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| **Sponsor:** Sanofi<br>**Drug substance(s):** rilzabrutinib | **Study Identifiers:** Not applicable<br>**Study code:** PRN1008-014/PKM17291 |
| **Title of the study:**<br>A Two-Part Study to Assess the Effects of Ritonavir on PRN1008 Pharmacokinetics, and the Effects of PRN1008 on QTc Interval Compared to Placebo and Moxifloxacin in Healthy Participants | |
| **Study center(s):**<br>This study was conducted at 1 center in Australia | |
| **Study period:**<br>Study initiation date: 14 June 2018 (signed informed consent)<br>Study completion date: 17 December 2018 (last participant last visit)<br>Study Status: Completed | |
| **Phase of development:** Phase 1 | |
| **Objectives:**<br>**Primary:**<br>• To evaluate the impact of ritonavir co-administration on PRN1008 pharmacokinetics(PK)<br>• To assess the effect of therapeutic and supratherapeutic concentrations of PRN1008 onthe QT interval corrected for heart rate (HR) using Fridericia's formula (QTcF)<br>**Secondary:**<br>• To assess the safety and tolerability of single oral doses of PRN1008 administered alone and with ritonavir<br>• To assess the effect on the corrected QT (QTc) interval of a single oral dose of 400 mg moxifloxacin | |

**Methodology:**

PRN1008-014 was a single center, two-part study in healthy adult participants.

Participants were screened for up to 29 days prior to dosing on Day 1.

Part A:

Part A was a randomized, open label, 3-period, complete crossover study with a 7-day washout between treatment periods. Participants were to complete three (3) treatment periods in Part A of the study and were randomized to receive one of the following treatments in each treatment period:

- Treatment 1: single oral dose of 100 mg PRN1008 under fasting conditions
- Treatment 2: single oral doses of 100 mg PRN1008 tablet plus concomitant 100 mg ritonavir tablet under fasting conditions, with a second dose of 100 mg ritonavir only 12 hours after the first dose
- Treatment 3: single oral dose of 1200 mg (4 x 300 mg tablet) PRN1008 under fasting conditions

Note: Following gastrointestinal AEs of nausea, dizziness, vomiting and diarrhea experienced by 3 of the 4 participants dosed with the tablet formulation of PRN1008 1200 mg in Period 1 of Part A of the study, and following consultation with the Principal Investigator (PI), it was recommended that the PRN1008 1200 mg dose be removed for the remaining dosing treatments in Period 2 and Period 3. Therefore, the remaining 8 participants did not receive Treatment 3 (PRN1008 1200 mg) in periods 2 and 3. The 4 participants that received the 1200 mg dose in Period 1, completed the remaining treatment periods and the study.

For Part A, participants were admitted to the clinical research unit (CRU) on Day -1 in each treatment period to confirm study eligibility. Following an overnight fast, eligible participants were randomized to receive Treatment 1, 2, or 3 on Day 1 for Treatment Periods 1-3. Blood samples for PK analysis of PRN1008 were collected over the 24 hours post-dose. Participants were discharged from the CRU following the last PK sample collection on Day 2.

Participants returned to the CRU 4 days after discharge for follow-up safety assessments and check-in for the next treatment period.

Upon completion of Treatment Period 3, participants returned to complete a follow-up visit approximately 7 days (± 1 day) after the last dose of study drug.

The PK data from Part A was analyzed and the dose selected for Part B. Cardiodynamic ECG analysis was performed for Part B only.

Part B:

Part B was a randomized, blinded, single dose, placebo-controlled, double dummy, 4- -period, complete crossover study with a 7-day washout between treatment periods. Treatments 1 through 3 were blinded; Treatment 4 was open label. The doses of PRN1008 for Part B were selected and informed based upon data from Part A. The 1200 mg dose in Part A was not well tolerated and was subsequently dropped from Part A. A sentinel dosing approach was implemented in that the first 4 participants in Part B. Participants were dosed (one receiving each treatment) followed by a 48-hour safety assessment. Following the 48- hour safety assessment, the next 8 participants were dosed (n=2 receiving each treatment) followed by a 48-hour safety assessment. The remaining participants were then dosed according to the randomization schedule.

Ritonavir was over encapsulated for Treatments 1 through 3 to blind the treatment to study participants. PRN1008 placebo tablets (300 mg) were used in over encapsulation as the ritonavir placebo to match weight between active and placebo.

Participants were to complete four (4) treatment periods in Part B of the study and were randomized to receive one of the following treatments in each treatment period:

- Treatment 1 (Therapeutic dose): 400 mg (1 x 100 mg tablet and 1 x 300 mg tablet) PRN1008 and ritonavir placebo (1 x 300 mg PRN1008 placebo tablet encapsulated) under fasting conditions. A second dose of ritonavir placebo (1 x 300 mg PRN1008 placebo tablet encapsulated) was administered 12 hours after the morning dose

- Treatment 2 (Supratherapeutic dose): 400 mg PRN1008 (1 x 100 mg tablet and 1 x 300 mg tablet) PRN1008 with 100 mg ritonavir tablet (encapsulated). The supratherapeutic regimen was determined following review of Part A data. A second dose of 100 mg ritonavir (encapsulated) was administered 12 hours after the morning dose.
- Treatment 3 (Placebo): PRN1008 placebo (1 x 100 mg placebo tablet and 1 x 300 mg placebo tablet) and ritonavir placebo (1 x 300 mg PRN1008 placebo tablet encapsulated) under fasting conditions. A second dose of ritonavir placebo (1 x 300 mg PRN1008 placebo tablet encapsulated) was administered 12 hours after the morning dose.
- Treatment 4 (Open- label Positive control): Single oral 400 mg dose of Moxifloxacin (400 mg tablet) under fasting conditions

The central ECG laboratory (ERT) was blinded to treatment assignment.

Participants were admitted to the CRU on Day -2 prior to Period 1 of Part B. Following confirmation of study eligibility on Day -1, participants were randomized to treatment order, and baseline pretreatment ECGs were collected via Holter monitor. On Day 1 of each period, following an overnight fast, participants received Treatment 1, 2, 3, or 4, and blood samples PK analysis of PRN1008 were collected over a period of 24 hours. Participants remained in the unit and were discharged following the last PK sample collection on Day 2. Once discharged, participants then returned to the study unit 4 days later (on Day 6/Day -1 of the next treatment period) for follow-up safety assessments and to check-in for dosing in the next treatment period (Periods 2, 3, and 4).

Part B enrolment was to include approximately 40 participants to ensure 28 participants completed all 4 study periods but could exceed that number by 10% if there was a higher than anticipated drop-out rate prior to completion of all 4 treatment periods. Participants were randomized for order of Treatments 1 to 4.

Upon completion of Treatment Period 4, participants returned to complete a follow-up visit approximately 7 days (± 1 day) after the last dose of study drug.

**Number of study participants:**

Number of planned participants: 52 (12 for Part A, 40 for Part B)

Number of enrolled participants: 51 (12 for Part A, 39 for Part B)

Safety analysis set: 49 (12 for Part A, 37 for Part B)

Pharmacokinetic analysis set: 49 (12 for Part A, 37 for Part B)

**Diagnosis and criteria for inclusion:**

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

- Healthy adult male or non-pregnant, non-lactating females, 18 to 55 years of age (inclusive) at the time of screening
- Body mass index (BMI) ≥18 and ≤30 (kg/m2) (inclusive) and a minimum body weight of 45 kg
- Female subjects of childbearing potential with a negative pregnancy test who are not abstinent from heterosexual intercourse as part of their usual and preferred lifestyle must agree for the duration of active treatment to use two effective means of contraception (hormonal contraception methods that inhibits ovulation, intrauterine device, intrauterine hormone-releasing system, vasectomized partner, condoms). Unless surgically sterile, postmenopausal females had menopause confirmed by follicle-stimulating hormone (FSH) testing.
- Negative urine drug and alcohol breath testing at Screening and at each period check-in (Day -1 or Day -2)
- Willing to or had abstained from consuming grapefruit- or Seville orange-containing products from 14 days prior to first dose of study medication through follow-up

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** (100 mg and 300 mg tablets)

Each PRN1008 tablet contained either 100 mg or 300 mg of PRN1008 drug substance. All tablets contained microcrystalline cellulose (filler), crospovidone (disintegrant), sodium stearyl fumarate (lubricant), and a non-functional film coating. The formulation is designed for immediate release of PRN1008 drug substance.

Part A

It was planned that Participants in Part A received either single oral 100 mg or 1200 mg doses of PRN1008 under fasting conditions as follows:

| Treatment | PRN1008 Dose | Reference Therapy |
|---|---|---|
| Treatment 1 | PRN1008 100 mg (1x100 mg tablet) | - |
| Treatment 2 | PRN1008 100 mg (1x100 mg tablet) | 2 x single 100 mg oral doses of ritonavir (second dose administered 12 hours after the first) |
| Treatment 3* | PRN1008 1200 mg (4x300 mg tablet) | - |

*Treatment 3 was dropped from further dosing due to intolerance after the first 4 participants received treatment. The remaining 8 participants did not receive Treatment 3.

Part B

Participants in Part B received a single oral 400 mg dose of PRN1008 either with or without ritonavir following an overnight fast of at least 10 hours as follows:

| Treatment | PRN1008 Dose | Reference Therapy |
|---|---|---|
| Treatment 1 | PRN1008 400 mg (1x100 mg and 1x300 mg tablet) | 2 x single oral doses of ritonavir placebo (1 x 300 mg PRN1008 placebo tablet encapsulated) (second dose administered 12 hours after the first) |
| Treatment 2 | PRN1008 400 mg (1x100 mg and 1x300 mg tablet) | 2 x single oral 100 mg doses of ritonavir (second dose administered 12 hours after the first) |
| Treatment 3 | PRN1008 placebo (1x100 mg placebo tablet and 1x300 mg placebo tablet) | 2 x single oral doses of ritonavir placebo (1 x 300 mg PRN1008placebo tablet encapsulated) (second dose administered 12 hours after the first) |
| Treatment 4 | - | Single oral 400 mg moxifloxacin dose |

For Part B (Treatments 1, 2, and 3), participants were blinded to treatment. Ritonavir was over encapsulated to blind the treatment to study participants. PRN1008 placebo 300 mg tablets were used in over encapsulation as the ritonavir placebo. Treatment 4 was open label. Food was restricted until 4 hours post-dose for morning doses (not applicable for evening ritonavir doses). Water was restricted for 1 hour pre- and post-dose. Following PRN1008 or placebo administration, 240 mL non-carbonated water was taken. Participants remained in an upright position for at least 2 hours post-dose.

**PRN1008 Placebo** (100 mg and 300 mg tablets)

Each PRN1008 placebo tablet contained microcrystalline cellulose (filler), crospovidone (disintegrant), sodium stearyl fumarate (lubricant), and a non-functional film coating. PRN1008 placebo tablets are packaged in 60 mL white HDPE bottles containing 35 tablets and a 1 g desiccant.

**Ritonavir**

Ritonavir Norvir® 100 mg was used in this study. Ritonavir Norvir® was purchased through commercial sources and was provided by the investigational site.

Each ritonavir tablet contained 100 mg of ritonavir drug substance as well as copovidone, sorbitan laurate, calcium hydrogen phosphate (anhydrous), silica (colloidal anhydrous), and sodium stearyl fumarate.

The 100 mg tablets are film-coated with hypromellose, titanium dioxide (E171), macrogols, hydroxypropyl cellulose, talc, silica (colloidal anhydrous), and polysorbate 80.

Norvir® tablets are supplied in white high-density polyethylene (HDPE) bottles with polypropylene caps. There are no special storage conditions for this product.

**Ritonavir Placebo**

PRN1008 placebo 300 mg tablets were over encapsulated and used as the ritonavir placebo.

**Moxifloxacin**

Moxifloxacin Avelox® 400 mg was used in this study. Moxifloxacin Avelox® was purchased through commercial sources and was provided by the investigational site.

Each moxifloxacin tablet contained 400 mg moxifloxacin drug substance as well as microcrystalline cellulose, croscarmellose sodium, lactose monohydrate, and magnesium stearate.

The 400 mg tablets are convex in shape and red film-coated with hypromellose, macrogel 4000, ferric oxide (E172) and titanium dioxide (E171).

Avelox® tablets are supplied in cartons containing colorless or white opaque polypropylene/aluminum blisters. The tablets were not to be stored above 25°C.

**Duration of study intervention:**

Part A

Up to 50 days (± 1 day, from Screening through to study completion)

Part B

Up to 57 days (± 1 day, 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 BP, pulse rate, body temperature, and RR), clinical laboratory tests (hematology, biochemistry, coagulation, serology, and urinalysis), 12-lead ECG, 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 WOCBP at Screening, Day -1 for each treatment period and at follow-up. Postmenopausal status was confirmed through testing of FSH levels at Screening. A drug and alcohol screen were conducted at Screening and on Day -1 for each treatment period.

Vital signs were measured at Screening, following Admission for each treatment period (Day -1 or Day -2), 2 hours post-dose for each treatment period (Day 1), on Day 2, and at follow-up. Vital signs were taken after at least 10 minutes resting in a supine position.

Blood and/or urine samples for biochemistry, hematology, and urinalysis were collected for laboratory testing at Screening, following Admission for each treatment period (Day -1 or Day -2), post-dose on Day 2, and at follow-up.

A complete physical examination (general appearance, skin, eyes, ears, nose, throat, heart, abdomen, neurological system, lymph nodes, spine & extremities [skeletal]) was performed at Screening and follow-up. A symptom-directed chest/breast examination

was performed if indicated by a report from a participant. An abbreviated physical examination (general appearance, abdomen, and cardiorespiratory examination) was performed following Admission for each treatment period (Day -1 or Day -2).

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.

For Part A, single ECGs were obtained at Screening, and triplicate ECGs were obtained following Admission (Day -1), pre-dose (Day 1), 2, 4, and 8 hours post-dose for each treatment period, and at follow-up.

For Part B, single ECGs were obtained at Screening. Single "Safety ECGs" were obtained following Admission (Day -2 in Period 1 and on Day -1 in Periods 2-4), pre-dose- (Day 1), at 2, 4, and 8 hours post-dose in each treatment period, and at follow-up. ECG measurements were taken after resting for at least 10 minutes in a supine position.

Safety ECGs were collected prior to, or during the extraction period and ECG safety leads were required to be in place prior to the start of the Holter extraction.

During Part B, the cardiodynamic ECG assessments were analyzed by the ECG Core laboratory (ERT) from continuous 12-lead ECG recordings (Holter). Continuous Holter recordings were performed on Day 1 in each treatment period and at time-matched time points on Day -1 of Period 1. ECGs were extracted from the following times in relation to dosing on the day of dosing: -1.0, -0.75, and -0.5 hours (pre-dose) and 0.5, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 7, 8, 10, 12, 13, 14, 16, and 24 hours postdose. At time points for ECG extraction, subjects were to be resting supine for at least 10 minutes prior to and 5 minutes after the nominal time.

The results of the cardiodynamic evaluation were analyzed by a cardiac core laboratory, ERT in which 400 mg PRN1008, 400 mg PRN1008 plus ritonavir, placebo, and moxifloxacin (positive control) were given in separate, randomized periods to healthy subjects in a 4-way crossover design (ERT Cardiac Safety Report, Version 1.0, dated 18 March 2019 provided in Appendix 16.1.9). Elicitation of AEs 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. The information on each AE included duration (start and stop time and date), severity, action taken, outcome and causality.

**Pharmacokinetics:**

For Part A, blood samples (approximately 4 mL each) were collected to determine the plasma PK of PRN1008 within 15 minutes pre-dose and at 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12, and 24 hours post-dose.

For Part B, blood samples (approximately 4 mL each) were collected to determine the plasma PK of PRN1008 and moxifloxacin within 15 minutes pre-dose and at 0.5, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 7, 8, 10, 12, and 24 hours post-dose.

Plasma samples were analyzed using validated assay methods. Exploratory assessment of metabolites and/or isomers are not included in this report.

**Statistical methods:**

**Safety**

Safety (Part A and Part B)

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

Adverse events were coded using Medical Dictionary for Regulatory Activities (MedDRA®) Version 21.0. A by participant AE data listing, including verbatim term, preferred term (PT), system organ class (SOC), treatment, severity, and relationship to study drug, is provided. The number of participants experiencing treatment emergent AEs (TEAE) and number of individual TEAEs were summarized by treatment, SOC and PT. TEAEs were also summarized by severity and by relationship to study drug.

Laboratory evaluations are listed using the International System of Units (SI units) for each participant and summarized by assigned treatment sequence and protocol specified collection time point. A summary of change from baseline at each protocol specified time point is also presented. Shifts from baseline are also be presented by assigned treatment sequence and protocol specified collection time point.

Prior and Concomitant medications are listed by participant and coded using World Health Organization (WHO) drug dictionary, version MAR-2018. Prior medications are summarized by Anatomical Therapeutic Chemical (ATC) classification level 2 and

Preferred Name, by treatment sequence, while concomitant medications are summarized by ATC level 2 and preferred name, by treatment.

Physical examination results and medical history is listed by participant.

For Part A:

Vital signs assessments and ECG parameters are listed for each participant and summarized by treatment and protocol specified collection time point. A summary of change from baseline at each protocol specified time point is also presented for Part A. ECG parameters and change from baseline is also summarized by assigned treatment sequence. Shift from baseline for ECG clinical assessments is presented by treatment and assigned treatment sequence.

For Part B:

Vital signs assessments and ECG parameters are listed for each participant and summarized by treatment and protocol specified collection time point.

ECG Assessment (Part B only):

The primary cardiodynamic analysis by ERT was based on exposure response modeling of the relationship between PRN1008 and placebo-corrected change from baseline QTcF (ΔΔQTcF) (excluding an effect > 10 msec) at clinically relevant PRN1008 plasma concentrations.

If a substantial heart rate effect was observed on-treatment with PRN1008 (peak mean ΔΔHR greater than 10 bpm), drug-free QT/RR data was to be collected over a wide range of HR to allow the generation of individualized QT correction methods. QTc was calculated from Day -1 both during the periods of supine rest (QTcS) and from all evaluable QT/RR pairs in the 24-hour recording (QTcI). These data were used to obtain RR interval (HR) and QT data to enable derivation of QTcS, and QTcI. The correction method that results in the average sum of squared slopes closest to zero for PRN1008 and placebo were deemed the most appropriate HR correction method and were therefore used as the primary outcome measure.

Assay sensitivity was to be evaluated by exposure response analysis of the effect on ΔΔQTcF. Assay sensitivity was deemed as met if the slope of the exposure response relationship was statistically significant at 10% level of significance in a 2-sided test and the predicted QT effect (i.e. the lower bound of the 2-sided 90% confidence interval) was above 5 msec at the observed geometrical mean Cmax of 400 mg moxifloxacin.

In addition, the effect of PRN1008 on ΔΔQTcF was evaluated at each post-dose time point ('by time point' analysis) using the Intersection Union Test.

An analysis of categorical outliers was performed for changes in HR, PR, QRS, QTcF, T-wave morphology and U-wave presence.

**Pharmacokinetics**

Pharmacokinetic data were presented for all participants included in the PK population.

Plasma concentrations and the computed PK parameters are listed for PRN1008 (Part A and Part B) and moxifloxacin (Part B only). Individual and mean concentration-versus-time data are plotted on linear and semi-logarithmic scales. Summary statistics of PK parameters (primary and secondary) are presented for each treatment period, including means, geometric means, standard deviations (SD), coefficient of variation (CV), medians and ranges, as appropriate. Plasma PK parameters were estimated using standard noncompartmental PK methods. The primary PK parameters included Cmax, Tmax, AUC0-last, AUC0-∞, and t1/2. Other PK parameters could be determined as needed.

Geometric mean ratios and 90% confidence limits of AUC and Cmax were computed to compare PRN1008 exposure and rate with and without ritonavir. Analysis of variance (ANOVA) was applied to the log-transformed primary PK parameters.

**Summary Results:**

**Pharmacokinetics Results:**

**Part A**

Following completion of Part A of the study, the following PK conclusions were made:

- PRN1008 $C_{max}$ is reached approximately 1 hour post-dose when administered orally at a therapeutic dose of 100 mg. The $t_{1/2}$ was rapid, estimated to be approximately 1.6 hours.
- Following a supratherapeutic dose (1200 mg), PRN1008 $T_{max}$ was estimated to be 3 hours, with a $t_{1/2}$ of approximately 3.2 hours. These results, while highly variable, appear to be in line with previous results seen at this dose level.
- When low dose 100 mg PRN1008 was co-administered with ritonavir, a strong CYP3A4 inhibitor, PRN1008 $C_{max}$ and $AUC_{0-\infty}$ were increased by approximately 7.5-fold and 17.7-fold, respectively, confirming PRN1008 to be a substrate for CYP3A4.

**Part B**

Following completion of Part B of the study, the following PK conclusions were made:

- PRN1008 $C_{max}$ is reached approximately 2.1 hours post-dose when administered orally at a therapeutic dose of 400 mg. The $t_{1/2}$ was rapid, estimated to be approximately 3.1 hours.
- When 400 mg PRN1008 was co-administered with ritonavir, a potent CYP3A4 and Pgp inhibitor, PRN1008 $C_{max}$ and $AUC_{0-\infty}$ were increased by approximately 5.2-fold and 8.3-fold, respectively, confirming PRN1008 to be a substrate for CYP3A4 and Pgp. The PRN1008 plasma concentrations observed after co-administration of 400 mg PRN1008 with ritonavir are expected to be representative of the worst-case clinical scenarios of PRN1008 exposures in patients (i.e., supratherapeutic exposure levels above 400 mg).
- $T_{max}$ of moxifloxacin was reach after 2.08 hours post administration of a 400 mg oral dose under fasted conditions. Elimination appeared to be bi-phasic, with a median t½ of approximately 10 hours.

Following completion of Part B of the study, the following cardiodynamic conclusions were made:

- Mean placebo-corrected change from baseline (ΔΔHR) varied between -1.9 and 2.2 bpm across all post-dose time points on all treatments, demonstrating that PRN1008 at the studied doses did not have an effect on heart rate.
- PRN1008 at the studied doses did not have a clinically relevant effect on cardiac conduction, i.e., the PR and QRS intervals.
- In summary, PRN1008 at the studied doses did not have a clinically relevant effect on the studied ECG parameters.

**Safety results:**

**Part A**

Following completion of Part A of the study, it appears that PRN1008 was safe and well tolerated in these healthy male and female volunteers at a single oral dose of 100 mg administered under fasting conditions either with or without ritonavir (100 mg with a second 100 mg dose 12 hours after the first). Following gastrointestinal AEs of nausea, dizziness, vomiting and diarrhea experienced by 3 of the 4 participants dosed in Period 1 with the tablet formulation of PRN1008 1200 mg, and following consultation with the PI, it was recommended that the PRN1008 1200 mg dose be removed for the remaining dosing treatments in Period 2 and Period 3. The gastrointestinal (GI) intolerance was consistent with that previously reported in the PRN1008 1200 mg dose using the liquid formulation in a prior study (PRN1008-001). It was determined that the nausea and vomiting could affect heart rate interpretation and, therefore, it was determined that the 1200 mg dose was not viable as an option for the purpose of

enabling a possible supratherapeutic dose for testing the effect of PRN1008 on QT in Part B. In addition to the GI intolerance observed at 1200 mg dose, post-study PK analysis of PRN1008 demonstrated less than proportional increases in exposure between 400 mg and 1200 mg, hence the 1200 mg dose was considered insufficient to obtain adequate supratherapeutic exposures of PRN1008 for assessment of cardiodynamics in Part B.

These conclusions were based on the following findings from all 12 enrolled participants:

- There were no serious adverse events (SAEs), life-threatening TEAEs, or TEAEs leading to death reported for Part A of the study.
- No TEAE in Part A led to study drug interruption or withdrawal and no TEAE led to the premature withdrawal of any participant from the study. The 4 participants receiving the 1200 mg dose in Period 1 completed the remaining treatment sequences and the study.
- Across all treatments, 66.7% of participants reported at least one TEAE. By treatment, the frequency was highest following Treatment 3 (PRN1008 1200 mg) at 75.0% following by Treatment 2 (PRN1008 100 mg plus ritonavir 100 mg) at 45.5% and Treatment 1 (PRN1008 100 mg) at 16.7%.
- The majority of TEAEs were mild, regardless of causality, and there were no severe TEAEs reported. One participant receiving 1200 mg had moderate events of nausea, vomiting and was given intravenous (IV) fluids with resolution of the events within 6 hours.
- The AEs were consistent with what has been reported for the 1200 mg dose using the liquid formulation in a prior study (PRN1008-001), and the GI intolerance observed was sufficient such that the PRN1008 1200 mg dose was dropped for subsequent dosing treatments in Period 2 and Period 3 and not taken forward as the supratherapeutic dose to achieve the objectives for Part B. There were no other patterns of note in the display of TEAEs, regardless of assigned treatment or treatment sequence.
- Of the TEAEs deemed related to treatment with PRN1008, the majority occurred following Treatment 3 (PRN1008 1200 mg) with 5 events in 3 (75.0%) participants compared to 1 event 1 (9.1%) participant following Treatment 2 (PRN1008 100 mg plus ritonavir 100 mg). There were no PRN1008-related TEAEs reported following Treatment 1 (PRN1008 100 mg).
- The majority of PRN1008-related TEAEs were mild and there were no severe PRN1008-related TEAEs. There were 3 moderate PRN1008-related TEAEs in 1 (25.0%) participant following Treatment 3 (PRN1008 1200 mg) only.
- There were no clinically significant and/or study drug-related changes in vital signs, ECG parameters, or laboratory values.

**Part B**

Compared to placebo and moxifloxacin, PRN1008 was less well tolerated in the SOC of Gastrointestinal Disorders, with the incidence of diarrhea and nausea in PRN1008 400 mg and PRN1008 400 mg plus ritonovir was higher than placebo and moxifloxacin.

Following completion of Part B of the study, it appears that PRN1008 was safe and well tolerated in these healthy male and female volunteers at a single oral dose of 400 mg administered under fasting conditions either with or without ritonavir (100 mg with a second 100 mg dose 12 hours after the first). These conclusions were based on the following findings from all 37 treated participants:

- There were no SAEs, life-threatening TEAEs, or TEAEs leading to death reported for Part B of the study.
- There was one instance of study drug interruption due to an unrelated TEAE of toothache and one instance of study drug withdrawal due to an unrelated TEAE of upper respiratory tract infection (URTI). Both participants were subsequently withdrawn from the study by the PI due to breaches of the exclusion criteria assessed upon re-admission.

- The incidence of TEAEs was highest following Treatment 1 (400 mg PRN1008) and Treatment 2 (400 mg PRN1008 + ritonavir) at 59.4% and 55.9%, respectively. The incidence was lower following Treatment 4 (400 mg moxifloxacin) and lowest following administration of placebo at 38.9% and 17.1%, respectively.
- The majority of TEAEs were mild, regardless of causality, and there were no severe TEAEs reported.
- Overall, the profile of TEAEs occurring in more than one participant suggests that PRN1008 (400 mg with and without ritonovir) was less tolerated in the SOC of Gastrointestinal Disorders than moxifloxacin and placebo.
- The incidence of treatment-related TEAEs was highest in PRN1008 treated participants (43.8% and 44.1% for 400 mg PRN1008 and 400 mg PRN1008 + ritonavir, respectively) compared to placebo (11.4%) and moxifloxacin (8.3%).
- There were no clinically significant and/or study drug-related changes in vital signs, ECG parameters or laboratory parameters.

Following completion of Part B of the study, the following cardiodynamic conclusions were made:

- Mean placebo-corrected change from baseline (ΔΔHR) varied between -1.9 and 2.2 bpm across all post-dose time points on all treatments, demonstrating that PRN1008 at the studied doses did not have an effect on heart rate.
- PRN1008 at the studied doses did not have a clinically relevant effect on cardiac conduction, i.e., the PR and QRS intervals.

In summary, PRN1008 at the studied doses did not have a clinically relevant effect on the studied ECG parameters.

**Issue date:** 01-Dec-2025