Sponsor: Sanofi **Drug substance(s):** rilzabrutinib	**Study Identifiers:** Not applicable **Study code:** PRN1008-002/INT17284

Title of the study:

A Phase 1, Single-Center, Open-label, Fixed-Sequence Study to Assess the Effects of PRN1008 on the Pharmacokinetics of Midazolam, a CYP3A4 Substrate, in Healthy Adults

Study center(s):

This study was conducted at 1 center in Australia

Study period:

Study initiation date: 07 December 2014 (signed informed consent)

Study completion date: 19 December 2014 (last participant last visit)

Study Status: Completed

Phase of development: Phase 1

Objectives:

Primary:

To evaluate the effect of a single oral dose of PRN1008 on the single-dose pharmacokinetics (PK) of midazolam, a CYP3A4 substrate, in healthy participants

Secondary:

- To evaluate single oral dose urinary PK of PRN1008
- To assess the safety and tolerability of single oral doses of PRN1008 when administered in combination with midazolam in healthy participants

Methodology:

This was a single-center, open-label, fixed-sequence study to investigate the effects of PRN1008 on the PK of midazolam, aCYP3A4 substrate, in healthy subjects. Participants completed a 2-period, fixed-sequence study, as follows:

- Period 1: Study Days 1 to 3
  Following a single oral 2 mg dose of midazolam on Day 1, blood samples were obtained over a period of 24 hours to characterize the PK profile of midazolam and its metabolite, α-hydroxymidazolam.
- Period 2: Study Days 4 to 5
  On Day 4, participants received an oral 600 mg dose of PRN1008 one hour prior to receiving an oral 2 mg dose of midazolam. Blood and urine samples for determination of PRN1008, midazolam, and α-hydroxymidazolam PK were obtained over a period of 25 hours.

Number of study participants:

The study enrolled 12 participants, all were male. The study was open to female subjects, as well, although none of the women who were screened met the criteria for enrollment.

Diagnosis and criteria for inclusion:

Healthy adults, 18 to 55 years of age (inclusive) at the time of screening, with a body mass index (BMI) ≥ 18 and ≤ 30 kg/m^2 (inclusive) and a minimum body weight of 45 kg.

Study products

PRN1008 Liquid Formulation (powder in bottle)

- Dose: 600 mg
- Mode of Administration: Oral

Midazolam Hydrochloride Solution (1 mg/mL)

- Dose: 2 mg
- Mode of Administration: The formulation used for this study was midazolam solution for intravenous use, which was administered orally via oral syringe, followed by 240 mL of water.
- The midazolam solution was commercially available and sourced locally.

Duration of study intervention:

Up to 43 days (from screening to study completion) for each enrolled participant, as follows:

- Screening: Up to 28 days
- In-House Stay: Days -1 to 5
- Follow-Up: 7-10 days after final study drug administration (study completion)

Criteria for evaluation:

Primary

The following PK parameters will be calculated for rilzabrutinib following a single dose:

- Maximum observed plasma concentration (C_{max}) and area under the plasma concentration-time curve (AUC) of midazolam and α-hydroxymidazolam

Secondary

- Time of maximum observed plasma concentration (T_{max}), plasma half-life ($t_{1/2}$), metabolite to parent (M/P) AUC ratio of midazolam and α-hydroxymidazolam
- C_{max}, AUC, T_{max}, $t_{1/2}$, renal clearance (CLr) and amount excreted unchanged in the urine (Ae) of PRN1008
- Safety and tolerability, including the assessment of physical examinations, electrocardiograms (ECGs), vital signs, clinical laboratory results, and AEs

Statistical methods:

Safety and Tolerability

Quantitative safety data were summarized by descriptive statistics (arithmetic mean, standard deviation, median, minimum, and maximum) by study period. Summaries are also presented for the change from baseline, when appropriate.

Pharmacokinetics

Plasma concentrations and the computed PK parameters using standard non-compartmental methods were listed for PRN1008, midazolam, and α-hydroxymidazolam. Individual and mean concentration versus nominal time data were plotted on linear and log-linear scales. Summary statistics of PK parameters were 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 midazolam AUC and C_{max} by treatment period were computed.

Summary Results:

Pharmacokinetics Results:

- Co-administration of oral PRN1008 liquid formulation with oral midazolam liquid formulation resulted in an approximately 3-fold increase in midazolam exposure, suggesting that PRN1008 is a moderate inhibitor of CYP3A
- The α-hydroxymidazolam/midazolam AUC_{0-24} ratio was reduced by approximately 58% when oral midazolam was administered with oral PRN1008 liquid
- The mean midazolam elimination $t_{1/2}$ was increased to 2.44 hours in presence of PRN1008, as compared to 1.86 hours when midazolam was administered alone
- The renal route does not appear to be a major contributor in the clearance of PRN1008
- The potential impact of oral PRN1008 on CYP3A substrates under different dosing conditions (e.g., lower doses, solid dosage forms, staggered dosing) is unknown.

Safety results:

A single 600 mg dose of PRN1008 was safe and well tolerated in this study. AEs related to PRN1008 administration were predominantly mild and self-limiting. No patients discontinued the study due to any AE. There were no deaths, SAEs, or other AEs of clinical significance, including laboratory abnormalities. There were no adverse physical findings and ECG parameters were within normal range. Certain AEs, primarily those affecting the throat, gastrointestinal, and nervous systems, were more common with the combination of midazolam + PRN1008 and are plausibly related to PRN1008 directly or indirectly. Nausea and diarrhea have been seen in prior studies of PRN1008 and are likely directly related to PRN1008. Given the 3-fold increase in exposure of midazolam with PRN1008, the increased incidence of sedation and somnolence with the combination of PRN1008 + midazolam is likely due to PRN1008 potentiating the sedating effect of midazolam.

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