A food effect and esomeprazole drug–drug interaction study of RLY-4008, a highly selective FGFR2 inhibitor, in healthy subjects

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INTRODUCTION

- The approval of pan-FGFR inhibitors (pan-FGFRi) in cholangiocarcinoma (CCA)[1–3] provides clinical proof-of-concept of FGFR2 as a therapeutic target
- However, the long-term benefit of pan-FGFRi has been limited owing to the emergence of *FGFR2* resistance mutations and side effects that may prevent optimal dosing[4–10]
- RLY-4008, a highly selective, irreversible, orally available small-molecule FGFR2i with broad mutational coverage, was developed by leveraging differences in the conformational dynamics between FGFR2 and other FGFRs
- RLY-4008 has shown promising preliminary efficacy in FGFRi-naïve patients with CCA bearing *FGFR2* fusions/rearrangements[11]
- This study investigated the effect of food and esomeprazole on the pharmacokinetics (PK) of RLY-4008 in healthy subjects

METHODS

Study design

- This was a Phase I, randomized, open-label, three-period, fed and fasted crossover, and drug–drug interaction (DDI) study
- Twenty-four healthy subjects (18–55 years of age) were randomized to receive a single oral dose of RLY-4008 (50 mg) under fasted or fed conditions or with esomeprazole (40 mg) under fasted conditions in one of two sequences (**Figure 1**):
  - Fasting–Fed–DDI
  - Fed–Fasting–DDI

Figure 1. Study design

No food was permitted for 4 hours post-dose. Each of the three study periods included a washout period of ≥7 days.
RLY-4008 PK was assessed up to 120 hours post-dose.
*For the fasted condition, RLY-4008 was administered after an overnight fast of ≥10 hours.
**For the fed condition, subjects received RLY-4008 after a high-fat, high-calorie meal (~800–1000 kcal).
†In the DDI part of the study, esomeprazole was administered alone to fasted subjects for 5 days; on Day 6, it was given to fasted subjects approximately 1 hour before the RLY-4008 dose.
DDI, drug–drug interaction; R, randomization.

Objectives

- The primary objectives were to assess the effect of food or esomeprazole on the PK of RLY-4008 in healthy subjects
- The secondary objective was to evaluate the safety and tolerability of RLY-4008 with and without co-administration of esomeprazole

Assessments

- Blood samples for PK assessments were collected at 0 (pre-dose), 0.5, 1, 1.5, 2, 4, 8, 12, 24, 48, 72, 96, and 120 hours post-RLY-4008 dosing
- Plasma concentrations of RLY-4008 were determined using a validated liquid chromatography–mass spectrometry assay
- Safety and tolerability were assessed based on adverse events (AEs; graded according to Common Terminology Criteria for Adverse Events version 5.0), clinical laboratory results, vital signs, and physical examination

Statistical analyses

- Considering an estimated intra-participant coefficient of variability of 25% and a true mean ratio of 1.00 for RLY-4008 PK parameters, 21 subjects were required to ensure a 90% confidence interval (CI) within an 80–125% range for the mean ratio of area under the concentration–time curve (AUC) and maximum concentration (C_{max}) between the test (RLY-4008 fed or with esomeprazole) and reference (RLY-4008 fasted)
  - Twenty-four subjects were enrolled to account for potential drop-out
- PK variables were calculated from the plasma concentrations data using noncompartmental methods (Phoenix™ WinNonlin® Version 8.0.0.3176, Certara, Princeton, New Jersey, USA)
- A linear mixed-effects model was fitted to log-transformed PK parameters, including C_{max} and AUC. Point estimates and associated 90% CI of geometric least squares mean ratios (LSGMR) were calculated to evaluate the difference between test and reference datasets

RESULTS

Study participants

- Overall, 24 healthy subjects were enrolled, randomized, and completed the study
- Subject demographics and baseline characteristics are shown in **Table 1**

Table 1. Subject demographics and baseline characteristics

	Fasting–Fed–DDI (N=12)	Fed–Fasting–DDI (N=12)	Total (N=24)
Age, median (range), years	38.0 (27–51)	32.5 (22–55)	36.5 (22–55)
Male, n (%)	8 (66.7)	7 (58.3)	15 (62.5)
Ethnicity, n (%)			
Hispanic/Latino	8 (66.7)	6 (50.0)	14 (58.3)
Not Hispanic/Latino	4 (33.3)	6 (50.0)	10 (41.7)
Race, n (%)			
Black or African American	3 (25.0)	6 (50.0)	9 (37.5)
White	8 (66.7)	5 (41.7)	13 (54.2)
Other	1 (8.3)	1 (8.3)	2 (8.3)
Weight, median (range), kg	76.4 (54.0–85.0)	73.1 (56.7–91.1)	75.2 (54.0–91.1)
BMI, mean (SD), kg/m^2	25.1 (2.5)	25.5 (2.9)	25.3 (2.7)

BMI, body mass index; DDI, drug–drug interaction; SD, standard deviation.

Effect of food on the PK of RLY-4008

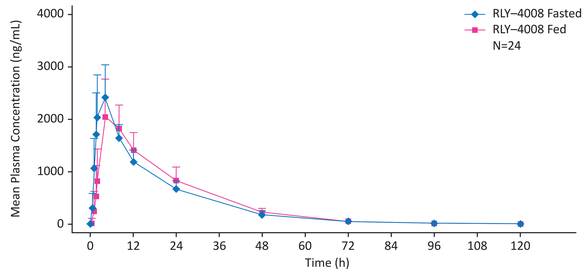
- The median time to maximum concentration (T_{max}) of RLY-4008 was similar when administered under fasted (4.0 h) or fed (4.0 h) conditions
- LSGMRs (90% CI) between RLY-4008 administered with food and under fasting conditions were 87% (77–97%) for C_{max}, 105% (100–110%) for AUC from time 0 to time of the last quantifiable concentration ($AUC_{0–tlast}$), and 106% (100–110%) for AUC from time 0 extrapolated to infinity ($AUC_{0–inf}$) (**Table 2, Figure 2**)
- The LSGMRs (90% CI) of AUCs were fully contained within the 80–125% range
- The lower bound of 90% confidence of C_{max} LSGMR was below 80%, but the 13% reduction in RLY-4008 C_{max} with food was not considered clinically relevant

Table 2. Effect of food on the PK of RLY-4008 (PK evaluable population; N=24)

PK parameter	Food condition	Geometric LS mean	Comparison of fed vs. fasted	
			Ratio	90% CI
C_{max} (ng/mL)	Fasted	2481	0.87	0.77–0.97
	Fed	2148		
$AUC_{0–tlast}$ (h*ng/mL)	Fasted	42245	1.05	1.00–1.10
	Fed	44408		
$AUC_{0–inf}$ (h*ng/mL)	Fasted	42452	1.06	1.00–1.10
	Fed	44612		

AUC, area under the plasma concentration–time curve; $AUC_{0–inf}$, AUC from time 0 extrapolated to infinity; $AUC_{0–tlast}$, AUC from time 0 to time of the last quantifiable concentration; CI, confidence interval; C_{max}, maximum observed plasma concentration; LS mean, least squares mean; PK, pharmacokinetic.

Figure 2. Mean (SD) plasma concentrations of RLY-4008 following a single dose of 50 mg in healthy subjects fed vs. fasted



Points and error bars show the mean + SD of plasma concentrations.
h, hour; SD, standard deviation.

Effect of esomeprazole on the PK of RLY-4008

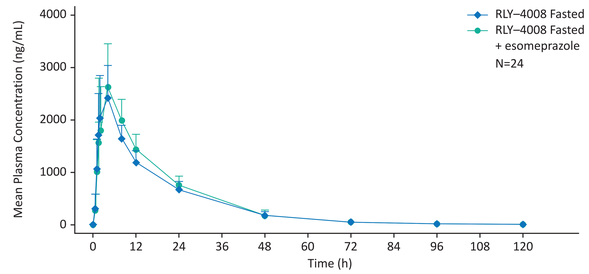
- The median T_{max} of RLY-4008 was similar when administered under fasted (4.0 h) conditions or fasted conditions with esomeprazole (4.0 h)
- LSGMRs (90% CI) between RLY-4008 administered with esomeprazole and alone, under fasting conditions, were 110% (102–119%) for C_{max}, 113% (109–117%) for $AUC_{0–tlast}$, and 113% (109–117%) for $AUC_{0–inf}$ (**Table 3, Figure 3**)
  - For all parameters, the 90% CIs were fully contained within the 80–125% range

Table 3. Effect of esomeprazole on the PK of RLY-4008 (PK evaluable population; N=24)

PK parameter	Condition	Geometric LS mean	Comparison of fasted + esomeprazole vs. fasted	
			Ratio	90% CI
C_{max} (ng/mL)	Fasted	2481	1.10	1.02–1.19
	Fasted + esomeprazole	2741		
$AUC_{0–tlast}$ (h*ng/mL)	Fasted	42245	1.13	1.09–1.17
	Fasted + esomeprazole	47821		
$AUC_{0–inf}$ (h*ng/mL)	Fasted	42452	1.13	1.09–1.17
	Fasted + esomeprazole	48028		

AUC, area under the plasma concentration–time curve; $AUC_{0–inf}$, AUC from time 0 extrapolated to infinity; $AUC_{0–tlast}$, AUC from time 0 to time of the last quantifiable concentration; CI, confidence interval; C_{max}, maximum observed plasma concentration; LS mean, least squares mean; PK, pharmacokinetic.

Figure 3. Mean (SD) plasma concentrations of RLY-4008 following a single dose of 50 mg in healthy subjects fasted vs. fasted with esomeprazole



Points and error bars show the mean + SD of plasma concentrations.
h, hour; SD, standard deviation.

Safety and tolerability

- Overall, eight subjects (33.3%) experienced an AE (**Table 4**)
- All AEs were mild/moderate (Grade 1/2) and had an outcome of recovered/resolved. No deaths or serious AEs were reported, and no AEs led to treatment discontinuation

Table 4. Treatment-emergent AEs (safety population)

AE, n (%)	RLY-4008 Fasted (N=24)	RLY-4008 Fed (N=24)	Esomeprazole (N=24)	RLY-4008 (Fasted) + esomeprazole (N=24)	Overall (N=24)
Subjects with any AE	3 (12.5)	2 (8.3)	4 (16.7)	2 (8.3)	8 (33.3)
ALT increase	1 (4.2)	1 (4.2)	0	1 (4.2)	3 (12.5)
AST increase	1 (4.2)	1 (4.2)	0	1 (4.2)	3 (12.5)
Constipation	1 (4.2)	0	1 (4.2)	0	2 (8.3)
Dyspepsia	0	1 (4.2)	1 (4.2)	1 (4.2)	2 (8.3)
Headache	1 (4.2)	0	1 (4.2)	0	2 (8.3)
Skin abrasion	0	1 (4.2)	0	0	1 (4.2)
Arthralgia	0	1 (4.2)	0	0	1 (4.2)
Back pain	0	0	1 (4.2)	0	1 (4.2)

AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase.

CONCLUSIONS

- Food does not have a clinically relevant effect on the PK of RLY-4008 in healthy subjects, indicating that RLY-4008 can be dosed with or without food
- Esomeprazole does not have a clinically relevant effect on the PK of RLY-4008 in healthy subjects, indicating that RLY-4008 can be dosed with or without proton pump inhibitors, histamine type-2 receptor blockers, and antacids
- A single dose of RLY-4008 was well tolerated in healthy subjects when administered fasted, fed, or with esomeprazole
- ReFocus (NCT04526106), a global, open-label Phase 1/2 study of RLY-4008 in adult patients with advanced, FGFR2-driven CCA or other solid tumors, is ongoing

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