Effects of a High-fat Meal on the Pharmacokinetics of the VEGFR Inhibitor Fruquintinib: A Randomized Phase I Study in Healthy Subjects

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ABSTRACT

Purpose: Fruquintinib is a potent and highly selective oral small-molecule tyrosine kinase inhibitor targeting vascular endothelial growth factor receptor and demonstrates promising activity against a broad spectrum of cancer types. The objective of the study was to investigate the tolerability and effect of high-fat food on the pharmacokinetic profile of a fruquintinib capsule in healthy Chinese subjects.

Methods: Healthy Chinese male subjects aged between 18 and 45 years were enrolled in the study. The study included 2 phases: a dose-escalation phase and a food effect–assessment phase. In the dose-escalation phase, subjects were administered a single dose of fruquintinib (2, 3, or 4 mg) in the fasted state. In the food effect–assessment phase, subjects were administered a 4-mg fruquintinib capsule in the fasted and fed states, respectively, in 2 cycles. Blood samples for pharmacokinetic analysis were collected at the designated time points. Tolerability was assessed throughout the study by physical examination including vital sign measurements, clinical laboratory tests, 12-lead ECG, clinical assessments, and monitoring for and spontaneous reporting of adverse events.

Findings: Twenty-nine eligible male subjects were enrolled in the study, including 9 in the dose-escalation phase and 20 in the food effect–assessment phase. In the food effect–assessment phase, the ratios (90% CI) of the geometric mean $AUC_{0-\infty}$ and C_{max} values for fruquintinib in the fed state to those observed in the fasted state were 97.2% (94.0%–100.4%) and 82.9% (76.7%–89.5%), respectively. The mean (SD) T_{max} values of fruquintinib were 3.0 (1.0) and 5.6 (4.5) hours in the fasted and fed states, respectively. The most common adverse events possibly related to the study drug were elevated blood uric acid, diarrhea, and decreased white blood cell count.

Implications: The overall bioavailability of the evaluated formulation of fruquintinib was not affected by the consumption of a high-fat, high-calorie meal prior to dosing. However, the consumption of a high-fat, high-calorie meal prior to dosing prolonged the T_{max}. These results indicate that the fruquintinib capsule can be administered with or without food. ClinicalTrials.gov identifier: NCT01955304. (*Clin Ther*. 2019;41:1537–1544)

Key words: food effect, fruquintinib, healthy Chinese subjects, pharmacokinetics, Phase I, tolerability.

INTRODUCTION

Angiogenesis plays a crucial role in cell proliferation, vascular remodeling, and cancer cell dissemination in numerous tumor types. The vascular endothelial

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growth factor (VEGF) pathway has been identified as one of the key drivers of angiogenesis, and there appears to be a correlation between VEGF expression and tumor microvessel density.[1] In fact, a number of antiangiogenic agents involving the inhibition of VEGF-mediated angiogenesis have demonstrated antitumor activity in clinical trials and have been approved by regulatory authorities in FDA, USA. These agents have since become important treatments for multiple cancer-related indications.[2,3] The earlier generation of the small-molecule VEGF receptor (VEGFR) inhibitors, such as sunitinib,[4] sorafenib,[5] regorafenib,[6,7] and pazopanib,[8] are characterized by poor kinase selectivity. Many of these drugs inhibit >10 kinases as well as VEGFR at a similar potency,[9] which may lead to "off-target" toxic effects.[10] Therefore, a more selective and potent inhibitor of VEGFR that is well tolerated and can achieve high drug exposure to ensure sustained target inhibition is needed.

Fruquintinib was developed, based on rational drug design, as a cancer therapy directed toward the VEGF/VEGFR pathway. Fruquintinib selectively blocks VEGF-mediated receptor autophosphorylation, thus inhibiting endothelial cell proliferation and migration. A preclinical *in vitro* study showed that fruquintinib selectively inhibited the tyrosine kinase activity associated with VEGFR-1, -2, and -3 (median inhibitory concentrations, 33, 25, and 0.5 nmol/L, respectively) with good selectivity over other kinases.[11] In a Phase I clinical study, fruquintinib monotherapy demonstrated antitumor activity in a variety of advanced solid tumors, including metastatic colorectal cancer, non−small cell lung cancer, breast cancer, thyroid cancer, gastric cancer, pheochromocytoma, malignant melanoma, pancreatic cancer, submandibular gland carcinoma, nasopharyngeal carcinoma, gallbladder cancer, peripheral primitive neuroectodermal tumor, and neuroendocrine carcinoma.[12] The activity observed in early-phase studies in patients with metastatic colorectal cancer and non−small cell lung cancer has been supported by findings from pivotal studies.[13,14]

A preclinical study of the pharmacokinetic (PK) properties of fruquintinib showed moderate oral bioavailability of 42%−53% and a $T_{max\ of}$ <4 h in mouse, rat, dog, and monkey, with exposure−dose linearity proved in rats and dogs. No significant food effect on PK properties was detected in dogs. The study demonstrated good preclinical PK characteristics, and enabled successful PK and dose projections in humans.[15] Fruquintinib was well absorbed when administered in Chinese patients with advanced solid tumors. Linear PK was observed at doses of 1−6 mg.[12]

As the effect of food on the PK properties of fruquintinib was not investigated, this study was conducted primarily to investigate the PK profile of fruquintinib after single-dose oral administration of 4 mg in the fasted and fed (high-fat food) states in healthy subjects. Since this was the first time the antitumor agent fruquintinib was administered in healthy subjects, the tolerability of fruquintinib at single oral doses of 2, 3, and 4 mg was evaluated prior to the food-effect study.

SUBJECTS AND METHODS

Subjects and Products

This study was registered as ClinicalTrials.gov identifier NCT01955304. The study protocol was approved by the Ethics Committee at the Shanghai Xuhui Central Hospital (Shanghai, China), and the study was conducted in accordance with the Declaration of Helsinki and the Good Clinical Practice guideline. All subjects were required to provide written informed consent before any study-related procedures were performed.

Healthy Chinese male subjects aged 18−45 years with a body mass index between 19 and 25 kg/m^2 were enrolled in the study. Eligible subjects did not have any clinically significant abnormalities in physical examination findings, including vital signs, 12-lead ECG, and laboratory tests, during the screening period. Subjects capable of fathering children and their sexual partners agreed to use effective contraceptive measures during the study and within 90 days after the end of study.

Subjects with any of the following criteria were excluded from the study: a history of serious allergy, hemorrhage, gastrointestinal disease, hepatic disease, renal disease, or psychiatric disease; consumption of an over-the-counter drug (except acetaminophen), herbal medicine, or vitamin within 14 days prior to enrollment; vaccination within 6 months prior to randomization; blood pressure if $\geq$ 140/$\geq$90 mm Hg; and/or a positive result on testing for hepatitis B virus, hepatitis C virus, or HIV.

The investigational product, fruquintinib capsules, was supplied by Hutchison MediPharma Ltd (Shanghai, China).

Study Design and Procedures

This single-center, single-dose, randomized, open-label, 2-cycle crossover clinical study was conducted at the Phase I Clinical Research Unit of Shanghai Xuhui Central Hospital from June 2012 to August 2012. The objective of the study was to investigate the effect of high-fat food on the PK properties of fruquintinib. The tolerability of fruquintinib administered as a single oral dose of 2–4 mg was also evaluated.

The entire study included 2 phases: a dose-escalation phase and a food effect–assessment phase. In the dose-escalation phase, subjects were administered a single dose of fruquintinib capsule (2, 3, or 4 mg) in the fasted state, with 3 subjects in each dose group (9 subjects in total) for a preliminary evaluation of the tolerability and PK profile of fruquintinib capsules in healthy subjects. In the food effect–assessment phase, the 20 subjects enrolled were randomly assigned to 1 of 2 groups, each comprising 2 treatment periods (fasted and fed), as shown in Figure 1. In the fasted period, a single oral dose of fruquintinib 4 mg was administered after a 10 h-fast. In the fed period, a single oral dose of fruquintinib 4 mg was administered within 30 min after consumption of a high-fat, high-calorie meal (total calories: approximately 800–1000 kcal, of which fat accounted for at least 50% of the meal).

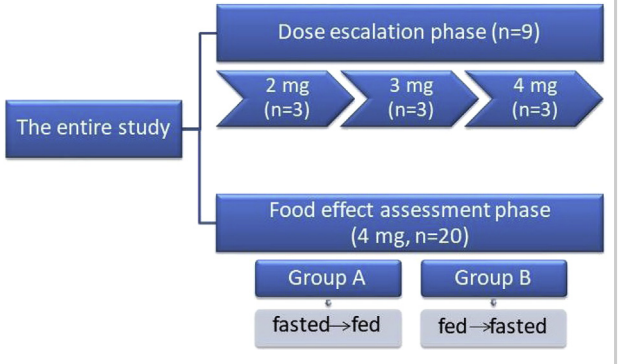

Figure 1. Study design.

The 2 treatment periods were separated by a washout period of at least 14 days. Subjects were required to adhere to certain restrictions, such as abstaining from all food and drink (except water), for at least 4 h after fruquintinib administration. Water was supplied *ad libitum* at any time except 1 h before and after administration. During confinement to the center, all of the subjects were given close medical monitoring for a 72-h period postdose. The postdose follow-up period in the dose-escalation phase was 7–14 days, while the postdose follow-up period in the food effect–assessment phase was 12–14 days after the second administration.

Blood Sampling

Blood samples (~3 mL each) were collected from a suitable forearm vein into an indwelling catheter or by immediate venipuncture at the following time points: 0 (predose), 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 24, 36, 48, 72, 96, and 120 h postdose. The blood samples collected were placed immediately in an ice bath, and the plasma was separated after centrifugation at 1000×*g* for 10 min. The separated plasma was divided into 3 polypropylene tubes with screwcaps (~0.5 mL plasma each) and stored frozen at −80 °C until analysis.

Quantification of Fruquintinib

The determination of fruquintinib concentrations in plasma was performed by Covance Pharmaceutical R&D Co Ltd (Shanghai, China) using a validated LC-MS/MS method. Following the protein precipitation with acetonitrile, the plasma supernatant produced was injected into the LC-MS/MS system for the determination of fruquintinib concentration. The analysis was performed with an Aquasil C_{18} analytical column (Thermo Fisher Scientific, Waltham, Massachusetts, 100 × 2.1 mm; internal diameter, 3 μm) and a gradient elution consisting of mobile phase A (0.5% formic acid and 10 mmol/L ammonium formate in water) and mobile phase B (0.5% formic acid in acetonitrile). The flow rate was 0.4 mL/min, and the injection volume was 5 μL. The mass spectrometer was set at the modes of positive ion electrospray and multiple reaction monitoring. Multiple reaction monitoring ions (Q1/Q3) for fruquintinib were *m/z* 394 → 363. The linear calibration curve for fruquintinib ranged from 0.5 to 1000 ng/mL. Intra- and interday precision and

accuracy were evaluated using the quality-control samples at 1.5, 75, and 750 ng/mL. The intraday precision was ≤8.9% (%CV), and the intraday accuracy was from −5.7% to 8.8% (bias). The interday precision was ≤8.2% (%CV), and the interday accuracy was from −0.4% to 4.0% (bias).

Tolerability Evaluation

Tolerability was assessed by physical examination including vital sign measurements (blood pressure, heart rate, respiratory frequency, and body temperature), clinical laboratory tests (hematology, blood biochemistry, coagulation function, urinalysis, urinary albumin/creatinine, and fecal analysis), 12-lead ECG, and monitoring for and spontaneous reporting of adverse events (AEs) throughout the study. After drug administration, vital signs were monitored on days 1, 2, and 3 of each cycle and during the follow-up period. Twelve-lead ECG was performed at 4 ± 1 h after drug administration and during the follow-up period. Physical examinations and clinical laboratory tests were conducted and the findings evaluated during the follow-up period. AEs were evaluated according to the National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE) version 4.03, and were managed and recorded promptly by qualified investigators (YML, QC, YL) according to relevant regulations. The prevalence of AEs was calculated by the number of subjects who experienced at least one AE divided by the total number of subjects.

Pharmacokinetic and Statistical Analysis

PK parameters were calculated with noncompartmental methods using WinNonlin software version 6.3 (Certara LP Software, Princeton, New Jersey) and Thermo Kinetica software version 4.4.1 (Thermo Fisher Scientific). Descriptive statistics were applied to all of the PK parameters in the appropriate states to calculate the means (SDs) of the parameters. The plasma PK parameters AUC, C_{max}, T_{max}, $t_{1/2}$, oral apparent volume of distribution during the terminal phase, apparent oral clearance, mean residence time, AUC_{0-t}, and $AUC_{0-\infty}$ were calculated using the linear trapezoidal rule method.

Statistical analysis of the effect of food on PK was based on the principle of bioequivalence. The bioequivalence module in the WinNonlin software version 6.3 was used for testing the exposure level. The Friedman rank sum test, which was carried out with Thermo Kinetica, was used to test for significance of the difference in T_{max} between the fasted and fed states. Based on the geometric means, if the 90% CIs of AUC_{0-t} and $AUC_{0-\infty}$ in the fed state were within 80%−125% of those in the fasted state, while the 90% CI of C_{max} in the fed state was within 70%−143% of that in the fasted state, it was possible to conclude that food had no effect on the bioavailability of fruquintinib.[16]

SAS software version 9.2 (SAS Institute, Cary, North Carolina) was used for statistical analysis of the tolerability data. Descriptive analysis was applied to summarize the demographic and baseline data. Frequency and percentage were used to summarize categorical variables.

RESULTS

Demographic Profile

A total of 29 eligible male subjects were enrolled in the study, including 9 in the dose-escalation phase and 20 randomized in the food effect−assessment phase. In the dose-escalation phase, the mean (range) age, weight, and body mass index of the subjects were 27.9 (20.5−38.9) years, 62.1 (51.4−74.6) kg, and 21.9 (19.1−24.7) kg/m^2, respectively. In the food effect−assessment phase, the mean (range) age, weight, and body mass index of the subjects were 25.9 (19.8−33.5) years, 63.9 (48.1−74.1) kg, and 22.0 (19.4−24.1) kg/m^2, respectively. All subjects completed the study and were included in the PK and safety populations.

Pharmacokinetic Properties

The mean PK properties in each dose group in the dose-escalation phase after a single dose of fruquintinib are summarized in Table I. The PK profiles of fruquintinib, indicated by the parameters of T_{max}, $t_{1/2}$, oral apparent volume of distribution during the terminal phase, and apparent oral clearance, were similar in the 3 dose groups, and AUC and C_{max} were dose dependent.

In the food effect−assessment phase, the effect of food on the PK properties of the fruquintinib capsule were evaluated. The key PK properties of fruquintinib in 20 subjects after a single dose of a 4-mg fruquintinib capsule administered orally in the fasted and fed states are listed in Table II, and the mean plasma drug concentration−time curves are

Table I. Key pharmacokinetic properties of fruquintinib after single-dose oral administration. Data are given as mean (SD).

Pharmacokinetic Parameter	Fruquintinib 2 mg (n = 3)	Fruquintinib 3 mg (n = 3)	Fruquintinib 4 mg (n = 3)	All Patients (n = 9)
$t_{1/2}$, h	25.2 (2.0)	28.2 (6.8)	19.2 (3.6)	24.2 (5.6)
T_{max}, h	2.8 (1.3)	3.0 (1.0)	3.2 (1.4)	3.0 (1.1)
C_{max}, ng/mL	54.7 (13.4)	76.9 (12.7)	117.8 (37.0)	NA
AUC_{0-t}, h · ng/mL	1767 (423)	2999 (385)	3506 (400)	NA
$AUC_{0-\infty}$, h · ng/mL	1839 (453)	3195 (527)	3565 (422)	NA
Vz/F, L	40.6 (6.9)	37.9 (4.5)	31.1 (4.7)	36.5 (6.4)
CL/F, mL/min	18.8 (4.4)	15.9 (2.5)	18.9 (2.4)	17.9 (3.2)
$MRT_{0-\infty}$, h	37.2 (3.3)	42.2 (9.9)	29.7 (6.3)	36.4 (8.2)

CL/F = apparent oral clearance; MRT = mean residence time; Vz/F = oral apparent volume of distribution during the terminal phase.

Table II. Key pharmacokinetic properties of fruquintinib after single-dose oral administration of a 4-mg capsule in the fasted and fed states. Data are given as mean (SD).

Pharmacokinetic Parameter	Fasted	Fed
$t_{1/2}$, h	25.7 (4.3)	26.1 (4.7)
T_{max}, h	3.0 (1.0)	5.6 (4.5)
C_{max}, ng/mL	129.1 (21.7)	108.4 (25.7)
AUC_{0-t}, h · ng/mL	4421 (790)	4258 (686)
$AUC_{0-\infty}$, h · ng/mL	4644 (881)	4490 (756)
Vz/F, L	32.4 (4.9)	34.0 (6.1)
CL/F, mL/min	14.9 (3.4)	15.3 (2.8)
$MRT_{0-\infty}$, h	39.7 (6.4)	42.3 (6.4)

CL/F = apparent oral clearance; MRT = mean residence time; Vz/F = oral apparent volume of distribution during the terminal phase.

shown in Figure 2. The ratios (90% CI) of the geometric means of $AUC_{0-\infty}$ and C_{max} for fruquintinib in the fed state to those observed in the fasted state were 97.2% (94.0%−100.4%) and 82.9% (76.7%−89.5%), respectively, in accordance with the range for bioequivalence within 90% CI issued by the China Food and Drug Administration (AUC, 80%−125%; C_{max}, 70%−143%).[16] The T_{max} values of fruquintinib in the fasted and fed states were 3.0 (1.0) and 5.6 (4.5) hours, respectively, and the rank sum test for T_{max} demonstrated a significant difference between the 2 states, indicating that high-fat food prolonged the T_{max}, with a trend of increasing individual difference.

Tolerability

In the dose-escalation phase (n = 9), AEs occurred in all 3 dose groups. The most common AE (>1 subject) was elevated blood uric acid (5 of 9 subjects), all cases of which were CTCAE grade 1. Most of the AEs resolved within 2 months, except in 1 subject with elevated blood uric acid, who was lost to follow-up.

In the food effect−assessment phase (n = 20), the numbers of subjects (prevalences) experiencing drug-related AEs were 13 (65%) and 10 (50%) in the fasted and fed states, respectively. All AEs were CTCAE grade 1 (except 1 case of diarrhea and 1 case of elevated blood bilirubin, which were grade 2) and resolved without any treatment. The most common drug-related AEs (>5%) were elevated blood uric acid, diarrhea, and decreased white blood cell count. No serious AEs occurred throughout the study, and none of the subjects withdrew from the study due to an AE.

The results of the other tolerability assessments (physical examinations, clinical laboratory tests,

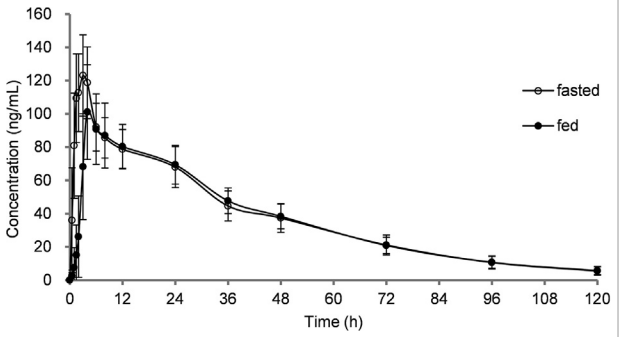

Figure 2. Mean (SD) plasma fruquintinib concentration–time curves after single-dose oral administration of a 4-mg capsule in the fasted and fed states.

vital signs, and ECG measurements [including QTc interval assessment]) did not indicate any unexpected risks of fruquintinib treatment in either the fasted or the fed state.

DISCUSSION

Fruquintinib is a potent and highly selective oral small-molecule tyrosine kinase inhibitor targeting VEGFR and demonstrates promising activity against a broad spectrum of cancer types. Its tolerability and PK properties in healthy subjects were not known. The dose-escalation phase was designed as a preliminary evaluation of the tolerability and PK profiles of a fruquintinib capsule in healthy subjects prior to the food effect–assessment phase. To assess the dose–exposure relationship in healthy male subjects, a single dose of 2, 3, or 4 mg of fruquintinib was administered to subjects. The linear regression for mean exposure in each dose group versus dose through the origin was plotted in the dose-escalation phase, and 1-factor ANOVA was performed for $AUC_{0-\infty}$/Dose and C_{max}/Dose in the 3 dose groups. No significant differences in $AUC_{0-\infty}$/Dose or C_{max}/Dose among the 3 dose groups were seen, and a good linear relationship between the mean exposure level and dose through the origin was observed. Thus, the exposure level of fruquintinib after a single dose of 2, 3, or 4 mg in these healthy male subjects increased in proportion with dose. Based on the results of the dose-escalation phase, we proceeded to the food effect–assessment phase. The administration of fruquintinib at 4 mg once daily has been found to be well tolerated and effective in patients with advanced solid tumors[12]; therefore, a single dose of fruquintinib 4 mg was chosen for the food effect–assessment phase.

In the fasted state, the T_{max} was ~3.0 h in these healthy male subjects, which indicates that the drug was absorbed rapidly. Fruquintinib demonstrated low clearance and moderate volume of distribution in humans. The $t_{1/2}$ and mean residence time of fruquintinib were about 30 and 40 h, respectively, in healthy subjects, showing a very long retention time of fruquintinib in humans. The %CVs for the major PK parameters, including C_{max}, AUC, and $t_{1/2}$, were <20%, indicating a small intersubject variability of fruquintinib PK properties in healthy subjects. Similar PK profiles (C_{max}, AUC, T_{max}) of fruquintinib were observed in healthy subjects and patients. Following a single oral dose of 4-mg fruquintinib in the fasting state, mean C_{max} values were 129 and 111 ng/mL in healthy subjects and patients, respectively, and mean $AUC_{0-\infty}$ values were 4644 and 5266 h · ng/mL, respectively. T_{max} was ~3 h in healthy subjects and patients. The above-mentioned PK data from patients were extracted from our previous study of fruquintinib in cancer patients, which has not been published yet (ClinicalTrials.gov ID number: NCT01645215).

In this study, the effects of high-fat food on the PK properties of fruquintinib were determined by a bioavailability analysis of the PK parameters in the fasted and fed states. The results demonstrated that the 90% CIs of the geometric mean ratios of $AUC_{0-\infty}$ and C_{max} of unchanged fruquintinib in the fed state to those in the fasted state were within the range for bioequivalence issued by the China Food and Drug Administration, indicating that food had no effect on the exposure level of unchanged fruquintinib. Therefore, fruquintinib was bioequivalent in the fasted and fed states, which provides a reference for clinical usage in patients with solid tumors.

The T_{max} values of unchanged fruquintinib were 3.0 (1.0) and 5.6 (4.5) hours in the fasted and fed states, respectively, with a significant difference on rank sum testing, indicating that high-fat food could prolong the T_{max} and result in a trend of increasing individual difference. The absorption rate was affected by food

intake, which may have been attributable to the change in gastric emptying time. The effects of food on the rate and extent of bioavailability differ by Biopharmaceutics Classification System (BCS) class. In BCS class 1 compounds, high-fat meals have no significant effect on the extent of bioavailability, but may delay stomach emptying and therefore cause an increase in T_{max}. In BCS class 2 compounds, high-fat meals increase the extent of bioavailability.[17] After *in vitro* experiments, fruquintinib was classified as BCS class 2; *in vivo,* however, fruquintinib demonstrated characteristics similar to those of BCS class 1 compounds, implying that fruquintinib may have better solubility in humans.

Given the mild slope of the fruquintinib concentration−time curve and the half-lives of fruquintinib (~30 h in healthy subjects and 40 h in patients with solid tumors)[12] being longer than the administration interval of once per day applied clinically (24 h), the slightly prolonged T_{max} would not affect the peak−trough fluctuation of plasma drug concentration at the steady state even though the rank sum test of T_{max} showed a significant difference.

Findings from the tolerability assessments were similar whether subjects received fruquintinib in the fasted or the fed state. A single 4-mg dose of fruquintinib resulted in an acceptable safety profile, as the majority of AEs were CTCAE grade 1 in severity and resolved readily.

One limitation of our study was that female subjects were not enrolled. Considering common hemorrhagic issues with VEGFR kinase inhibitors, and the physiologic cycle in female subjects from ages 18−45 years, the study enrolled only healthy male subjects. The PK characteristics of fruquintinib might be different in women. In addition, our study investigated the effect of only a high-fat meal on fruquintinib PK properties in healthy subjects who were fasted for at least 10 h prior to drug administration. Supplemental studies may be necessary to further assess the intravariability of fruquintinib, the effect of fasting timing on fruquintinib PK properties, as well as pH-dependent drug−drug interactions with fruquintinib in healthy volunteers or cancer patients.

CONCLUSIONS

The overall bioavailability of the evaluated formulation of fruquintinib was not affected by the consumption of a high-fat, high-calorie meal prior to dosing, but the meal did prolong the T_{max} of its absorption. These results indicate that fruquintinib capsules can be administered with or without food.

CONFLICTS OF INTEREST

This study was sponsored by Hutchison MediPharma Ltd. S.-H. Fan, K. Li, Y. Sai, and W.-G. Su are employees of Hutchison MediPharma. The authors have indicated that they have no other conflicts of interest with regard to the content of this article.

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All of the authors contributed to writing and review of the manuscript. H.-J. Qian wrote the initial draft. S.-H. Fan, K. Li, Y. Sai, and W.-G. Su designed and analyzed the study and reviewed and revised the manuscript. Q. Chen, Y. Liu, T.-T. Li, W. Wang, and J.-Y. Jia conducted the study and reviewed the manuscript. C. Yu and Y.-M. Liu designed and supervised the study and reviewed and revised the manuscript. All of the authors read and approved the final version of the manuscript.

REFERENCES

1. Bellamy WT, Richter L, Frutiger Y, et al. Expression of vascular endothelial growth factor and its receptors in hematopoietic malignancies. *Cancer Res.* 1999;59:728−733.
2. Veeravagu A, Hsu AR, Cai W, et al. Vascular endothelial growth factor and vascular endothelial growth factor receptor inhibitors as anti-angiogenic agents in cancer therapy. *Recent Pat Anticancer Drug Discov.* 2007;2:59−71.

3. Boere IA, Hamberg P, Sleijfer S. It takes two to tango: combinations of conventional cytotoxics with compounds targeting the vascular endothelial growth factor-vascular endothelial growth factor receptor pathway in patients with solid malignancies. *Cancer Sci*. 2010;101:7—15. Accessed March 02 2018, Available at: https://doi.org/10.1111/j.1349-7006.2009.01369.x.
4. Grandinetti CA, Goldspiel BR. Sorafenib and sunitinib: novel targeted therapies for renal cell cancer. *Pharmacotherapy*. 2007;27:1125—1144. Accessed March 02 2018, Available at: https://doi.org/10.1592/phco.27.8.1125.
5. Keating GM, Santoro A. Sorafenib: a review of its use in advanced hepatocellular carcinoma. *Drugs*. 2009;69:223—240.
6. Mross K, Frost A, Steinbild S, et al. A phase I dose-escalation study of regorafenib (BAY 73-4506), an inhibitor of oncogenic, angiogenic, and stromal kinases, in patients with advanced solid tumors. *Clin Cancer Res*. 2012;18:2658—2667. Accessed March 02 2018, Available at: https://doi.org/10.1158/1078-0432.CCR-11-1900.
7. Sartorebianchi A, Zeppellini A, Amatu A, et al. Regorafenib in metastatic colorectal cancer. *Clin Adv Hematol Oncol*. 2012;10:324—325.
8. Van Geel RM, Beijnen JH, Schellens JH. Concise drug review: pazopanib and axitinib. *Oncologist*. 2012;17:1081—1089. Accessed March 02 2018, Available at: https://doi.org/10.1634/theoncologist.2012-0055.
9. Glade-Bender J, Kandel JJ, Yamashiro DJ. VEGF blocking therapy in the treatment of cancer. *Expert Opin Biol Ther*. 2003;3:263—276. Accessed March 02 2018, Available at: https://doi.org/10.1517/14712598.3.2.263.
10. Chen HX, Cleck JN. Adverse effects of anticancer agents that target the VEGF pathway. *Nat Rev Clin Oncol*. 2009;6:465—477. https://doi.org/10.1038/nrclinonc.2009.94.
11. Sun Q, Zhou J, Zhang Z, et al. Discovery of fruquintinib, a potent and highly selective small molecule inhibitor of VEGFR 1, 2, 3 tyrosine kinases for cancer therapy. *Cancer Biol Ther*. 2014;15:1635—1645. Accessed March 02 2018, Available at: https://doi.org/10.4161/15384047.2014.964087.
12. Cao J, Jian Z, Wei P, et al. A Phase I study of safety and pharmacokinetics of fruquintinib, a novel selective inhibitor of vascular endothelial growth factor receptor-1, -2, and -3 tyrosine kinases in Chinese patients with advanced solid tumors. *Cancer Chemother Pharmacol*. 2016;78:259—269. Accessed March 02 2018, Available at: https://doi.org/10.1007/s00280-016-3069-8.
13. Li J, Qin S, Xu RH, et al. Effect of fruquintinib vs placebo on overall survival in patients with previously treated metastatic colorectal cancer: the FRESCO randomized clinical trial. *JAMA*. 2018;319:2486—2496. Accessed March 02 2018, Available at: https://doi.org/10.1001/jama.2018.7855.
14. Lu S, Chang J, Liu X, et al. Randomized, double-blind, placebo-controlled, multicenter phase II study of fruquintinib after two prior chemotherapy regimens in Chinese patients with advanced nonsquamous non–small-cell lung cancer. *J Clin Oncol*. 2018;36:1207—1217. Accessed March 02 2018, Available at: https://doi.org/10.1200/JCO.2017.76.7145.
15. Gu Y, Wang J, Li K, et al. Preclinical pharmacokinetics and disposition of a novel selective VEGFR inhibitor fruquintinib (HMPL-013) and the prediction of its human pharmacokinetics. *Cancer Chemother Pharmacol*. 2014;74:95—115. Available at: https://doi.org/10.1007/s00280-014-2471-3. Accessed March 2, 2018.
16. State Food and Drug Administration. Guideline for bioavailability and bioequivalence studies of generic drug products [in Chinese]. Accessed March 2 2018, http://samr.sfda.gov.cn/gsz05106/08.pdf. Accessed March 2, 2018.
17. Custodio JM, Wu CY, Benet LZ. Predicting drug disposition, absorption/elimination/transporter interplay and the role of food on drug absorption. *Adv Drug Deliv Rev*. 2008;60:717—733. Accessed March 2 2018, Available at: https://doi.org/10.1016/j.addr.2007.08.043.

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