Sponsor: Sanofi **Drug substance(s):** rilzabrutinib	**Study Identifiers:** Not applicable **Study code:** PRN1008-020/POP17091

Title of the study:

An Open-Label, Phase 1 Study to Evaluate the Effect of Mild and Moderate Hepatic Impairment on the Single-Dose Pharmacokinetics of Rilzabrutinib (PRN1008)

Study center(s):

This study was conducted at 2 centers in United States

Study period:

Study initiation date: 02-Nov-2020 (signed informed consent)

Study completion date: 23-Mar-2021 (last participant last visit)

Study Status: Completed

Phase of development: Phase 1

Objectives:

Primary

• To compare the pharmacokinetics (PK) of rilzabrutinib in adult subjects with mild and moderate hepatic impairment (HI) to subjects with normal hepatic function.

• To evaluate the safety and tolerability of rilzabrutinib in subjects with HI.

Secondary

• To compare the PK of rilzabrutinib metabolites in adult subjects with mild and moderate HI to subjects with normal hepatic function.

Methodology:

This was an open-label, non-randomized, single-dose study to evaluate the effect of mild or moderate HI on the PK of rilzabrutinib.

Screening of subjects occurred within 28 days prior to dosing.

Up to 32 evaluable adult male and female subjects were to be enrolled in 3 cohorts; 8 subjects with mild HI, 8 subjects with moderate HI, and 8 to 16 healthy subjects with normal hepatic function. Overall, 29 subjects were enrolled in the study:

Cohort 1: Eight (8) subjects with mild HI (Child-Pugh A: a score of 5 to 6 on the Child-Pugh scale) were enrolled.

Cohort 2: Eight (8) subjects with moderate HI (Child-Pugh B: a score of 7 to 9 on the Child Pugh scale) were enrolled.

Cohort 3: A total of 13 healthy subjects with normal hepatic function were enrolled.

Each healthy subject was matched with at least 1 subject with HI. However, a healthy control subject could not be matched to more than 1 subject in the same HI cohort. Matched-control subjects were matched for age (± 10 years), body mass index (BMI; ± 15%), and sex.

Cohorts 1 and 2 were conducted in parallel.

On Day 1, all subjects received a single dose of 400 mg rilzabrutinib under fasting conditions. Plasma samples for determination of total and unbound rilzabrutinib and rilzabrutinib metabolites PK were collected at protocol-specified times. Safety was monitored throughout the study by repeated clinical and laboratory evaluations.

Number of study participants:

A total of 29 subjects entered the study, with 13 subjects in the healthy-matched control cohort and 8 subjects each in the mild HI and moderate HI cohorts. All 29 subjects completed the study and were included in the safety analysis. Twenty-eight (28) subjects were included in the PK analysis (1 subject with moderate HI was excluded due to vomiting within 2 times the median Tmax for rilzabrutinib; the corresponding healthy-matched control subject was retained in the analysis).

Diagnosis and criteria for inclusion:

All healthy control subjects enrolled in this study were judged by the Investigator to be normal, healthy volunteers who met all inclusion and none of the exclusion criteria. All HI subjects were judged by the Investigator to be volunteers who met all inclusion and none of the exclusion criteria.

Study products

The test product was 400 mg rilzabrutinib (PRN1008) tablets. Each subject received a single oral dose of 400 mg rilzabrutinib (1 x 400 mg tablet) with approximately 240 mL of water at 0 hour on Day 1 following an overnight fast of at least 10 hours.

Duration of study intervention:

The total duration of participation for each subject was approximately 2 days. Subjects were housed on Day -1, at the time indicated by the clinical research unit (CRU), until after the 30-hour postdose blood draw.

Criteria for Evaluation:

Pharmacokinetics:

Blood samples for determination of plasma total rilzabrutinib and metabolite, were collected on Day 1 at predose (0 hour) and at 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12, 16, 24, and 30 hours postdose. Blood samples for determination of rilzabrutinib metabolite (thiocyanate) were collected at predose and at 4, 12, and 24 hours postdose.

The following PK parameters were calculated using noncompartmental analysis for total rilzabrutinib in plasma: AUC0-t, AUC0-inf, AUC%extrap, Cmax, Tmax, t½, and Kel. Additionally, CL/F and Vz/F were calculated for total rilzabrutinib. The following PK parameters were calculated for thiocyanate in plasma: AUC0-t, Tmax, and Cmax. Additionally, metabolite-to-parent ratios (MRAUC and MRCmax) were determined for thiocyanate.

Blood samples for determination of unbound fraction of rilzabrutinib in plasma were collected at predose and at 2, 4, 12, and 24 hours postdose. Additionally, predose samples prespiked with rilzabrutinib at 100 ng/mL were analyzed for total and unbound rilzabrutinib. The %fu was determined as unbound/total x 100 at each postdose time point (%fu,2h, %fu,4h, %fu,12h, and %fu,24h) and for the prespiked samples (Spiked %fu). The Spiked %fu was multiplied (or divided) by the total rilzabrutinib PK parameters for the determination of the following PK parameters for unbound rilzabrutinib: AUC0-t,u, AUC0-inf,u, Cmax,u, CL,u/F, and Vz,u/F.

Safety:

Safety was evaluated by 12-lead electrocardiograms (ECGs), vital signs, clinical laboratory tests (hematology, serum chemistry, coagulation, and urinalysis), adverse events (AEs) and/or serious AEs (SAEs), and physical examinations.

Statistical methods:

Pharmacokinetics:

Plasma concentrations and PK parameters for rilzabrutinib (total and unbound) and thiocyanate were summarized using descriptive statistics.

A statistical comparison of the natural-log (ln)-transformed PK parameters (AUC0-t, AUC0-inf, and Cmax) for total rilzabrutinib were performed for each HI status (mild HI or moderate HI versus the appropriate healthy-matched controls) using analysis of variance (ANOVA). The ANOVA model included the HI status (mild HI, moderate HI, and healthy-matched control) as a fixed effect. Each ANOVA included calculation of least-squares means (LSMs), the difference between LSMs of the subjects with HI (Cohorts 1 and 2) and the healthy-matched control subjects (Cohort 3 [3a or 3b]), and the standard error and 90% confidence interval (CI) associated with the difference. These results (LSMs, difference between LSMs, and 90% CIs of the differences) were exponentiated to the

original scale. Geometric LSMs, geometric mean ratios (GMRs), and 90% CIs were presented. The GMRs and 90% CIs were expressed as a percentage relative to the healthy-matched control subjects (Cohorts 3a or 3b). Statistical comparisons of ln-transformed plasma unbound rilzabrutinib PK parameters (AUC0-t,u, AUC0-inf,u, and Cmax,u) were performed according to the model described above. A post-hoc exploratory ANOVA with the pooled healthy-matched control cohort (Cohort 3) was added. Statistical comparisons of thiocyanate PK parameters were not conducted, due to insufficient quantifiable data for the healthy-matched control groups.

An exploratory analysis was carried out to evaluate the relationship between plasma total rilzabrutinib PK parameters (including AUC0-inf and Cmax) and measures of HI (e.g., Child-Pugh scores, albumin levels, bilirubin levels, and prothrombin time [PT]) via scatter plots. A regression line with 95% CI was included in each plot, with a linear scale for both axes.

Safety:

All AEs that occurred during this clinical trial were coded using the Medical Dictionary for Regulatory Activities (MedDRA®), Version 23.0. Treatment-emergent AEs (TEAEs) were tabulated by System Organ Class (SOC) and Preferred Term. Summary tables included the number of subjects reporting the AE and as a percent of the number of subjects dosed by cohort. The number of AEs was also tabulated. Descriptive statistics were presented for clinical laboratory, ECG, and vital sign parameters by assessment time point and cohort. Change from baseline for these safety parameters was also summarized. All concomitant medications recorded during the study were coded with the World Health Organization (WHO) Drug Dictionary March 2020 b3 Global and listed. All safety data results were presented in individual listings. No inferential statistics were planned or performed for safety assessments.

Summary Results

Pharmacokinetic Results:

Total Rilzabrutinib

A summary of total rilzabrutinib PK parameters is presented in the following table:

Pharmacokinetic Parameters	Mild HI	Moderate HI	Healthy-Matched Control to Mild HI	Healthy-Matched Control to Moderate HI	Healthy-Matched Control (Pooled)
AUC0-t (ng*hr/mL)	683.4 (75.5) [n=8]	2049 (99.4) [n=7]	445.9 (111.3) [n=8]	412.6 (75.4) [n=8]	418.4 (91.9) [n=13]
AUC0-inf (ng*hr/mL)	693.6 (76.9) [n=8]	2075 (99.2) [n=7]	513.6 (106.4) [n=7]	466.5 (69.6) [n=7]	452.6 (89.0) [n=12]
AUC%extrap (%)	1.426 ± 3.0691 [n=8]	1.203 ± 1.4413 [n=7]	1.186 ± 1.6807 [n=7]	0.4668 ± 0.43532 [n=7]	0.8384 ± 1.3169 [n=12]
Cmax (ng/mL)	217.1 (59.2) [n=8]	487.1 (67.6) [n=7]	141.8 (128.1) [n=8]	114.1 (91.0) [n=8]	121.3 (106.2) [n=13]
Tmax (hr)	2.000 (1.50, 3.00) [n=8]	2.000 (0.50, 4.00) [n=7]	2.000 (0.50, 3.00) [n=8]	2.250 (1.00, 4.00) [n=8]	2.000 (0.50, 4.00) [n=13]
t½ (hr)	5.786 ± 1.9886 [n=8]	6.656 ± 2.9549 [n=7]	7.526 ± 2.8297 [n=7]	5.813 ± 2.0179 [n=7]	6.484 ± 2.5160 [n=12]
Kel (1/hr)	0.1299 ± 0.034942 [n=8]	0.1187 ± 0.039136 [n=7]	0.1047 ± 0.040291 [n=7]	0.1295 ± 0.037434 [n=7]	0.1204 ± 0.040208 [n=12]
CL/F (L/hr)	699.8 ± 440.50 [n=8]	242.8 ± 142.85 [n=7]	1207 ± 1599.7 [n=7]	1024 ± 695.13 [n=7]	1217 ± 1261.9 [n=12]
Vz/F (L)	5825 ± 3907.4 [n=8]	2436 ± 1751.8 [n=7]	15790 ± 26085 [n=7]	8206 ± 5409.3 [n=7]	13030 ± 19916 [n=12]

One subject in the moderate HI group was excluded from the summary statistics due to vomiting within 2 times the median Tmax for total rilzabrutinib.
AUCs and Cmax are presented as geometric mean (geometric CV%).
Tmax is presented as Median (Minimum, Maximum).
Other parameters are presented as arithmetic mean ± SD.
HI = Hepatic impairment
Source: Tables 14.2.1.1.6 through 14.2.1.1.10
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The statistical comparisons of total rilzabrutinib PK parameters in subjects with mild HI or moderate HI compared to the respective healthy-matched control subjects are summarized in the following tables:

	Mild HI (Test)		Healthy-Matched Control to Mild HI (Reference)				
Parameter	Geometric LSM	n	Geometric LSM	n	Geometric Mean Ratio (%)	90% Confidence Interval	*Intra-subject CV%
AUC0-t (ng*hr/mL)	683.4	8	445.9	8	153.25	76.25 - 308.02	93.52
AUC0-inf (ng*hr/mL)	693.6	8	513.6	7	135.04	66.41 - 274.61	90.64
Cmax (ng/mL)	217.1	8	141.8	8	153.15	75.88 - 309.10	94.27

Parameters were ln-transformed prior to analysis.
Geometric Mean Ratio = 100*(test/reference)
Intra-subject CV% = 100 x (square root (exp[MSE]-1)), where MSE = Residual variance from ANOVA.
*Intra-subject CV% is the within pair variability of the HI patient and her/his matched healthy subject.
HI = Hepatic impairment
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	Moderate HI (Test)		Healthy-Matched Control to Moderate HI (Reference)				
Parameter	Geometric LSM	n	Geometric LSM	n	Geometric Mean Ratio (%)	90% Confidence Interval	*Intra-subject CV%
AUC0-t (ng*hr/mL)	1997	7	412.6	8	484.00	265.22 - 883.25	65.14
AUC0-inf (ng*hr/mL)	2040	7	455.4	7	447.98	219.11 - 915.93	73.77
Cmax (ng/mL)	482.6	7	114.1	8	423.06	224.43 - 797.51	70.39

One subject in the moderate HI group was excluded from the statistical analysis due to vomiting within 2 times the median Tmax for total rilzabrutinib.
Parameters were ln-transformed prior to analysis.
Geometric Mean Ratio = 100*(test/reference)
Intra-subject CV% = 100 x (square root (exp[MSE]-1)), where MSE = Residual variance from ANOVA.
*Intra-subject CV% is the within pair variability of the HI patient and her/his matched healthy subject.
HI = Hepatic impairment
Source: Table 14.2.1.1.13
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Total rilzabrutinib exposures (AUCs and Cmax) were approximately 1.4- to 1.5-fold higher in subjects with mild HI and 4.2- to 4.8-fold higher in subjects with moderate HI compared to the respective healthy-matched control cohorts. The results from the exploratory ANOVA with the pooled healthy-matched control cohort were similar. Intra-subject CV% (based on the within-pair variability) was relatively high (> 65%), and considerable overlap in individual total rilzabrutinib exposures was observed for subjects with mild HI and the respective healthy-matched control subjects.

Median Tmax and mean t½ values were similar across cohorts. Mean CL/F and Vz/F values tended to decrease with increasing HI, though there was considerable overlap in individual values for mild HI and healthy-matched control subjects.

A relationship could not be established between total rilzabrutinib exposure (based on AUC0-inf and Cmax) and measures of HI (i.e., Child-Pugh score, albumin levels, bilirubin levels, or PT) based on the exploratory scatter plots.

Unbound Rilzabrutinib

A summary of unbound rilzabrutinib PK parameters is presented in the following table

Pharmacokinetic Parameters	Mild HI	Moderate HI	Healthy-Matched Control to Mild HI	Healthy-Matched Control to Moderate HI	Healthy-Matched Control (Pooled)
AUC0-t,u (ng*hr/mL)	7.842 (112.7) [n=8]	57.22 (113.9) [n=7]	11.09 (124.2) [n=8]	10.16 (88.6) [n=8]	10.26 (105.1) [n=13]
AUC0-inf,u (ng*hr/mL)	7.959 (113.0) [n=8]	57.92 (114.2) [n=7]	12.75 (121.5) [n=7]	11.45 (85.9) [n=7]	11.07 (103.7) [n=12]
Cmax,u (ng/mL)	2.491 (122.2) [n=8]	13.60 (78.4) [n=7]	3.527 (145.0) [n=8]	2.809 (108.3) [n=8]	2.973 (123.1) [n=13]
CL,u/F (L/hr)	69080 ± 57094 [n=8]	9524 ± 7994.6 [n=7]	54210 ± 81447 [n=7]	45360 ± 39670 [n=7]	54730 ± 65658 [n=12]
Vz,u/F (L)	594900 ± 504200 [n=8]	91280 ± 74342 [n=7]	735400 ± 1313400 [n=7]	364600 ± 306820 [n=7]	601500 ± 1006600 [n=12]
Spiked %fu (%)	1.496 ± 1.1717 [n=8]	2.868 ± 0.7105 [n=7]	2.520 ± 0.4341 [n=8]	2.489 ± 0.3825 [n=8]	2.480 ± 0.3908 [n=13]
%fu,2h (%)	0.341 ± 0.1125 [n=3]	0.485 ± 0.1568 [n=6]	0.202 ± 0.0529 [n=3]	0.163 ± . [n=1]	0.202 ± 0.0529 [n=3]
%fu,4h (%)	0.339 ± 0.0726 [n=2]	0.531 ± 0.0655 [n=5]	.	.	.
%fu,12h (%)	.	0.745 ± . [n=1]	.	.	.

One subject in the moderate HI group was excluded from the summary statistics due to vomiting within 2 times the median Tmax for total rilzabrutinib.
AUCs and Cmax,u are presented as geometric mean (geometric CV%).
Other parameters are presented as arithmetic mean ± SD.
%fu = (unbound rilzabrutinib/total rilzabrutinib) x 100; where Spiked %fu was based on predose samples prespiked with rilzabrutinib at 100 ng/mL.
AUC0-t,u, AUC0-inf,u, and Cmax,u were calculated as: unbound parameter = (total rilzabrutinib parameter) x Spiked %fu.
CL,u/F and Vz,u/F were calculated as: unbound parameter = (total rilzabrutinib parameter) / Spiked %fu.
. = Value missing or not reportable
HI = Hepatic impairment
Source: Tables 14.2.2.1.6 through 14.2.2.1.10
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There were limited quantifiable unbound rilzabrutinib concentration data in the postdose samples analyzed, particularly for the mild HI and healthy-matched control cohorts, and %fu was not calculable where concentrations were below the limit of quantitation (BLQ). Therefore, the Spiked %fu was used for the calculation of the unbound rilzabrutinib PK parameters (AUC0-t,u, AUC0-inf,u, Cmax,u, CL,u/F, and Vz,u/F). Rilzabrutinib was highly bound to plasma proteins, with mean Spiked %fu concentrations close to the expected 2.5% value for all cohorts with the exception of the mild HI group (mean Spiked %fu was approximately 1.5%). The apparently lower Spiked %fu value for mild HI appeared to be due to lower than expected values for 5 subjects with mild HI. Where postdose unbound

rilzabrutinib concentrations were quantifiable, the associated mean %fu values were lower (ranging from approximately 0.2% to 0.7%) than the mean Spiked %fu values. The impact of time on %fu could not be assessed, as %fu was not calculable (due to BLQ unbound concentrations) at the majority of the later time points. These results should be interpreted with caution due to the lower than expected Spiked %fu for 5 of the subjects with mild HI and the limited quantifiable postdose unbound rilzabrutinib concentrations.

Thiocyanate

A summary of thiocyanate PK parameters is presented in the following table:

Pharmacokinetic Parameters	Mild HI	Moderate HI	Healthy-Matched Control to Mild HI	Healthy-Matched Control to Moderate HI	Healthy-Matched Control (Pooled)
AUC0-t (ng*hr/mL)	103100 (134.6) [n=6]	103800 (59.0) [n=5]	26800 (20.5) [n=3]	95080 (.) [n=1]	36780 (73.1) [n=4]
Cmax (ng/mL)	4797 (132.6) [n=6]	4961 (54.6) [n=5]	1404 (7.5) [n=3]	4510 (.) [n=1]	1880 (64.1) [n=4]
Tmax (hr)	14.000 (4.00, 24.00) [n=6]	4.000 (4.00, 24.00) [n=5]	24.000 (24.00, 24.00) [n=3]	24.000 (24.00, 24.00) [n=1]	24.000 (24.00, 24.00) [n=4]
MRAUC	3352 ± 5084.2 [n=6]	931.1 ± 915.28 [n=5]	1833 ± 2616.3 [n=3]	1221 ± . [n=1]	1680 ± 2158.0 [n=4]
MRCmax	500.7 ± 700.01 [n=6]	163.5 ± 120.36 [n=5]	293.6 ± 412.13 [n=3]	232.9 ± . [n=1]	278.4 ± 337.87 [n=4]

One subject in the moderate HI group was excluded from the summary statistics due to vomiting within 2 times the median Tmax for total rilzabrutinib.
AUC0-t and Cmax are presented as geometric mean (geometric CV%).
Tmax is presented as Median (Minimum, Maximum).
MRAUC and MRCmax are presented as arithmetic mean ± SD.
. = Value missing or not reportable
HI = Hepatic impairment
Source: Tables 14.2.3.1.6 through 14.2.3.1.10
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The mean predose (baseline) plasma concentrations of the metabolite thiocyanate were higher in subjects with mild or moderate HI compared to healthy-matched control subjects. Subsequently, geometric mean thiocyanate AUC0-t and Cmax were comparable between subjects with mild and moderate HI and higher than those for healthy-matched control subjects (where calculable). However, across cohorts, there was no appreciable increase in thiocyanate exposure after administration of rilzabrutinib. The high mean MRAUC and MRCmax values (≥ 163.5) and observation of generally high baseline relative to postdose concentrations were consistent with endogenous thiocyanate accounting for the bulk of total exposure. However, only limited data are available due to undetectable plasma levels of thiocyanate in several subjects. As such, thiocyanate data should be interpreted with caution.

Safety Results:

There were no deaths, SAEs, or subjects discontinued due to AEs during this study.

Overall, a total of 7 TEAEs (2 TEAEs in 2 mild HI subjects and 5 TEAEs in 3 moderate HI subjects) were reported by 5 (31%) HI subjects. Two (2) TEAEs were reported by 2 (15%) subjects in the healthy-matched control cohort. The most frequently reported TEAE was diarrhea. All TEAEs were Grade 1 (mild) in severity, with the exception of 1 Grade 2 (moderate) TEAE (diarrhea) in the moderate HI cohort. The PI considered all TEAEs related to study drug.

There were no remarkable findings regarding clinical laboratory, vital signs, ECG, or physical examinations in this study with respect to subject safety.
Issue date: 01-Dec-2025