Sponsor: Sanofi **Drug substance(s):** rilzabrutinib	**Study Identifiers:** Not applicable **Study code:** PRN1008-008/PKM17289
Title of the study: A Phase 1, Single-Center, Open-label Study to Evaluate the Safety and Pharmacokinetics of Two Tablet Formulations of PRN1008	
Study center(s): This study was conducted at 1 center in Australia	
Study period: Study initiation date: 26 August 2016 (signed informed consent) Study completion date: 24 October 2016 (last participant last visit) Study Status: Completed	
Phase of development: Phase 1	
Objectives: **Primary:** To evaluate the relative oral bioavailability of a single oral dose of PRN1008 when administered as animmediate release (IR) and delayed release (DR) tablet formulation in the fasted state. To assess the effect of food on the pharmacokinetics (PK) of single oral doses of the DR tabletformulation. **Secondary:** To assess the safety and tolerability of single oral doses of PRN1008 when administered as an immediate release (IR) and as a delayed release (DR) tablet formulation in healthy participants. To assess the pharmacodynamics (PD) effects of PRN1008 (Bruton's agammaglobulinemia tyrosine kinase (BTK) occupancy assay) when administered as an IR and as a DR tablet formulation.	

Methodology:

This study was a single-center, open-label, 4-period study to investigate the relative bioavailability of a single dose of PRN1008 when administered as an immediate release (IR) tablet formulation compared to a delayed release (DR) tablet formulation under fasted and fed conditions.

Participants were screened for study eligibility within 28 days of dosing.

Period 1

The objective of Period 1 was to investigate the PK of the 100 mg DR tablet formulation, administered at a dose of 200 mg. The PK profile determined in Period 1 informed the appropriate DR dosing for the relative bioavailability crossover portion of the study (Periods 2 to 4). Eligible participants were admitted to the study unit the day before dosing in Period 1 (Day -1). Following an overnight fast, participants received a single oral 200 mg dose of the DR tablet formulation (Treatment 1), and remained in the clinic until the final PK and PD samples were collected on the morning of Day 2. Following discharge, a follow-up call 7 ± 2 days after Period 1 study drug administration was scheduled to monitor participant safety and to facilitate the collection of adverse events (AEs).

Periods 2, 3 and 4

Initial dosing was followed by a washout period of up to 28 days to allow review of the safety and tolerability data, and PK and PD parameters of the DR tablet formulation administered in Period 1. Following data review, the Sponsor and Principal Investigator (PI) confirmed a dose of 400 mg DR for use in Periods 2, 3 and 4. The dose of PRN1008 for the DR formulation selected for Periods 2, 3 and 4 did not exceed the previously established tolerated dose level of 800 mg and was chosen to approximate the expected exposure ($AUC_{0-\infty}$)of the IR tablet reference formulation.

Participants were re-admitted to the study unit the day before dosing in Period 2 (Day -1) and those who continued to be eligible received Treatment 2, Treatment 3 and Treatment 4 (see treatment description below), approximately 72 hours apart, in the sequence determined at randomization and as summarized below.

Treatment 2 (Test Formulation Fasted):

A single oral 400 mg dose of PRN1008 administered as DR tablet (4 x 100 mg tablet) under fasted conditions.

Treatment 3 (Test Formulation Fed):

A single oral 400 mg dose of PRN1008 administered as DR tablet (4 x 100 mg tablet) under fed conditions.

Treatment 4 (Reference Formulation Fasted):

A single oral 400 mg dose of PRN1008 administered as an IR tablet (300 mg tablet and 100 mg tablet) under fasted conditions.

Treatment Sequence	Period 1	Period 2	Period 3	Period 4
Sequence A	Treatment 1 DR 200 mg Fasted	Treatment 2 DR 400 mg Fasted	Treatment 3 DR 400 mg Fasted	Treatment 4 IR 400 mg Fasted
Sequence B	Treatment 1 DR 200 mg Fasted	Treatment 2 DR 400 mg Fasted	Treatment 4 IR 400 mg Fasted	Treatment 3 DR 400 mg Fasted
Sequence C	Treatment 1 DR 200 mg Fasted	Treatment 4 IR 400 mg Fasted	Treatment 2 DR 400 mg Fasted	Treatment 3 DR 400 mg Fasted
Sequence D	Treatment 1 DR 200 mg Fasted	Treatment 4 IR 400 mg Fasted	Treatment 3 DR 400 mg Fasted	Treatment 2 DR 400 mg Fasted
Sequence E	Treatment 1 DR 200 mg Fasted	Treatment 3 DR 400 mg Fasted	Treatment 4 IR 400 mg Fasted	Treatment 2 DR 400 mg Fasted
Sequence F	Treatment 1 DR 200 mg Fasted	Treatment 3 DR 400 mg Fasted	Treatment 2 DR 400 mg Fasted	Treatment 4 IR 400 mg Fasted

Blood samples for analysis of PRN1008 PK and PD parameters were collected over each 24-hour post-dose period.

Following discharge from the study unit after Period 4, participants returned for a follow-up assessment 7 ± 2 days after the final administration of study drug.

Number of study participants:

Recruitment of 14 healthy adult male and female participants were planned for this study.

A total of 51 potential participants were screened and a total of 16 participants were enrolled into the study.

Two (2) participants were lost to follow-up and one participant withdrew consent.

Data is reported for the following analysis populations:

Safety population: 16 participants

PK population:

Treatment 1: 13 participants

Treatment 2: 14 participants

Treatment 3: 13 participants

Treatment 4: 14 participants

PD population:

Treatment 1: 13 participants

Treatment 2: 9 participants

Treatment 3: 7 participants

Treatment 4: 9participants

Diagnosis and criteria for inclusion:

This study was conducted in healthy adult male or non-pregnant, non-lactating females, aged from 18 to 65 years of age (inclusive) at the time of screening, with a BMI ≥ 18 and ≤ 35 (kg/m^2) (inclusive) and a minimum body weight of 45 kg.

Participants met all stated inclusion criteria and none of the exclusion criteria.

Participants had normal clinical laboratory values and parameters but were excluded if the history or presence of any other medical condition made them unsuitable for the study, as assessed by the PI.

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

Delayed Release (DR) formulation

The PRN1008 DR tablet formulation was administered orally.

Each PRN1008 DR tablet contained 100 mg of PRN1008 drug substance. In addition, the tablet contained Microcrystalline Cellulose (filler), Mannitol (filler), Croscarmellose Sodium (disintegrant), and Sodium Stearyl Fumarate (lubricant). The 100 mg DR tablets were oval, white and enteric-coated.

Reference therapy, dose and mode of administration:

This study evaluated the relative bioavailability and impact of food on a DR formulation of PRN1008 compared to the IR formulation which had been previously tested in Phase I and Phase II studies.

Immediate Release (IR) formulation

The PRN1008 IR tablet was administered orally.

Each PRN1008 film-coated tablet contained either 100 mg or 300 mg of PRN1008 drug substance. In addition, the tablet contained Microcrystalline Cellulose (filler), Croscarmellose Sodium (disintegrant) and Sodium Stearyl Fumarate (lubricant). The 100 mg tablet was a round shape and orange in color. The 300 mg tablet was an oval shape and was white in color.

Duration of study intervention:

Participants received single administration of PRN1008 DR formulation (Treatment 1) on Day 1 of Period 1.

Initial dosing was followed by a washout period of up to 28 days.

Single doses of PRN1008 DR or IR formulation (Treatment 2, Treatment 3 and Treatment 4) were given to participants on Day 1 of each treatment period, administered approximately 72 hours apart.

Criteria for evaluation:

Pharmacokinetics and Pharmacodynamics:

The PK and PD properties of PRN1008 were examined following dosing of participants with the IR or DR tablet formulations. Comparison of the relative bioavailability of PRN1008 administered under fed and fasted conditions was assessed for the DR tablet formulation.

Pharmacokinetic Assessments:

Blood samples for PK determination of PRN1008 in plasma were collected at each of the following treatment periods:

Period 1: A single oral 200 mg dose of PRN1008 DR formulation (2 x 100 mg tablets) was administered on Day 1 with a full glass of water following an overnight fast of at least 8 hours.

Period 2, 3 and 4: A single oral 400 mg dose of PRN1008 DR formulation (4 x 100 mg tablets) or IR formulation (1 x 300 mg; 1 x 100 mg tablet) was administered on Day 1 with a full glass of water following an overnight fast of at least 8 hours (Treatment 2; Treatment 4), or following a moderate fat meal (Treatment 3).

PK samples were collected pre-dose (< 15 minutes prior to dosing) and at 0.5, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 8, 10, 12 and 24 hours after dosing, as specified in the Schedule of Assessments Table. Samples were analyzed using validated assay methods (liquid chromatography tandem mass spectrometry [LC/MS/MS]).

Exploratory assessments of metabolites and/or isomers of PRN1008 in plasma or whole blood, as defined in the clinical protocol, was not undertaken.

Pharmacodynamic Assessments

Samples for exploratory assessments of PD response (as determined by BTK receptor occupancy in peripheral blood mononuclear cells (PBMCs), were collected pre-dose (< 15 minutes prior to dosing) and at 4, 8, 12, and 24 hours post-dose.

The exploratory secondary endpoints defined in the clinical protocol and associated analyses, including the assessment of PRN1008 in the BTK occupancy assay, are summarized in this study report and are presented in detail in a separate PD report (DVR0293, dated 2 February 2017).

Safety:

The safety and tolerability of PRN1008 in IR and DR tablet formulations were assessed by physical examination, monitoring vital signs, laboratory tests (hematology, serum chemistry, urinalysis and viral serology), electrocardiograms (ECGs) and AEs.

The PI and site staff were responsible for detection, documentation, and reporting of events that met the definition of an AE or serious adverse event (SAE). Elicitation of AEs and SAEs occurred at each interaction with the participant. The information on each AE or SAE included duration (start and stop time and date), severity, action taken, outcome and causality.

Review of all available safety and tolerability data, and PK and PD parameters from each study period was performed by the Sponsor's medical monitor, clinical pharmacology consultant, statistician, and the PI.

Statistical methods:

Pharmacokinetics:

Pharmacokinetic parameters were determined by standard noncompartmental methods.

Estimated PK parameters included the following:

- C_{max}: Maximum observed plasma PRN1008 concentration
- T_{max}: Time of maximum observed plasma PRN1008 concentration
- $t_{1/2}$: Terminal elimination half-life of PRN1008
- $AUC_{0-\infty}$: Area under the plasma PRN1008 concentration-time curve from time 0 extrapolated to infinity
- AUC_{0-last}: Area under the plasma PRN1008 concentration-time curve from time 0 to the last measureable concentration.
- CL/F: Apparent oral clearance for PRN1008
- Vz/F: Apparent volume of distribution for PRN1008

Individual and mean plasma PRN1008 concentration-versus-nominal time plots were created in both linear and semi-logarithmic scale for each treatment. Descriptive statistics (arithmetic means [mean], standard deviations [SDs], coefficients of variation [CVs], sample size [N], minimum [min], maximum [max], and median) were used to summarize the PK parameters by treatment. The same statistics were applied to individual plasma PRN1008 concentrations at each nominal time point. Geometric mean ratios and 90% confidence limits of $AUC_{0-\infty}$, AUC_{0-last}, and C_{max} by formulation were computed via a mixed model using logged parameters in Phoenix WinNonlin v7.0 (Pharsight Corporation, Cary, NC).

Pharmacodynamics:

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 (CSR) and are presented in detail in a separate PD report (DVR0293; dated 2 February 2017).

PD parameters were summarized by cohort using descriptive statistics (arithmetic means, standard deviations [SD], coefficients of variation [CV], sample size [N], minimum, maximum and median).

Additional exploratory analyses of PK/PD relationships were undertaken as appropriate.

Safety

Data for AEs, clinical laboratory tests, urinalysis and other safety variables were presented for individual participants in data listings (including assessments of abnormality and clinical significance, where applicable).

All AEs were coded using the Medical Dictionary for Regulatory Activities (MedDRA 18.0). 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.

Treatment-emergent AEs (TEAEs) were listed and summarized per treatment. The frequency of each AE was summarized by severity and relatedness to investigational product. Treatment emergent AE's were also summarized with frequency counts by system organ class (SOC; i.e. body system) and preferred term (PT), for each treatment dose group.

Clinical laboratory findings, ECGs, and vital signs were analyzed both separately, i.e. by formulation, and together, i.e. pooled data for both tablet formulations.

Summary Results:

Pharmacokinetics Results:

- All 14 enrolled participants were included in the PK analyses for comparison of Treatment 2 (400 mg PRN1008 DR tablet under fasted conditions) and Treatment 4 (400 mg PRN1008 IR tablet under fasted conditions), whereas 13 participants were included in the PK analyses of Treatment 1 (200 mg PRN1008 DR tablet under fasted conditions) and Treatment 3 (400 mg PRN1008 DR tablet under fed conditions).
- The median PRN1008 T_{max} was approximately 2 hours for both DR and IR tablet formulations under fasted conditions. The arithmetic mean PRN1008 C_{max} and AUC0-∞were decreased by approximately 58.4% and 47.7%, respectively, for the DR tablet compared to the IR tablet.
- Based on a comparison of the geometric mean ratios, the relative bioavailability of the DR tablet (test formulation) was determined to be approximately 52% compared to the IR tablet (reference formulation) under fasted conditions.
- Co-administration of the PRN1008 DR tablet formulation with food reduced exposures to 79.7% and 70.7% for $AUC_{0\text{-last}}$ and C_{max}, respectively, when compared to administration under fasted conditions. In addition, a delay in T_{max} (from 2 hours to 5 hours without and with food, respectively) was suggestive of a decrease

Pharmacodynamics results:

BTK occupancy in PBMC was demonstrated following administration of PRN1008, regardless of formulation or dose level. Compared to all other treatments, mean BTK occupancy was lowest at 4 and 8 hours post dose following administration of the 400 mg DR tablet formulation under fed conditions. Nevertheless, mean peak BTK occupancies of at least 70% were achieved at some point in all treatment groups over the 24 hour post dose assessment period.

Safety results:

PRN1008 when administered as an immediate release (IR) and as a delayed release (DR) tablet formulation under fed or fasted conditions was well tolerated in these healthy volunteers.

- Across all treatments, a total of 14 (87.5%) participants had at least one TEAE, with a total of 47 events reported. Of these, 10 (62.5%) participants had 29 TEAEs deemed by the PI to be treatment related.
- Whilst the highest frequency of TEAEs occurred with 200 mg DR (fasted) (Treatment 1) with 16 TEAEs in 8 (61.5%) participants, only 5 of these events in 3 (23.1%) participants were considered to be treatment related.
- Participants administered with the 400 mg DR tablet formulation under fasted conditions (Treatment 2) reported more events and more treatment related TEAEs compared to participants dosed with the same formulation and PRN1008 dose level after ingesting a moderate fat meal (Treatment 3).
- Half of all participants had TEAEs with the reference treatment (Treatment 4, 400 mg IR; fasted) with a total of 14 events reported in these 7 participants. Of these, 8 events were considered to be treatment related in 5 (35.7%) participants, which was similar to the DR 400 mg tablet formulation when administered under fasted conditions (Treatment 2).
- There were no SAEs or deaths during the study and no AEs led to discontinuation or withdrawal of any participant from the study.
- The most common TEAEs, regardless of causality, across all treatments were gastrointestinal disorders, nervous system disorders, musculoskeletal and connective tissue disorders, infections and infestations, and metabolism and nutrition disorders and psychiatric disorders. All other TEAEs by SOC across all treatments occurred in one participant.
- Treatment related diarrhea occurred with the highest frequency in participants following administration of the 400 mg IR tablet formulation under fasting conditions (Treatment 4; 5 [35.7%] participants with 5 events). In comparison, single treatment related events of diarrhea occurred in each of 3 (21.4%) participants following administration of the 400 mg DR tablet formulation after an overnight fast and in one participant per treatment following Treatment 1 (200 mg DR; fasted) and Treatment 3 (400 mg DR; fed). Two events of treatment-related nausea occurred in 2 participants at

Treatment 2 (400 mg DR; fasted) and in one participant following treatment with 400 mg IR under fasted conditions. Single treatment related events of abdominal discomfort occurred in one participant per treatment with the 400 mg DR tablet formulation (under fed and fasted conditions) and with the 400 mg IR tablet formulation administered after an overnight fast (Treatment 4). Treatment related vomiting only occurred with the 400 mg IR tablet formulation.

- There were no severe treatment related TEAEs. The majority of treatment related TEAEs in the SOC of gastrointestinal disorders were mild (Grade 1) and all resolved without intervention, however, one participant had a treatment related TEAE of vomiting of Grade 2 (moderate) intensity and another participant had moderate treatment related events of abdominal discomfort and diarrhea. All treatment related TEAEs of Grade 2 (moderate) intensity occurred with the 400 mg IR tablet formulation (administered under fasting conditions).
- Overall, treatment related gastrointestinal AEs occurred with higher frequency with the IR tablet formulation compared to the DR tablet formulation. Furthermore, whilst treatment related TEAEs occurred at a lower incidence with the low dose compared to the high dose DR tablet formulation, gastrointestinal tolerability was improved when the 400 mg DR tablet formulation was given with food.
- Treatment related TEAEs in the SOC of nervous system disorders occurred with the DR tablet formulation only. Mild treatment related TEAEs of headache, dizziness, presyncope and paraesthesia occurred in ≤2 participants each, all resolved without intervention.
- All other treatment-related TEAEs by SOC and PT occurred in one participant per treatment only, were of mild (Grade 1) intensity, and resolved without intervention.
- One participant (K3031) had a TEAE of neutropenia that was of Grade 3 severity at Treatment 4 (400 mg IR; fasted). The TEAE was considered unrelated to study treatment, no specific intervention was required and the AE resolved.
- With the exception of a single participant with unrelated Grade 3 neutropenia, clinically significant changes in hematological parameters did not occur in the majority of participants and were not observed in any participant following treatment with the DR formulation under fed or fasted conditions.
- There were no clinically significant derangements in biochemistry parameters or pattern of changes in laboratory values evident with PRN1008 dose level or formulation and no abnormal urinalysis findings of clinical significance during the study.
- Regardless of treatment period, there were no remarkable findings in this group of healthy volunteers with respect to vital signs, ECG assessments and physical examinations.

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