INTRODUCTION

- The approval of pan-FGFR inhibitors (pan-FGFRi) in cholangiocarcinoma (CCA) 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.

- RLY-4008 is a highly selective, orally available small-molecule FGFR2 inhibitor with broad mutational coverage, was developed by leveraging differences in the binding affinity of FGFR2 between and other FGFRs.

- RLY-4008 has shown promising preliminary efficacy in FGFR2-naive patients with CCA bearing FGFR2 fusions/rearrangements.

- 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 1, 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 conditions or with esomeprazole (40 mg) under fasted conditions in one of two sequences (Figure 1):
  - Fasting–Fed–DDI
  - Fed–Fasting–DDI

RESULTS

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

- The median Tmax of RLY-4008 was similar when administered under fasted (4.0 h) and fed conditions.

- The median Cmax of RLY-4008 was similar when administered under fasted (2481 ng/mL) and fed conditions (2417 ng/mL).

- The lower bound of 90% confidence interval of RLY-4008 PK parameters was below 80%, but the 13% geometric LS mean ratio of Cmax and AUC was within the 80%–125% range.

- Overall, eight subjects (33.3%) experienced an AE, and no deaths or serious AEs were reported, and no AEs led to treatment discontinuation.

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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 (NC04521601), a global, open-label Phase 1/2 study of RLY-4008 in adult patients with advanced, FGFR2-driven CX or other solid tumors, is ongoing.