment 2: Single 400 mg oral dose of PRN1008 (Test Formulation #1) with simultaneous administration of a single 2 mg oral dose of midazolam

Treatment 3: Single 400 mg oral dose of PRN1008 (Test Formulation #2) followed by a single 2 mg oral dose of midazolam 2 hours later.

Treatment 4: Participants received single 20 mg oral doses of famotidine in the evening of days 5, 6, and 7. On Day 7, participants received two 400 mg oral doses of PRN1008 (Reference Formulation), one in the morning and a second in the evening (approximately 12 hours after the morning dose).Participants then received a final famotidine dose 2 hours after the evening PRN1008 dose. All participants received Treatment 4 in dosing Period 4 following an overnight fast.

All treatments were administered following an overnight fast of at least 10 hours with doses administered approximately 48 hours apart for the first three treatments.

Participants who completed the study were to have received all four treatments.

Beginning on Day 1, dosing occurred according to a participant's randomized assignment to one of the following sequences

Sequence	**Dosing Period**			
Sequence A	1	2	3	4
Sequence B	**Treatment**			
A	1	2	3	4
B	1	3	2	4
C	2	1	3	4
D	2	3	1	4
E	3	1	2	4
F	3	2	1	4

Number of study participants:

Number of planned participants: 14

Number of enrolled participants: 14

Safety analysis set: 14

Pharmacokinetic analysis set: 14

Pharmacodynamics analysis set: 14

Diagnosis and criteria for inclusion:

To be eligible for this study, participants met the following main inclusion criteria:

- Healthy adult males or females (non-pregnant, non-lactating) aged 18 to 75 years, inclusive
- In general good health, with no history or presence of any other medical condition that made the participant unsuitable for the study, in the opinion of the Investigator
- Body mass index (BMI) ≥18 and ≤35 kg/m2 and a minimum body weight of 45 kg
- Negative urine drug and alcohol breath testing at Screening and Admission (Day -2)
- Were willing to abstain from consuming grapefruit- or Seville orange-containing products from Day -14 to EOS

All participants understood the study requirements and the treatment procedures, and were willing to comply with all restrictions. Participants provided written informed consent before any study-specific tests or procedures were performed.

Study products

PRN1008 (Reference Formulation)

PRN1008 Reference tablets contained either 100 mg or 300 mg of PRN1008 drug substance.

PRN1008 Reference Tablets (100 mg and 300 mg) were packaged in 75 mL white high-density

polyethylene (HDPE) bottles with child-resistant induction sealed caps containing 35 tablets and a 1 g desiccant. The bottles were stored at 2–8 °C.

PRN1008 (Test Formulation #1, from micronized drug substance)

PRN1008 Test Formulation # 1 contained 400 mg of PRN1008 drug substance, micronized. In addition, the tablet contained Microcrystalline Cellulose (filler), Crospovidone (disintegrant), and Sodium Stearyl Fumarate (lubricant). The 400 mg tablets were orange film-coated oval tablets, packaged in 75 mL white HDPE bottles with child-resistant induction sealed caps containing

35 tablets and a 2 g desiccant. The bottles were stored at 2–8 °C.

PRN1008 (Test Formulation #2, from precipitated drug substance)

PRN1008 Test Formulation # 2 contained 400 mg of PRN1008 drug substance, precipitated. In addition, the tablet contained Microcrystalline Cellulose (filler), Crospovidone (disintegrant), and Sodium Stearyl Fumarate (lubricant). The 400 mg tablets were orange film-coated oval tablets, packaged in 75 mL white HDPE bottles with child-resistant induction sealed caps containing 35 tablets and a 2 g desiccant. The bottles were stored at 2–8 °C.

Midazolam

Midazolam is commercially available in Australia and was supplied by Alphapharm Pty Limited. A 2 mg solution (1 mg/mL solution) was administered at Day -1 and in Periods 1-3 under fasting conditions with 240 mL non-carbonated water.

Famotidine

Famotidine is commercially available in Australia and was supplied by Apotex Pty Ltd. A 20 mg tablet was administered in Period 4 under fasting conditions with 240 mL non-carbonated water.

Duration of study intervention:

Up to 44 days (± 2 days) from Screening through to study completion.

Criteria for evaluation:

Safety:

The safety and tolerability of PRN1008 were investigated according to the following specific assessments: vital signs (systolic and diastolic blood pressure, heart rate, body temperature, and respiratory rate), clinical laboratory tests (hematology, coagulation, serum chemistry, and urinalysis), physical examination, and assessment of AEs.

Serology for Hepatitis B surface antigen (HBsAg), hepatitis C virus (HCV) antibodies and anti-human immunodeficiency virus (HIV)-1 and HIV-2 antibodies were determined at Screening.

Pregnancy testing was conducted for participants who were WOCBP at Screening, Day -2 and Follow-up. Post-menopausal status was confirmed through testing of FSH levels at Screening. A urine drug screen and alcohol breath test was conducted at Screening.

Vital signs were measured at Screening, Admission (Day -2), and in the mornings post-dose on days 2, 4, 6, 8, and EOS. In addition, vital signs were taken at 60 minutes prior to and 4 hours after each PRN1008 dose on days 1, 3, 5, and 7. Vital signs were also taken 60 minutes before and after each midazolam dose on days -1, 1, 3, and 5. Blood pressure and heart rate were taken after remaining for 5 minutes in a seated or semi-supine position.

Blood and/or urine samples for serum chemistry, hematology, coagulation, and urinalysis were collected for laboratory testing at Screening, Day -2, post-dose on days 4 and 7, and at EOS. Additional blood or urine samples were taken at the discretion of the Investigator if the results of any test fell outside the laboratory reference ranges, or clinical symptoms necessitated additional testing to monitor participant safety.

A standard 12-lead ECG was recorded after remaining in a semi-supine position for at least 10 minutes at multiple time points throughout the study. Heart rate, QT interval, PR interval, QRS duration, RR interval, and QTc (corrected) were evaluated by the Investigator.

A complete physical examination (consisting of a check of the following body systems: general appearance, skin, eyes, ears, nose, throat, heart, abdomen, neurological system, lymph nodes, spine & extremities [skeletal]) was performed at Screening, Admission (Day -2), and EOS, and a symptom-directed chest/breast examination was performed if indicated by a report from the participant. An abbreviated physical examination (consisting of general appearance, abdomen, and cardiorespiratory examination) was performed on days 1, 2, 3, 4, 5, 6, 7, and 8.

Results of physical examination, vital signs and laboratory tests were recorded, and values outside of the laboratory reference ranges were documented together with Investigator comments as to their clinical significance.

Elicitation of AEs and serious adverse events (SAEs) occurred at each interaction with the participant and AEs were recorded from the time of Informed Consent until the end of the post-treatment follow-up or until they had returned to baseline status or stabilized. The information on each AE or SAE included duration (start and stop time and date), severity, action taken, outcome and causality.

The safety and tolerability endpoints for the study included:

- The results of physical examinations, ECGs, vital signs, clinical laboratory tests and AEs

Pharmacokinetics (PK):

Blood samples for analysis of PRN1008 (Test Formulation #1, Test Formulation #2 and Reference Formulation) and midazolam PK were collected at multiple time points throughout the study at <15 minutes pre-dose, and within ±5 minutes of the scheduled time post-dose until 4 hours and then within ±10 minutes of scheduled time thereafter. Where PK sampling time points for midazolam and PRN1008 coincided (i.e., periods 1 and 2 only), a single blood sample of 4 mL was sufficient for both analyses.

The PK endpoints included:

- Relative oral bioavailability (area under the curve [AUC] from time zero extrapolated to infinity [$AUC_{0-\infty}$] and from time zero until the last measurable concentration [AUC_{0-last}], maximum serum concentration [C_{max}]) of PRN1008 when administered as a tablet (Reference Formulation) compared to Test Formulations #1 and #2

- Single dose PK of PRN1008, including plasma C_{max}, time to maximum concentration (T_{max}), AUC and plasma half-life (t½) when administered as a tablet (Reference Formulation) compared to Test Formulations #1 and #2
- Impact of PRN1008 formulations on midazolam PK, including the impact of dosing midazolam two hours after PRN1008. The primary PK parameters of midazolam and its metabolite α-hydroxymidazolam included $AUC_{0-\infty}$, AUC_{0-last}, C_{max}, T_{max}, and $t_{1/2}$.
- Impact of famotidine on the PK of PRN1008 ($AUC_{0-\infty}$, AUC_{0-last}, C_{max}, T_{max}, and $t_{1/2}$) when famotidine is administered the evening prior to PRN1008 and when famotidine is administered two hours after PRN1008

Pharmacodynamics (PD):

Blood samples for determination of BTK occupancy in peripheral blood mononuclear cells (PBMCs) were collected pre-dose and at 4, 8, and 12 hours post PRN1008 dosing on days 1, 3, and 5 in periods 1-3 only. All BTK occupancy samples were collected within <15 minutes pre-dose, and post-dose ±5 minutes of the scheduled time until 4 hours and then within ±10 minutes of scheduled time after 4 hours.

The PD endpoints were:

- To assess the impact of PRN1008 on BTK occupancy in PBMCs

Statistical methods:

Safety

Safety data were presented for all participants included in the Safety population.

Data for participant disposition, demographics and baseline characteristics, medical history, prior and concomitant medications, AEs, clinical laboratory tests, vital signs, ECG and other safety variables were presented for individual participants in data listings (including assessments of abnormality and clinical significance, where applicable).

Prior and concomitant medications were coded using the World Health Organization Drug Dictionary (WHO-DDE) Version March-2017. Prior medication and concomitant medications were listed and summarized, separately. Prior medications were summarized by assigned treatment sequence, whilst concomitant medications were summarized by treatment.

All AEs were coded using the Medical Dictionary for Regulatory Activities (MedDRA 20.1). Incidence of AEs as well as the severity, relationship to treatment, outcome, and actions taken were presented for each participant. In addition, listings of AEs leading to discontinuation of the study, SAEs, and deaths, were provided as applicable.

Each AE was assigned into one of six treatment periods – midazolam only, Treatment 1, 2, 3, 4, and famotidine only. Treatment-emergent adverse events (TEAEs) were listed and summarized by severity and relationship to study drug, overall and by system organ class (SOC) and preferred term (PT) per each treatment period. In addition, TEAEs related to PRN1008, midazolam, and famotidine were summarized by severity, overall and SOC and PT, separately.

Clinical laboratory findings, vital signs and ECG parameter results were listed and summarized descriptively by treatment and protocol-specified collection time point. Change from baseline to scheduled measurements were summarized descriptively for clinical laboratory findings, vital signs and ECG. Clinical assessment of the clinical laboratory findings, vital signs and ECG (i.e., Normal, Abnormal not clinically significant [NCS], Abnormal clinically significant [CS]) were summarized, by treatment and protocol-specified time point, using frequency tabulations. In addition, shift from baseline for clinical laboratory findings, vital signs and ECG by treatment sequence are presented.

PK

The PK endpoints defined in the clinical protocol and associated analyses are summarized in this clinical study report and are presented in detail in a separate PK report (Final Version, dated 28 August 2018).

Pharmacokinetic parameters for PRN1008 were determined by standard non-compartmental methods using appropriate software (Phoenix WinNonlin Version 8). Nominal time was used to calculate the PK parameters. Concentrations below the lower limit of quantification was set to 0 for PK parameter calculations.

The primary PK parameters of PRN1008 included $AUC_{0-\infty}$, AUC_{0-last}, C_{max}, T_{max}, and $t_{1/2}$, by formulation. The primary PK parameters of midazolam and its metabolite, α-hydroxymidazolam, included $AUC_{0-\infty}$, AUC_{0-last}, C_{max}, T_{max}, and $t_{1/2}$.

Mean-concentration-versus-time data were plotted on linear and semi-logarithmic scales. Summary statistics of PK parameters are presented for each treatment period including means, geometric means, standard deviations, coefficient of variation (CV), medians and ranges, as appropriate.

Geometric mean ratios and 90% confidence limits of AUC and Cmax by formulation were computed to determine the relative bioavailability of the two Test Formulation 400mg tablets compared to the Reference Formulation (1 x 100 mg + 1 x 300 mg tablets). Analysis of variance (ANOVA) was applied to the log-transformed primary PK parameters. Additional summaries or analyses were applied to the data as appropriate.

PRN1008 PK when administered with famotidine were summarized, but no formal statistical comparisons were conducted.

Geometric mean ratios and 90% confidence intervals of AUC and Cmax were calculated for midazolam and α-hydroxymidazolam with and without PRN1008 for each treatment formulation.

PD

The exploratory secondary endpoints defined in the clinical protocol and associated analyses, including the assessment of PD effects of PRN1008 in the BTK occupancy assay, are summarized in this clinical study report and are presented in detail in a separate PD report (DVR0382; dated 18 July 2018).

Pharmacodynamic parameters were summarized by cohort using descriptive statistics (arithmetic means, SD, sample size [N]).

Summary Results:

Pharmacokinetics Results:

The results of this study demonstrate that the relative oral bioavailability of both PRN1008 Test Formulation #1 and Test Formulation #2 are generally similar to the Reference Formulation (PRN1008 tablet).

In addition, administering PRN1008 at least 2 hours before an H2-receptor antagonist was sufficient to mitigate the observed modest reduction in exposure associated with medications which reduce gastric pH. Administration of PRN1008 in the morning after an evening dose of famotidine resulted in a modest reduction in PRN1008 exposure. These results also demonstrate that the impact of an H2-receptor antagonist on reducing PRN1008 exposure is less significant compared to prior experience with the proton-pump inhibitor esomeprazole (Study PRN1008-006), which is likely related to the higher potency of proton-pump inhibitors in raising gastric pH.

Administration of PRN1008 increased the exposure of midazolam, a probe substrate for CYP3A. These results are consistent with *in vitro* liver microsome data, which demonstrate PRN1008 to be a CYP3A inhibitor. The effect on midazolam was more pronounced when midazolam was given 2 hours after PRN1008 compared to simultaneous dosing. When midazolam was administered 2 hours after a 400 mg dose of PRN1008, midazolam exposure increased by approximately 2-fold.

Based on the current Food and Drug Administration (FDA) criteria, a 400 mg dose of PRN1008 is classified as a weak inhibitor of drugs which are metabolized by CYP3A.

In addition, administration of PRN1008 the morning following an evening dose of famotidine demonstrated a modest reduction in exposure, whereas administering PRN1008 2 hours prior to famotidine had no clinically relevant impact on PRN1008 PK.

Safety results:

PRN1008 was safe and well tolerated when administered to these healthy adult volunteers in all three formulations (Test Formulation #1, Test Formulation #2 and Reference Formulation) when co-administered with midazolam or famotidine. These conclusions were based on the following findings from all 14 enrolled participants:

- There were no SAEs, life-threatening events or deaths throughout the study.
- No TEAE led to premature withdrawal of any participant from the study or to discontinuation of the study drug.
- The incidence of TEAEs was similar for Treatments 1, 2, and 3 (PRN1008 Reference Formula, Test Formulation #1, and Test Formulation #2, respectively - all taken with midazolam) with 10 (71.4%) participants reporting at least one TEAE for each treatment. The incidence was slightly lower for Treatment 4 (Reference Formulation and famotidine) with 8 (57.1%) participants reporting at least one TEAE.
- There were no patterns of note associated with TEAEs or treatment-related TEAEs by treatment sequence.
- A total of 20 events in 8 (57.1%) participants were deemed related to PRN1008 by the Investigator. The incidence of PRN1008-related TEAEs was slightly higher for Treatment 3 (Test Formulation #2 and midazolam), similar for Treatment 2 and 4 (Test Formulation #1 and midazolam, and Reference Formulation and famotidine, respectively) and lowest for Treatment 1 (Reference Formulation and midazolam).
- The only pattern of note in PRN1008-related TEAEs by SOC and PT by treatment was an increased frequency of gastrointestinal TEAEs following Treatment 3 (PRN1008 Test Formulation #2 and midazolam) and Treatment 4 (PRN1008 Reference Formulation and famotidine). In particular, would appear that Treatment 3 (PRN1008 Test Formulation #2 and midazolam) was slightly less tolerated compared to the other treatments groups.
- The maximum severity of TEAEs in the majority of treated participants was mild except for 1 (7.1%) participant that reported a moderate TEAE of vessel puncture site pain during administration of midazolam only (pre-PRN1008 treatment) deemed not related to midazolam, and 1 (7.1%) participant that reported a moderate TEAE of reduced visual acuity following Treatment 4 (PRN1008 Reference Formulation and famotidine) administration that was deemed related to treatment with famotidine. There were no severe TEAEs reported on study.

• There were no ECG or clinical laboratory AEs in this study and all ECG and individual laboratory abnormalities were considered by the Investigator to be not clinically significant. • Vital signs parameters for all participants were assessed as normal or not clinically significant. • The only physical examination finding not present at baseline was associated with a TEAE that was deemed unrelated to study drug.
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