Sponsor: Sanofi **Drug substance(s):** rilzabrutinib	**Study Identifiers:** Not applicable **Study code:** PRN1008-001/TDU17293

Title of the study:

A Phase 1, Randomized, Double-Blind, Placebo-Controlled, Ascending-Dose Study of the Safety, Tolerability, and Pharmacokinetics of Orally Administrated PRN1008

Study center(s):

This study was conducted at 1 center in Australia

Study period:

Study initiation date: 23 April 2014 (signed informed consent)

Study completion date: 03 December 2014 (last participant last visit)

Study Status: Completed

Phase of development: Phase 1

Objectives:

Part A: Single-Dose Administration

Primary:

- To assess the safety and tolerability of single oral doses of PRN1008 when administered to healthy adult participants

Secondary:

- To assess the pharmacokinetics (PK) of single oral doses of PRN1008 whenadministered to healthy adult participants
- To assess the impact of PRN1008 on pharmacodynamic (PD) markers

Part B: Repeat-Dose Administration

Primary:

- To assess the safety and tolerability of multiple oral doses of PRN1008 when administered to healthy adult participants for 10 days

Secondary:

- To determine the PK of repeat oral doses of PRN1008 when administered to healthy adult participants
- To evaluate the impact of food on the PK of PRN1008
- To assess the impact of PRN1008 on PD markers

Methodology:

Part A: This was a double-blind, placebo-controlled, randomized, ascending single-dose study to determine the initial safety, tolerability, and PK/PD of PRN1008. Each participant was randomized to receive either a single dose of PRN1008 oral liquid or a single dose of matching placebo (6 active: 2 placebo, N=8 per cohort). Up to 6 dosing cohorts were to be evaluated.

Part B: This was a double-blind, placebo-controlled, randomized, ascending repeat-dose study to determine the safety, tolerability, and PK of PRN1008. Each participant was randomized to receive either repeat doses of PRN1008 oral liquid or matching placebo (8 active: 2 placebo, N=10 per cohort). The first cohort of Part B included an assessment of the impact of food on PRN1008 PK on Day -1.

Number of study participants: Planned Enrollment: The planned enrollment was up to 98 healthy subjects: 48 subjects in Part A and 50 subjects in Part B. Analyzed Populations: In total, 80 subjects were enrolled in the study. In Part A, 5 cohorts were enrolled (dose levels of 50, 150, 300, 600, and 1200 mg). In Part B, 4 cohorts were enrolled (300 mg once daily [QD], 300 mg twice daily [BID], 600 mg QD, and 450 mg BID). Of the 80 subjects enrolled in the study, 62 subjects received active PRN1008 and were included in the PK analysis population. All 80 subjects were included in the safety analysis population.
Diagnosis and criteria for inclusion: Healthy male subjects and surgically sterile or postmenopausal female subjects aged 18 to 55 years, with a body mass index (BMI) between 18 to 30.5 kg/m^2.
Study products • PRN1008 liquid formulation • PRN1008 liquid formulation placebo All doses of PRN1008 were administered under fasting conditions, with the exception of Cohort B1, Day -1, when PRN1008 was administered within 30 minutes of eating a moderate-fat meal.
Duration of study intervention: For Part A, the total duration of the study was up to 39 days (from screening through study completion) for each enrolled subject. For Part B, the total duration of the study was up to 47 days (from screening through study completion).
Criteria for evaluation: **Pharmacokinetics/Pharmacodynamics:** Blood samples were collected at predefined time points to determine plasma concentrations of PRN1008, and BTK receptor occupancy in peripheral blood mononuclear cells (PBMCs). Part A: Single-dose PK of PRN1008, including plasma Cmax, Tmax, AUC, and plasma half-life; urinary PK (one cohort only), including renal clearance and amount excreted unchanged in urine; evaluation of the PD (BTK receptor occupancy in PBMCs) of PRN1008. Part B: PK of PRN1008 when administered for multiple doses at steady state, including plasma Cmax, Tmax, AUCtau, half-life and accumulation ratio; impact of food on the PK of PRN1008 (Cohort B1); evaluation of the PD (BTK receptor occupancy in PBMCs) of PRN1008. **Safety:** The following were monitored throughout the study: adverse events (AEs); laboratory assessments (hematology, chemistry, and urinalysis); vital sign measurement; physical examination; 12-lead electrocardiograms (ECGs); and concomitant medications.
Statistical methods: The PK parameters for PRN1008 metabolite were determined by standard noncompartmental methods using Phoenix® WinNonlin® (Pharsight Corporation, Cary, NC, U.S.A.). The safety analysis consisted of evaluating all subjects who received at least 1 dose of study drug and had at least 1 post-dose safety assessment. Safety analysis was performed by presenting data on AEs; clinical laboratory tests (hematology, biochemistry, and urinalysis); vital signs; and ECG results. AEs were coded using the Medical Dictionary for Regulatory Activities (MedDRA) Version 16.1 and AE severity was characterized as mild, moderate, or severe.

Summary Results:

Pharmacokinetic Results:

Part A

- Following single oral doses of a liquid formulation of PRN1008, the mean plasma $AUC_{0-\infty}$ increased more than dose-proportionally from 50 mg to 600 mg. Increasing the dose from 600 mg to 1200 mg did not result in further increases in $AUC_{0-\infty}$, suggesting a plateau in absorption with doses greater than 600 mg with the liquid formulation administered in this study.
- The mean PRN1008 Cmax increased with increasing doses up to 600 mg. The increase in Cmax was dose-proportional from 50 mg to 300 mg, and with greater than dose proportionality from 300 mg to 600 mg. No substantive increase in Cmax was observed when the dose was increased from 600 mg to 1200 mg.
- The mean apparent terminal elimination half-life of PRN1008 was approximately 3 to 4 hours
- The median Tmax of PRN1008 increased from 0.5 to 2.5 hours as doses increased from 50 mg to 1200 mg

Part B

- Following multiple oral doses of PRN1008 on Day 10, the mean plasma $AUC_{0-\infty}$ of PRN1008 in plasma increased in a dose-proportional fashion over a dose range of 300 mg to 600 mg
- The mean apparent terminal elimination half-life ranged from 3.82 to 4.50 hours for all cohorts on Day 10 and did not appear to change with changing doses
- Minimal accumulation was observed for PRN1008 after multiple oral dose administration of PRN1008.
- Co-administration of PRN1008 with food reduced exposures by approximately 40 to 51% as measured by Cmax and AUC, respectively, suggesting oral administration of PRN1008 with food in clinical studies may decrease PRN1008 exposure

Safety Results:

Part A

- PRN1008 was generally safe and well tolerated in healthy adult volunteers when administered orally as single doses ranging from 50 mg to 1200 mg
- No clinically significant changes in vital signs, electrocardiogram (ECG) parameters, or laboratory values were observed at doses up to 1200 mg
- No serious AEs or treatment-related study discontinuations were reported
- The single-dose safety and tolerability profile of PRN1008 was similar to placebo at doses ranging from 50 mg to 600 mg. Mild to moderate gastrointestinal AEs were reported in all 6 subjects receiving 1200 mg doses.

Part B

- PRN1008 was generally safe and well tolerated in healthy adult volunteers when administered orally as multiple doses ranging from 300 mg QD (300 mg/day) to 450 mg BID (900 mg/day)
- No clinically significant changes in vital signs, ECG parameters, or laborator values were observed at doses up to 450 mg BID
- No serious AEs (SAEs) or treatment-related study discontinuations were reported
- The multiple-dose safety and tolerability profile of PRN1008 was similar to placebo at doses ranging from 300 mg QD to 450 mg BID. Mild to moderate gastrointestinal AEs were reported in several subjects receiving doses of 600 mg QD or 450 mg BID, as was mild throat irritation in a few subjects receiving 600 mg QD.

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