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Assessment of Food Effect and pH-Dependent Drug–Drug Interactions of Fruquintinib in Healthy Subjects

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ABSTRACT

This two-sequence, three-period study (NCT04645940) was designed to evaluate the effect of food and concomitant rabeprazole, a proton pump inhibitor, on the pharmacokinetics (PK) and safety of fruquintinib and its metabolite M11 after a single oral dose of fruquintinib 5 mg in healthy subjects. In the food effect treatment periods, 14 subjects were randomized in a 1:1 ratio utilizing a two-sequence (fed/fasted vs. fasted/fed), two-period, cross-over design. Fruquintinib was administered on Day 1 (Period 1) and Day 15 (Period 2). In the drug-interaction period (Period 3), all subjects received rabeprazole 40 mg 1 h prior to fruquintinib under fasted conditions, following a 6-day lead-in of rabeprazole 40 mg once daily. PK samples to measure fruquintinib and M11 were collected pre-dose and over 168 h after fruquintinib dosing. Administration of fruquintinib with a high-fat meal resulted in similar systemic exposure compared with fasted conditions. In addition, coadministration of fruquintinib with rabeprazole resulted in similar exposure compared with fruquintinib alone. For both evaluations, 90% confidence intervals for the ratio of geometric least square mean of the area under the curve and peak concentration for fruquintinib and M11 were entirely within 80%–125% bounds. The study results showed no effects of food or rabeprazole on fruquintinib PK, and support that fruquintinib can be taken without regard to food or concurrent gastric acid-reducing agents.

1 | Introduction

Fruquintinib (HMPL-013) is a highly selective, oral, small-molecule tyrosine kinase inhibitor of all three vascular endothelial growth factor (VEGF) receptors VEGFR-1, -2, and -3 [1, 2]. Based on results from the FRESCO clinical trial, fruquintinib was approved in China in September 2018 for the treatment of metastatic colorectal cancer (mCRC) in patients who had failed two prior lines of systemic therapy [3, 4]. Following this, in 2023, as a result of data from both FRESCO and FRESCO-2, fruquintinib was approved in the United States for the treatment of adult patients with mCRC who have been previously treated with fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapy, an anti-VEGF therapy, and, if RAS wild-type and medically appropriate, an anti-epidermal growth factor receptor (EGFR) therapy, at a dose of 5 mg once daily (QD) 3 weeks on/1 week off in a 28-day cycle [5, 6]. Subsequently, fruquintinib was approved in June 2024 by the European Commission for the treatment of adult patients with mCRC who have been previously treated with available standard therapies, including fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapies, anti-VEGF and anti-EGFR therapies, and who have progressed on or are intolerant to treatment with either trifluridine-tipiracil (TAS-102) or regorafenib [7].

Martha Gonzalez and Zhao Yang were employed at HUTCHMED at the time of the final study report.

Summary

- What is the current knowledge on the topic?
  - Fruquintinib, an oral small-molecule tyrosine kinase inhibitor, is a highly selective inhibitor of all three vascular endothelial growth factor receptors -1, -2, and -3.
  - It is a biopharmaceutical classification system (BCS) Class 2 weak base drug that exhibits pH-dependent solubility.
- What question did this study address?
  - This clinical study evaluated the effects of food and rabeprazole, a proton pump inhibitor, on the pharmacokinetics (PK) of fruquintinib to provide fruquintinib prescribing information on food intake and concomitant use with proton pump inhibitors.
- What does this study add to our knowledge?
  - Consumption of a high-fat meal did not significantly alter fruquintinib exposure.
  - Concomitant administration with rabeprazole did not result in any change in fruquintinib exposure, supporting that fruquintinib can be taken without regard to food or concurrent use of acid-reducing agents.
- How might this change clinical pharmacology or translational science?
  - The in vitro pH-dependent solubility of a BCS class 2 weak base drug may not necessarily correlate with its clinical food effect or pH-dependent drug–drug interaction (DDI).
  - Our findings emphasize the need to enhance the current paradigm, which is predominantly reliant on in vitro solubility when deciding to conduct clinical pH-dependent DDI studies.

The solubility of fruquintinib was examined in an in vitro study including various aqueous buffer systems across the pH range of 1 to 6.8 at 37°C. Fruquintinib, a weak base with a pKa of 2.78, exhibited pH-dependent aqueous solubility. In the study, solubility decreased from 129.9 μg/mL at pH 1 to 0.9 μg/mL at pH 4.5 and 6.8 (Figure S1). A significant difference in the dissolution profiles of fruquintinib was also noted across various pH conditions, with fruquintinib 5 mg capsules completely dissolving within 45 min in 0.1 N hydrochloric acid, whereas less than 50% dissolution occurred within the same time frame in buffers of pH 4.5 and 6.8 (Takeda data on file). Fruquintinib showed high permeability in a colorectal adenocarcinoma-2 cell study, with an apical-to-basolateral apparent permeability of 30×10^{-6} cm/s, which was similar to the highly permeable compound propranolol. The efflux ratio was close to 1, suggesting that fruquintinib was not subject to efflux transport [1]. Based on the low aqueous solubility and high in vitro permeability, fruquintinib was classified as a biopharmaceutical classification system (BCS) class 2 compound. It is generally acknowledged that BCS class 2 weak base drugs are more inclined to demonstrate food effects and undergo pH-dependent drug–drug interactions [8]. Additionally, the solubility of fruquintinib in simulated intestinal fluid under fed conditions (FeSSIF; 8.67 μg/mL or 2.2 mg/250 mL) exceeded that in simulated intestinal fluid under fasted conditions (FaSSIF; 2.07 μg/mL or 0.52 mg/250 mL) (Takeda data on file). Based on the totality of data, it cannot be ruled out that factors like food intake and coadministration with acid-reducing agents may influence the absorption of fruquintinib.

Proton pump inhibitors (PPIs) are widely prescribed for the management of gastric acid-related disorders [9]. A majority of oncology patients frequently take gastric acid-reducing agents to alleviate symptoms of gastroesophageal reflux disease, thereby raising the potential for a common but underappreciated drug–drug interaction (DDI) that could decrease the exposure of anticancer medication and result in subsequent failure of therapy [10]. However, the potential DDI between fruquintinib and PPIs has not been investigated.

The aim of this study was to assess the pharmacokinetics (PK) and safety of fruquintinib in various conditions, including administration under both fasted and fed conditions, and in combination with rabeprazole, a PPI (NCT04645940). The implications of these results on the fruquintinib product label are also discussed.

2 | Methods

2.1 | Study Design

This was a single-center, open-label, randomized, two-sequence, three-period study to evaluate the effect of food and rabeprazole, a PPI, on the PK of fruquintinib in healthy subjects (Figure 1). The food effect treatment periods (i.e., Periods 1 and 2) were from a two-sequence and two-period cross-over design to evaluate the effect of food, in which subjects were randomized in a 1:1 ratio to two sequences (fed/fasted vs. fasted/fed). For the sequence of fasted/fed, fruquintinib was administered 5 mg orally (PO) without food on Day 1 (Period 1) and with food on Day 15 (Period 2). In the sequence of fed/fasted, fruquintinib was administered 5 mg PO with food on Day 1 (Period 1) and without food on Day 15 (Period 2). Then, in Period 3 (i.e., drug-interaction period), all subjects received rabeprazole 40 mg 1 h prior to fruquintinib under fasted conditions. Overall, the study consisted of a screening phase, a treatment phase, with the aforementioned three periods, and an end of study phase. Screening occurred within 21 days before the first study drug administration. There was at least a 14-day washout of fruquintinib between treatment periods.

Subjects were admitted to the study center prior to each fruquintinib dose in treatment Periods 1 and 2: from Day -1 until the 168-h blood draw in Period 1 (morning of Day 8) and from the evening of Day 14 until the 168-h blood draw in Period 3 (morning of Day 36). Subjects visited the study center on the mornings of study Days 23–28 for rabeprazole administration and were discharged after completion of end-of-study procedures on study Day 36 or at early withdrawal.

In the food effect treatment Periods 1 and 2, subjects received a single oral dose of fruquintinib 5 mg under fasted conditions or 30 min after a high-fat breakfast consisting of approximately 800–1000 kcal, with fat contributing to 50% of the total caloric content of the meal.

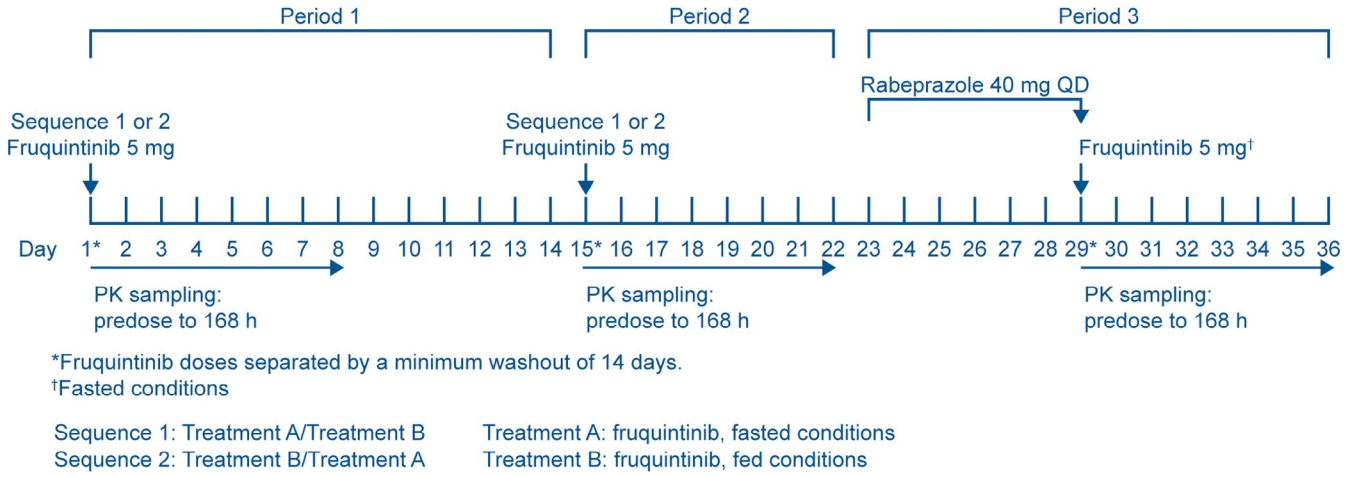

FIGURE 1 | Study design. h, hour; PK, pharmacokinetic; QD, once daily.

In the drug-interaction period, rabeprazole was selected to evaluate the effect of higher gastric pH on the absorption of fruquintinib, as the clearance of rabeprazole is largely nonenzymatic and less dependent on CYP2C19 than other drugs in its class [9]. The use of rabeprazole therefore minimized potential interaction via cytochrome P450 enzymes, which are commonly involved in the metabolism of the majority of small molecule drugs. The dosing regimen for rabeprazole was selected based on published pharmacodynamic data, in which the 40 mg QD regimen produced the highest acid-lowering effect in healthy subjects and resulted in significantly decreased gastric acidity compared with both 10 and 20 mg doses; intragastric pH was also maintained at >3 and >4 for longer when using 40 mg, compared with 10 and 20 mg, respectively [11]. As such, rabeprazole was administered QD for 6 days to achieve maximal effect on gastric pH before dosing with fruquintinib, but was not administered throughout the PK sampling collection interval, as its effect is limited to the stomach and no further effect was expected in the intestines. It was given 1 h prior to fruquintinib, as the antisecretory effect of rabeprazole begins within 1 h after oral administration. In Period 3, all subjects began a 6-day lead-in of rabeprazole 40 mg QD with breakfast on study Days 23–28. On the morning of Day 29, all subjects took 40 mg rabeprazole without food 1 h before taking fruquintinib 5 mg.

2.2 | Subjects

Healthy nonsmoking males and females between the ages of 18 and 55 years with a body mass index (BMI) 18–29 kg/m^2 were enrolled at WCCT Global Inc. (Cypress, CA). Females were of nonchildbearing potential (e.g., postmenopausal or surgically sterile). Males agreed to use highly effective contraception. Subjects were excluded from the study if they had evidence of clinically significant cardiovascular, gastrointestinal (GI), hepatic, renal, respiratory, endocrine, hematological, neurological, psychiatric diseases, or Gilbert's syndrome. Other key exclusion criteria included a known history of any GI surgery or any condition possibly affecting drug absorption; a history of smoking or use of nicotine-containing substances within the previous 2 months or a positive cotinine test at screening and check-in for any one of the treatment periods; a history of drug or alcohol misuse within 6 months prior to screening or a positive urine drug test at screening or check-in for any one of the treatment periods; diagnosis of acquired immune deficiency syndrome or positive for human immunodeficiency virus, hepatitis B virus, or hepatitis C virus; participation in a clinical study of another drug before screening when the time since the last use of the other study drug was less than five times the half-life or 4 weeks, whichever was longer, or the subject was currently enrolled in another clinical study; use of CYP3A inducers (including St. John's wort) or CYP3A inhibitors within the 2 weeks prior to Day 1; consumption of grapefruit, starfruit, Seville oranges, and herbal preparations/medications including, but not limited to, kava, ephedra (ma huang), *Ginkgo biloba*, dehydroepiandrosterone, yohimbe, saw palmetto, and ginseng within 7 days prior to the first dose; and use of a PPI within 4 days prior to the first dose or a histamine 2 (H_2) receptor antagonist (H_2 blocker) within 2 days prior to the first dose.

The protocol and consent form were approved by an institutional review board (Salus Independent Review Board, Austin, Texas) before study initiation, and all subjects signed informed consent forms prior to any study procedures. The study was performed in accordance with the requirements of the Declaration of Helsinki, the International Council for Harmonization Guideline for Good Clinical Practice, and other applicable local laws and regulations.

2.3 | Pharmacokinetic Assessments

Blood samples for determination of fruquintinib and metabolite M11 plasma concentrations were collected at pre-dose and at 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 24, 36, 48, 72, 96, 120, 144, and 168 h after fruquintinib dosing. Plasma samples were analyzed by LabCorp Bioanalytical (Indianapolis, Indiana) using a validated, specific, and sensitive liquid chromatography with tandem mass spectrometry assay method with an analytical range of 1.00 ng/mL (lower limit of quantitation) to 750 ng/mL (upper limit of quantitation). Inter-run variability was $\leq 8.2\%$ and $\leq 6.5\%$ for fruquintinib and M11, respectively. Quality control samples at 4 concentrations (3, 30, 300, and 600 ng/mL) were assayed along with study samples, and the bias quality control

sample concentrations deviated by ±3.7% and ±2.5% from the nominal concentrations for fruquintinib and M11, respectively.

PK parameters were determined by noncompartmental analysis using Phoenix® WinNonlin® version 8.2 (Certara, L.P. Princeton, New Jersey) and included maximum plasma concentration (C_{max}), time to reach C_{max} (T_{max}), area under the plasma concentration-time curve from 0 to the time of the last measurable concentration (AUC_{0-t}), AUC from time 0 to infinity (AUC_{0-inf}), half-life ($t_{1/2}$), and the metabolite-to-parent ratios for C_{max} (MPR C_{max}), AUC_{0-t} (MPR AUC_{0-t}), and AUC_{0-inf} (MPR AUC_{0-inf}). Apparent oral clearance and volume were also estimated for fruquintinib.

2.4 | Safety Assessments

Safety was assessed by evaluation of adverse events (AEs), serious AEs, AEs of special interest, physical examinations, vital signs, single 12-lead electrocardiograms and cardiac monitoring, and clinical laboratory data. All AEs were coded using MedDRA version 23.0, and their severity was graded using the National Cancer Institute Common Terminology Criteria for Adverse Events version 5.0.

2.5 | Statistical Analysis

Based on historical data, it was expected that the maximum intrasubject coefficient of variation would be around 15.5% for PK parameters such as C_{max} after the administration of a single dose of fruquintinib 5 mg. Hence, assuming a true ratio of the geometric mean between test and reference being 1.0, a total of 12 subjects were estimated to give at least 82% power for the 90% confidence interval (CI) for the geometric mean ratio (GMR) falling within the limits of 80% and 125%. Approximately 14 subjects were randomized to accommodate a 10% dropout rate.

PK parameter analyses were based on the PK evaluable population, which included all subjects who received at least one dose of the study drug and had a sufficient PK profile to derive at least one PK parameter. The effect of food on fruquintinib, based on the log-transformed PK parameters such as AUC_{0-t}, AUC_{0-inf}, and C_{max}, was analyzed using a linear mixed-effects model with treatment (i.e., fruquintinib fed [test]) and fruquintinib fasted (reference), period, and sequence as fixed effects and subject within sequence as a random effect. The effect of rabeprazole, based on the PK parameters of fruquintinib, was evaluated using a linear mixed-effect model with treatment (i.e., fruquintinib with rabeprazole [test] and fruquintinib alone [reference]) as a fixed effect and subject as a random effect. For both analyses, the ratios of geometric least square means (LSM) and their two-sided 90% CIs between test and reference were calculated by back transformation (exponent) of LSMs from the aforementioned models. Safety evaluations were performed in the safety population, which included all subjects who received at least one dose of fruquintinib.

All statistical analyses were performed using SAS version 9.4 or higher (SAS Institute, Cary, NC).

3 | Results

3.1 | Subject Disposition

Fourteen healthy subjects were randomized, of which 93% (13 of 14 subjects) were male, 57% (8 of 14 subjects) were White, 21% (3 of 14 subjects) were Asian, and 14% (2 of 14 subjects) were Black. Among the 14 participants, 7% (1 of 14) were of Hispanic ethnicity. All patients received at least one dose of fruquintinib and were included in the safety population. The mean (standard deviation) age, weight, height, and BMI of the safety population were 40.9 (8.0) years, 76.7 (8.8) kg, 174.4 (8.6) cm, and 25.2 (2.0) kg/m^2, respectively.

Two subjects withdrew consent during the study. One subject discontinued prior to starting Period 2 and only received fruquintinib 5 mg under fed conditions in Period 1. The other subject discontinued after the 96-h PK assessment in Period 2. This subject received fruquintinib 5 mg under fasted conditions in Period 1 and under fed conditions in Period 2, but did not proceed to the drug-interaction period. Consequently, 12 subjects completed Period 3.

3.2 | Food Effect Evaluation

The mean fruquintinib concentration-time profiles following oral administration of fruquintinib 5 mg under fed and fasted conditions were similar, with peak concentrations achieved approximately 4 h after dosing, followed by a linear decline (Figure 2). The mean $t_{1/2}$ was also similar for fruquintinib under fasted and fed conditions (Table 1). Results from the statistical analysis showed that systemic exposure to fruquintinib, as assessed by C_{max} and AUCs, was not affected by a high-fat meal with least squares GMRs for C_{max}, AUC_{0-t}, and AUC_{0-inf} close to 1 and 90% CIs falling within 80%–125% limits.

Concentration-time profiles for metabolite M11 were also comparable under fed and fasted conditions (Figure 2). The rate of formation was similar, with peak M11 concentrations achieved approximately 48 h after dosing, as was the overall systemic exposure to M11, with the 90% CIs for C_{max} and AUCs falling within 80%–125% limits. MPRs were also similar under fed and fasted conditions.

3.3 | Effect of Rabeprazole on the PK of Fruquintinib

The mean plasma concentration-time profiles of fruquintinib following a single dose of fruquintinib 5 mg under fasted conditions administered alone or with rabeprazole were comparable (Figure 3). Peak concentrations of fruquintinib were observed at a median T_{max} of 0.5 h earlier, and mean $t_{1/2}$ was slightly longer when given with rabeprazole (Table 1). However, coadministration of rabeprazole had no effect on the systemic exposure to fruquintinib. Results of the statistical comparison of PK parameters showed least squares GMRs for C_{max}, AUC_{0-t}, and AUC_{0-inf} close to 1 and 90% CIs within 80%–125% limits.

Concentration-time profiles for metabolite M11 were also comparable, with peak concentrations observed at approximately

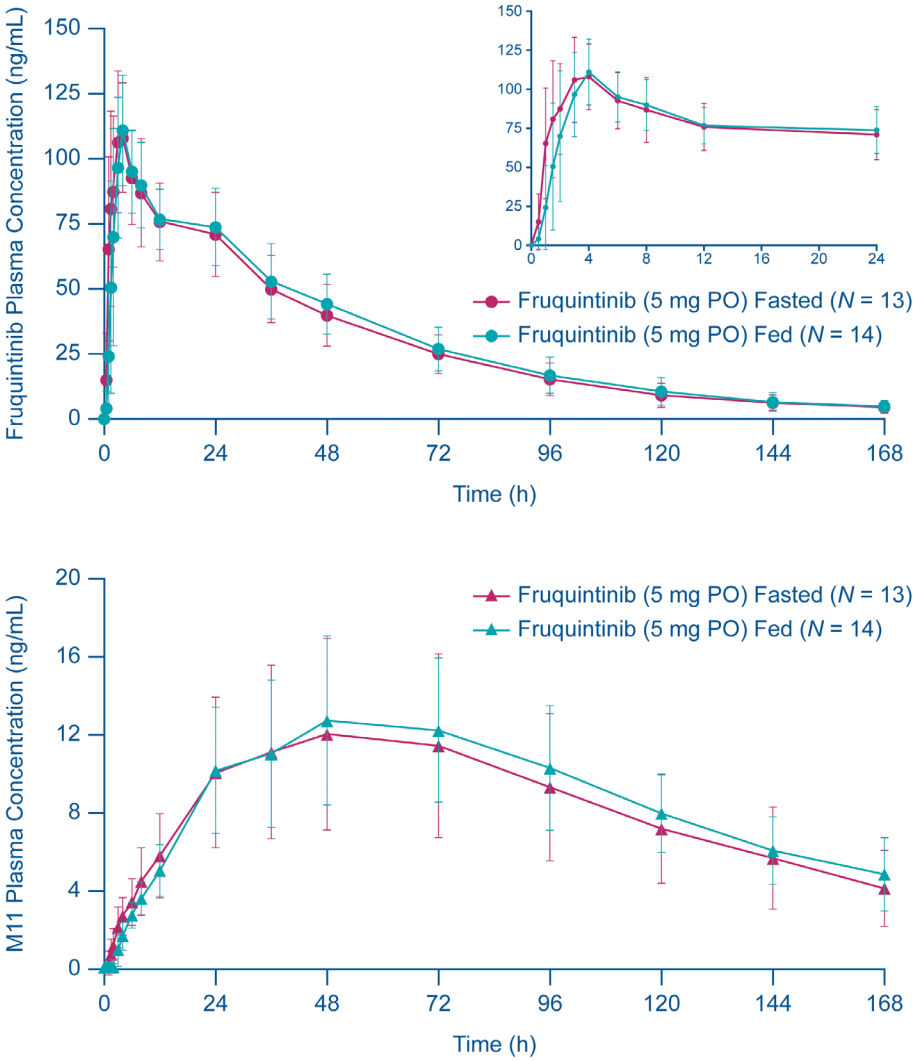

FIGURE 2 | Mean (±SD) plasma concentration-time profiles for fruquintinib (top panel) and M11 (bottom panel) after administration of fruquintinib 5 mg alone under fed and fasted conditions. h, hours; PO, by mouth; SD, standard deviation.

48 h (Figure 3). Coadministration with rabeprazole had no effect on the M11 formation as the 90% CIs for M11 C_{max}, AUC_{0-t}, and AUC_{0-inf} were also within 80%–125% confidence limits (Table 1). MPRs were also unchanged following fruquintinib and rabeprazole coadministration.

3.4 | Safety and Tolerability

A total of five AEs were reported in four of the 14 subjects (29%; Table S1). All AEs were mild in severity and not related to fruquintinib. AEs were epididymal cyst (one subject; fruquintinib with rabeprazole), constipation (one subject; fruquintinib fasted), foot and knee sprain (one subject; fruquintinib fed and rabeprazole alone), and flu-like symptoms (one subject; fruquintinib fed).

There were no clinically significant changes in chemistry, hematology, urinalysis, and coagulation laboratory test results over time during the study. Also, there were no clinically significant changes in post-dose vital signs, post-dose electrocardiogram results, or post-dose physical examination findings compared with baseline that were attributable to fruquintinib.

4 | Discussion

Identifying factors that may modify drug absorption is crucial to ensure patients receive a dose that will have systemic exposure within the expected therapeutic window. The FDA has provided guidance to evaluate both food effect [12] and drug interactions with acid-reducing agents [13]. In vitro solubility data indicated that fruquintinib may be susceptible to food effects and that absorption may be reduced at higher gastric pH (Takeda data on file). As many patients with cancer take acid-reducing agents, it was also important to evaluate the effect of a PPI on fruquintinib systemic exposure [10]. Fruquintinib is metabolized in humans by cytochrome P450 (CYP450) and non-CYP450 enzymes. A clinical mass balance study showed that following the administration of radiolabelled fruquintinib, 60% of the dose was recovered in urine and 30% was recovered in feces. Accounting for approximately 17% of total radioactivity in plasma, M11 was identified as the major circulating metabolite [6, 14]. A subsequent in vitro assay indicated that the potency of M11 for inhibiting VEGFR-2 kinase activity is ten times lower than that of fruquintinib (Takeda data on file); therefore, M11 is not considered to be a pharmacologically active metabolite.

TABLE 1 | PK parameters following a single oral dose of fruquintinib 5 mg under fed or fasted conditions or with rabeprazole 40 mg.

PK parameter	Fruquintinib fasted (reference)	Fruquintinib fed (test)	Fruquintinib + Rabeprazole fasted (test)
Fruquintinib	***n* = 13**	***n*=14[a]**	***n* = 12**
C_{max} (ng/mL)	117 (22.2)	114 (17.6)	121 (15.8)
AUC_{0-t} (ng•h/mL)	4860 (26.2)	5230 (22.9)	5275 (24.4)
AUC_{0-inf} (ng•h/mL)	5058 (27.6)	5287 (25.7)	5523 (26.6)
T_{max} (h)	4.00 (1.50–8.00)	4.00 (2.00–6.00)	3.50 (2.00–12.0)
$t_{1/2}$ (h)	33.6 (9.46)	32.1 (6.89)	36.3 (10.7)
CL/F (mL/min)	17.1 (5.22)	16.3 (4.32)	15.6 (4.59)
V_z/F (L)	47.0 (9.71)	43.5 (8.19)	46.1 (8.10)
LS GMR AUC_{0-t} [90% CI]	—	1.06 [0.99–1.13]	1.07 [1.01–1.14]
LS GMR AUC_{0-inf} [90% CI]	—	1.04 [0.97–1.11]	1.08 [1.01–1.15]
LS GMR C_{max} [90% CI]	—	0.97 [0.86–1.10]	1.03 [0.94–1.14]
M11	***n* = 12**	***n* = 13[b]**	***n* = 10**
C_{max} (ng/mL)	12.2 (30.1)	13.0 (30.7)	12.9 (26.4)
AUC_{0-t} (ng•h/mL)	1336 (31.4)	1474 (24.0)	1431 (26.4)
AUC_{0-inf} (ng•h/mL)	1729 (36.6)	1969 (30.6)	1882 (31.4)
T_{max} (h)	48.0 (36.0–72.0)	48.0 (24.0–96.0)	48.0 (48.0–72.0)
$t_{1/2}$ (h)	65.2 (37.3)	65.7 (25.2)	68.2 (28.1)
MPR C_{max}	0.111 (0.036)	0.125 (0.038)	0.117 (0.037)
MPR AUC_{0-t}	0.300 (0.080)	0.301 (0.087)	0.306 (0.088)
MPR AUC_{0-inf}	0.370 (0.081)	0.403 (0.099)	0.384 (0.106)
LS GMR AUC_{0-t} [90% CI]	—	1.05 [0.96–1.15]	1.04 [0.96–1.11]
LS GMR AUC_{0-inf} [90% CI]	—	1.08 [0.96–1.21]	1.08 [0.99–1.17]
LS GMR C_{max} [90% CI]	—	1.03 [0.93–1.15]	1.03 [0.95–1.10]

Note: AUCs and C_{max} are presented as geometric mean (geometric CV%); T_{max} is presented as median (minimum–maximum); other parameters are presented as arithmetic mean (SD).
Abbreviations: AUC, area under the plasma concentration-time curve; AUC_{0-inf}, AUC from time 0 to infinity; AUC_{0-t}, AUC from 0 to time of the last measurable concentration; CI, confidence interval; C_{max}, maximum observed concentration; LS GMR, least squares geometric mean ratio; MPR, metabolite-to-parent ratio; SD, standard deviation; $t_{1/2}$, half-life; T_{max}, time to reach C_{max}.
[a]$n = 13$ for AUC_{0-t}.
[b]$n = 12$ for AUC_{0-t}; $n = 11$ for AUC_{0-inf} and $t_{1/2}$.

In a previous study conducted in healthy Chinese subjects given fruquintinib 4 mg (the maximum-tolerated dose determined in a Phase 1 dose-escalation study) [15], a high-fat meal was shown to have no clinically significant effect on the PK of fruquintinib [16]. However, the protocol for the dose-escalation study was subsequently amended to evaluate an alternate dosing regimen of fruquintinib 5 mg QD 3 weeks on/1 week off, since most of the dose-limiting toxicities reported with QD dosing occurred during the fourth week of the first cycle, and in view of the long half-life of fruquintinib. Fruquintinib 5 mg QD 3 weeks on/1 week off was ultimately selected as the recommended Phase 2 dose [15]. As such, this study was conducted to confirm no food effect at the intended clinical dose of fruquintinib 5 mg, which was also the highest commercially available strength for fruquintinib capsules.

In the current study, a high-fat meal did not affect systemic exposure to fruquintinib or M11 after a single dose of fruquintinib 5 mg. Systemic exposure was comparable under fed and fasted conditions, with the 90% CIs around the ratios of LSM AUCs and C_{max} for fruquintinib and M11 being entirely within 80%–125% limits. In addition, median T_{max} was not affected by food intake. These results are consistent with data from the prior study conducted among healthy Chinese subjects, as least squares GMRs and the 90% CIs for C_{max} and $AUC_{0\text{-}inf}$ were 82.9% (76.7%–89.5%) and 97.2% (94.0%–100.4%), respectively [16]. By confirming that the absorption of fruquintinib remains unaffected by food intake, this study provides additional evidence supporting the convenience of fruquintinib for patients with mCRC and may help facilitate global development [17]. This is particularly advantageous for those who have difficulty adhering to potential

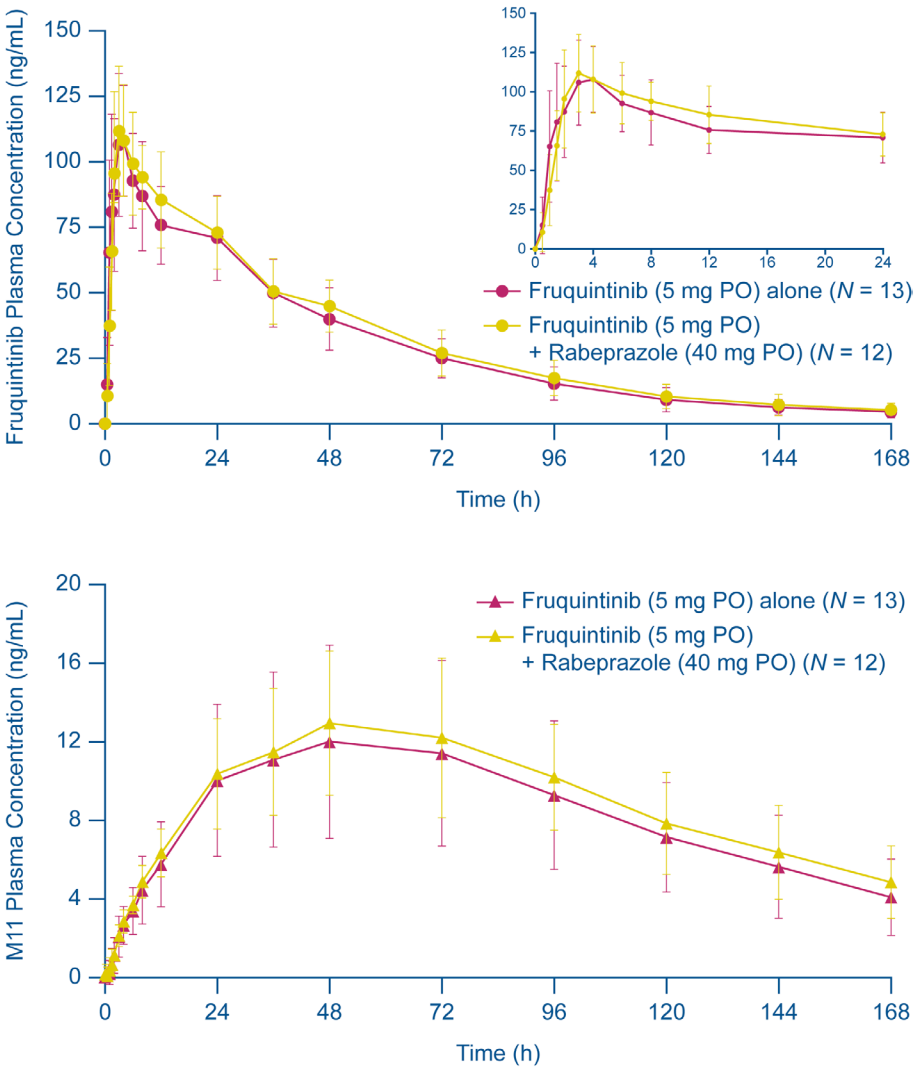

FIGURE 3 | Mean (±SD) plasma concentration-time profiles for fruquintinib (top panel) and M11 (bottom panel) after administration of fruquintinib 5 mg alone or with rabeprazole 40 mg. h, hours; PO, by mouth; SD, standard deviation.

food restrictions, distinguishing it from other medications for the treatment of mCRC that require ingestion with meals, such as regorafenib [18] or TAS-102 [19].

Following a single oral administration of a radiolabeled dose of fruquintinib 5 mg, approximately 60% of the dose was recovered in urine and 30% in feces [14]. Unchanged fruquintinib accounted for 0.50% of the administered dose in urine and 5.34% of the administered dose in feces, and the remainder of radioactivity was excreted in the form of metabolites [14]. Fruquintinib is extensively metabolized by CYP450 and non-CYP enzymes [6]. A recent study evaluating the effects of CYP3A inhibition and induction on the PK of fruquintinib in healthy subjects reported that coadministration of fruquintinib with a CYP3A inhibitor resulted in no clinically meaningful change in fruquintinib AUC or C_{max}; however, coadministration with a CYP3A inducer decreased fruquintinib exposure [20]. According to the metabolic profile of fruquintinib, only oxidative metabolites are detected in feces, with these metabolites also present in plasma and urine. This observation suggests the absence of unique metabolites formed by gut microbiota. All identified metabolites are presumed to have originated post-absorption, indicating that the fraction of the dose absorbed after a single 5 mg dose of fruquintinib in humans was at least > 85%. Moreover, fruquintinib was shown to be stable for at least 1 h in simulated gastric fluids and at least 3 h in simulated intestinal fluids, thus providing supportive evidence that changes to fruquintinib were not due to degradation in the GI tract (Takeda data on file). The totality of data suggests that fruquintinib was almost completely absorbed after oral administration. This could explain the absence of any substantial food effect, as there was limited potential for enhanced bioavailability through increased gastric residence or solubilization by bile salts with food intake.

As depicted in Figure S1, the aqueous solubility of fruquintinib is pH dependent and decreases at higher pH; thus, co-administered agents, such as a PPI, which increase gastric pH, may affect the absorption of fruquintinib. Because tyrosine kinase inhibitor absorption is multifactorial, a DDI with PPIs cannot always be fully ascertained based on physiochemical properties alone. Moreover, acid-reducing agents are commonly used by patients with cancer [10]. Therefore, the potential of a drug interaction

and its clinical relevance should be verified in an in vivo setting, as was done in this study for fruquintinib. Unexpectedly, our study showed no changes in the rate and extent of absorption, as measured by systemic exposure, for fruquintinib and its M11 metabolite when fruquintinib was co-administered with rabeprazole compared with when fruquintinib was administered alone, with the 90% CIs around the ratios of LSM AUCs and C_{max} for fruquintinib and M11 being entirely within 80%–125% limits. As PPIs pose a worst-case scenario for pH-dependent DDIs due to their prolonged effects on gastric pH, this lack of interaction with rabeprazole suggests the absence of a pH-dependent DDI for fruquintinib. These findings could potentially be extrapolated to other classes of acid-reducing agents, such as H2-antagonists and antacids.

A review of the literature revealed that more than 100 compounds, as reported by Patel and colleagues, have exhibited a discrepancy between in vitro solubility and in vivo pH-dependent DDI findings [21]. Notably, axitinib, a VEGFR2 inhibitor and a weak base drug that is administered at a clinical dose of 5 mg, showed no clinically meaningful food effect and exhibited pH-dependent solubility, yet displayed no clinically meaningful DDI (based on AUC) when combined with rabeprazole [22]. Considering that both fruquintinib and axitinib exhibit no food effect, and that food intake elevates gastric pH, a question arises regarding whether the absence of a food effect can reliably predict that a drug would not undergo pH-dependent DDI. According to an analysis conducted by Owens and colleagues, there was no causal relationship between food effect and pH-dependent DDI based on 20 BCS class 2 drugs that are weak bases [23]. In particular, of the nine BCS class 2 drugs lacking a food effect, more than half exhibited a pH-dependent DDI resulting in significantly reduced exposure. Overall, the inconsistency between in vitro and in vivo findings across multiple compounds underscores the need to refine the existing paradigm, which relies heavily on in vitro solubility to decide whether to conduct an in vivo pH-dependent DDI study. Recent advancements in physiologically based PK (PBPK) modeling propose that optimized PBPK models, developed using PK data after oral administration without acid-reducing agents (ARAs) and verified with additional PK studies in the presence and absence of food, can effectively predict the lack of ARA effects on the PK of drugs showing no pH-dependent DDIs in vivo [24]. Hence, PBPK modeling is emerging as a comprehensive approach to enhance the assessment of pH-dependent DDI potential [25].

Concomitant administration of fruquintinib with or without food or with rabeprazole was well tolerated and did not result in increased incidence of treatment-emergent AEs relative to fruquintinib given alone. A total of four subjects reported five AEs in this study. All five events were mild in severity and not related to the study drug. Fruquintinib demonstrated favorable tolerability, and its safety profile remained consistent with observations from prior studies conducted in healthy subjects [14, 16].

In conclusion, this study characterized the effect of food and coadministration of rabeprazole on the bioavailability of fruquintinib in healthy subjects. No clinically relevant effects of food or rabeprazole were observed on fruquintinib PK; thus, fruquintinib can be taken without regard to food or ARAs. No fruquintinib dose adjustment is necessary for patients concurrently taking fruquintinib with any agents or experiencing medical conditions that modify gastric pH.

Author Contributions

M.G., X.Z., N.G., and C.C. wrote the manuscript. M.G., Z.Y., X.Z., and C.C. designed the research. M.G., Z.Y., W.R.S., and X.Z. performed the research. M.G., Z.Y., W.R.S., X.Z., and C.C. analyzed the data.

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Conflicts of Interest

M.G. was employed by and owned stock in HUTCHMED at the time of the study. W.R.S. and C.C. are employed by and own stock in HUTCHMED. X.Z. is employed by Takeda Development Center Americas Inc. (TDCA). N.G. is an employee of and reports ownership of stocks/shares in Takeda. All other author(s) declared no competing interests for this work.

Data Availability Statement

The datasets, including the redacted study protocol, redacted statistical analysis plan, and individual participants' data supporting the results reported in this article, will be made available from the completed study within 3 months from the initial request, to researchers who provide a methodologically sound proposal. The data will be provided after its de-identification, in compliance with applicable privacy laws, data protection, and requirements for consent and anonymization.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section.