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ORIGINAL RESEARCH

Effect of Food on the Pharmacokinetics and Safety of a Novel c-Met Inhibitor SCC244: A Randomized Phase I Study in Healthy Subjects

Juan Wu[1,2], Hongrong Xu[1], Hui Li[1], Lei Ma[3], Juan Chen[3], Fei Yuan[1], Lei Sheng[1], Chao Liu[1], Weili Chen[1], Xuening Li[1]

[1]Department of Clinical Pharmacology & Cancer Center, ZhongShan Hospital, Fudan University, Shanghai, People's Republic of China; [2]Department of Pharmacy, Shanghai Children's Medical Center, School of Medicine, Shanghai JiaoTong University, Shanghai, People's Republic of China; [3]Haihe Biopharma Co., Ltd, Shanghai, People's Republic of China

Correspondence: Xuening Li, Department of Clinical Pharmacology & Cancer Center, ZhongShan Hospital, Fudan University, 180 Fenglin Road, Shanghai, People's Republic of China, 200032, Tel +86 21 3158 7860, Fax +86 21 3158 7866, Email li.xuening@zs-hospital.sh.cn

Objective: This study aimed to investigate the effect of food on the pharmacokinetics and safety profiles of SCC244, a novel oral c-Met inhibitor in healthy Chinese male subjects.

Methods: It was a randomized, open-label, and 3-period crossover design, single-dose phase I clinical trial. A total of 18 healthy male subjects were enrolled. These subjects received a single oral 300 mg dose of SCC244 with a 14-day washout between each period. Blood samples were collected at the designated time points and determined using a validated liquid chromatography tandem mass spectrometry method. Pharmacokinetic parameters were calculated by noncompartmental methods. Tolerability was assessed by physical examination, vital sign measurements, 12-lead ECG, clinical laboratory tests, and adverse events (AEs) monitoring throughout the study.

Results: Eighteen eligible subjects were enrolled in the study. The ratios (90% CI) of C_{max} values for SCC244 in high-fat and low-fat meal states to that observed in fasted state were 194.8% (174.3–217.7%) and 194.6% (174.1–217.5%), respectively. The ratios of $AUC_{0\text{-}t}$ and $AUC_{0\text{-}inf}$ in the high-fat meal state versus the fasted state were 237.4% (208.7–270.0%) and 235.9% (207.5–268.3%), respectively. The ratios of $AUC_{0\text{-}t}$ and $AUC_{0\text{-}inf}$ in the low-fat meal state versus the fasted state were 219.2% (192.7–249.3%) and 218.3% (192.0–248.3%), respectively. Median T_{max} values and mean $t_{1/2}$ were similar in all groups. The most common AEs were headache, blood fibrinogen decreased, head discomfort, dizziness, and protein urine presence. All AEs were Common Terminology Criteria for Adverse Events (CTCAE) grade 1 (except 1 case of grade 2) and have resolved by the end of the study.

Conclusion: The bioavailability of the tablet formulation of SCC244 was significantly increased when administered with high- and low-fat meals. However, the meals did not affect the median T_{max} and $t_{1/2}$. Safety under different fed conditions was comparable to fasted conditions in this study.

Keywords: SCC244, c-Met inhibitor, food effect, pharmacokinetics, safety

Introduction

Cellular-mesenchymal to epithelial transition factor (c-Met), an important member of a subfamily of receptor tyrosine kinases (RTK), is highly expressed and abnormally activated in a wide variety of human malignancies.[1,2] This abnormal activation can induce tumor cell proliferation, survival, motility, and invasion, which is closely related to poor prognosis.[1–3] Further studies showed that aberrant c-Met activity is an important resistance mechanism to targeted kinase inhibitors, including those targeting EGFR, BRAF, and MEK, as well as cytotoxic chemotherapy.[4–6] Therefore, the development of targeted c-Met inhibitors remains a promising strategy for antitumor therapy.

SCC244 is a novel, potent, and highly selective oral inhibitor of c-Met that showed greater than 2400-fold selectivity for c-Met over a panel of 312 kinases, and has an IC_{50} in the subnanomolar range. SCC244 has potent antitumor activity

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in c-Met-dependent non-small cell lung cancer (NSCLC) and other tumor models in vitro and in vivo. In addition, the efficacy of SCC244 at 10 mg/kg is comparable with that of capmatinib at 15 mg/kg and crizotinib at 50 mg/kg.[7] Currently, Phase I dose escalation trial of SCC244 in patients with advanced solid tumors and Phase Ib/II studies in patients with advanced NSCLC with c-Met overexpression have been completed. Preliminary clinical data showed that SCC244 has manageable toxicity and good efficacy in patients with NSCLC with c-Met overexpression. Thus, SCC244 was proved to be a very promising anti-tumor drug.

However, like most tyrosine kinase inhibitors,[8] SCC244 is practically insoluble in water and shows pH-dependent solubility. Consequently, food can affect the rate and extent of absorption of these drugs by altering the luminal conditions in the human gastrointestinal tract.[9] Since the effect of food on the PK properties of SCC244 is currently unknown, this Phase I trial was conducted to evaluate the impact of food on the PK profile and safety after a single oral administration of 300 mg SCC244 in healthy Chinese male subjects.

Materials and Methods

Study Design and Procedures

This was a Phase I, single-center, randomized, open-label, single-dose, three-period crossover clinical study conducted at the Phase I Clinical Research Unit of ZhongShan Hospital affiliated to Fudan University from Mar 2021 to April 2021.

18 healthy adult male subjects were enrolled randomly into 6 meal sequences (S1-S6), with 3 subjects per sequence. The three periods were separated by a washout period of 14 days. The study design is given in Figure 1. Each subject received SCC244 under fasted condition, after a high-fat, high-calorie meal, or after a low-fat meal, respectively, in three periods. The high-fat, high-calorie meal or low-fat meal would be finished within 30 minutes (eat up all meals). SCC244 300 mg tablets would be orally administered with 240 mL warm water within 30 minutes after starting the meal. No food was allowed for at least 4 hours after dosing. Water was allowed as desired except for 1 hour before and 2 hours after study drug administration. Regular meals were then provided approximately 9 hours after dosing. The post-dose follow-up period was 8 days after administration.

This study was registered both at chinadrugtrials.org.cn identifier CTR20202582 (registered on 2020–12–17) and at clinicaltrials.gov identifier NCT05507294 (registered on 2022–08–18), and was conducted in accordance with the principles of the Declaration of Helsinki and Good Clinical Practice. The protocol was approved by the Ethics

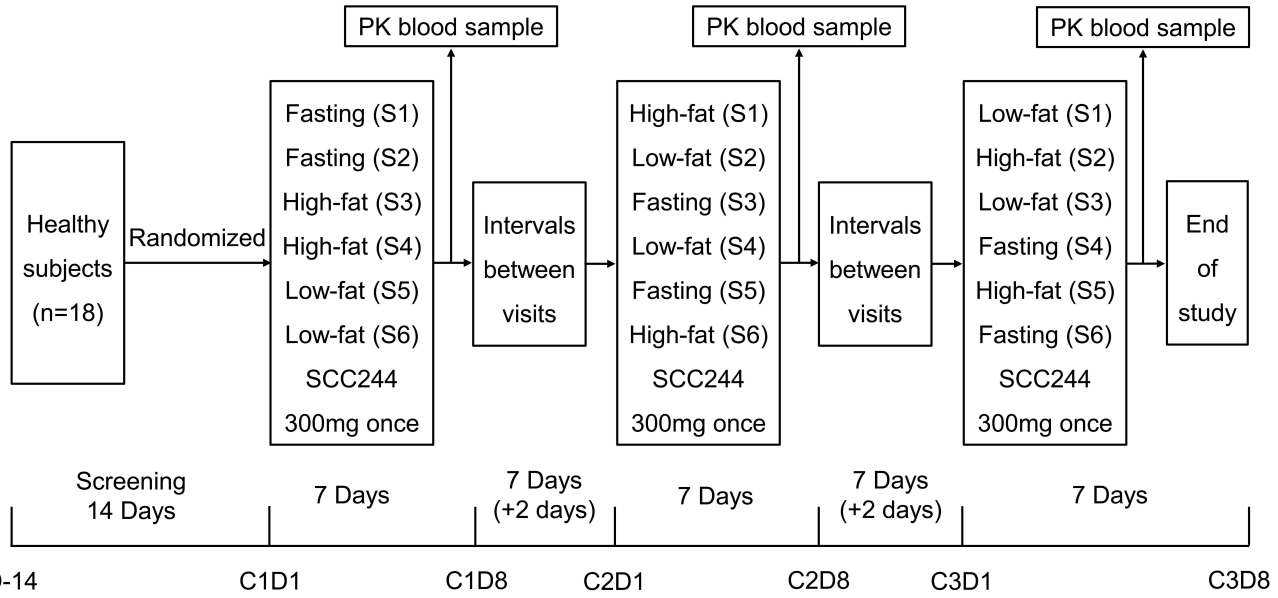

Figure 1 Study design.

Committee of ZhongShan Hospital. All subjects provided written informed consent before any study-related procedures started.

Study Population

Eligible subjects were healthy Chinese males aged 18–45 years, and with a bodyweight ≥50.0 kg and body mass index (BMI) between 19.00 and 26.00 kg/m^2. Before enrollment, each subject did not have any clinically significant abnormalities in medical history interview, physical examinations, vital sign measurements, clinical laboratory tests, chest X-ray (PA), and 12-lead ECGs. Subjects should be able to take adequate and effective contraceptive measures and to avoid sperm donation during the study, and within 6 months after the end of the study.

Exclusion criteria included: known malignancy, psychiatric disorder, respiratory diseases; a history of diabetes mellitus, pancreatitis, gastrointestinal surgery, headache, allergic diseases, allergies to any component of the study drug or similar drugs; any known diseases or consumption of drugs or foods that may affect drug absorption, distribution, metabolism, and excretion; a history of drug or alcohol abuse or heavy smoking; mean corrected QT interval (QTcF) at rest > 450 ms by 12-lead ECG; positive results for hepatitis B virus, hepatitis C virus, Treponema pallidum, or HIV test.

Blood Sampling and Quantification of SCC244

Blood samples (~2 mL each) were collected into EDTA vacutainers from each subject before dosing (0 h) and at 0.5, 1, 2, 2.5, 3, 3.5, 4, 6, 8, 12, 24, 36, 48, 72, 96, 120 and 168 h post-dose. The plasma samples were separated after centrifugation at 1500×g for 10 min at room temperature and stored at −80°C until analysis. The determination of SCC244 plasma concentrations was performed by Teddy Clinical Research Laboratory Shanghai Ltd (Shanghai, China) using a validated LC-MS/MS method. Chromatographic separation was performed on Shimadzu LC-30 AD system (Kyoto, Japan) with a Hypersil AQ C_{18} column (Thermo Fisher Scientific, USA; 100×3.0 mm; internal diameter, 3 μm) and a gradient elution consisting of mobile phase A (0.2% formic acid and 5 mM ammonium acetate in water) and mobile phase B (acetonitrile: methanol (7:3, v/v)). The flow rate was 0.8 mL/min, and the injection volume was 2 μL. Mass spectrometric analysis was performed on Triple Quad^{TM} 5500+ mass spectrometer (AB Sciex, USA) equipped with ESI source. Multiple reaction monitoring (MRM) transitions were *m/z* 460.1→198.1 for SCC244; *m/z* 466.1→201.2 for d6-SCC244 (the internal standard), respectively.

Safety Evaluation

Safety was evaluated by physical examination, vital sign measurements (ear temperature, supine blood pressure, pulse rate, and respiratory rate), 12-lead ECG, clinical laboratory tests (hematology, urinalysis, biochemistry, coagulation panel), and adverse events (AEs) monitoring throughout the study. After drug administration, vital signs and 12-lead ECG were examined at each visit, within 1 h pre-dose and 3 h ± 30 min post-dose on the day of administration in each period, and once daily at other visit. Physical examinations and clinical laboratory tests were conducted and the findings evaluated during the follow-up period. AEs were assessed according to the National Cancer Institute's Common Terminology Criteria for Adverse Events (NCI CTCAE) version 5.0 and were managed, recorded, and reported according to relevant regulations.

Pharmacokinetic and Statistical Analysis

SAS® version 9.4 (SAS Institute, Cary, North Carolina) was used for statistical analysis. PK parameters were calculated by non-compartmental analysis (NCA) methods using Phoenix WinNonlin® version 8.3 by dMed Biopharmaceutical Co., Ltd. (Shanghai, China) according to the SCC244 plasma concentrations of each subject and actual sampling time points. The maximum plasma concentration (C_{max}) and the time to maximum plasma concentration (T_{max}) were obtained directly from experimental data. Elimination half-life ($t_{1/2}$) was calculated from the elimination rate constant (k_e), which was estimated by the log-linear regression of the terminal phase of each curve. Area under the plasma concentration - time curve (AUC) was estimated by the linear trapezoidal method to the last measured concentration time point (AUC_{0-t}) and extrapolated to infinity ($AUC_{0\text{-inf}}$).

The food effect was evaluated based on the bioavailability analysis set (BAS). The primary PK parameters AUC_{0-t}, AUC_{0-inf}, and C_{max} were log-transformed and analyzed using a linear mixed-effects model, with sequence, period, meal type as fixed effects and individual subject (sequence) as a random effect. Then, geometric means of AUC_{0-t}, AUC_{0-inf}, and C_{max} with their 90% CIs were calculated after exponential transformation for each meal condition. The absence of food effect on the bioavailability of SCC244 was defined as the 90% CI of the geometric means of the primary PK parameters in the high-fat state or low-fat state falling within 80.00% to 125.00% of those in the fasted state, respectively.[10]

Results

Demographics

A total of 18 healthy Chinese male subjects who participated and were dosed in this study had a mean (range) age, weight, and BMI of 31.0 (23–39) years, 66.5 (55.5–77.3) kg, and 22.6 (20.2–25.0) kg/m^2. 1 (5.6%, 1/18) subject reported a history of appendicitis, which was considered as having no impact on this food effect study.

A total of 18 subjects were treated and included in the safety set (SS) and pharmacokinetics parameter set (PKPS); 17 subjects were included in the BAS. 1 subject withdrew prematurely due to positive urine morphine and was not included in the BAS.

Effect of Food on Pharmacokinetics of SCC244

Mean plasma concentration of SCC244 versus time curves are presented in Figure 2. The 90% CIs for the geometric mean ratios of PK exposure between the fed (both high-fat and low-fat meals) and fasted states were all above the specified upper limit of the food effect (80% to 125%) (Table 1). Relative to the fasted state, the high-fat and low-fat meals were associated with approximately 2-fold geometric mean increases in C_{max} and AUC, respectively. Inter-subject variability in C_{max}, AUC_{0-t}, and AUC_{0-inf} decreased in both high-fat and low-fat meal groups compared with fasted group. The median T_{max} value of SCC244 was 4.0 h in all three meal states. The mean $t_{1/2}$ under different meal conditions was similar in the low-fat meal group, the high-fat meal group, and the fasted group (24.7–26.1 h). These indicated that food has no effect on the rate of absorption and elimination of SCC244. The mean CL/F values in the high-fat meal group (5.7 L/h) and the low-fat meal group (6.3 L/h) were about half of that in the fasted group (12.8 L/h). The apparent volume of distribution (V/F) in the high-fat meal group (192.6 L) and the low-fat meal group (217.9 L) were also lower than that in the fasted group (461.5 L). The listing of the PK parameters for SCC244 for the three meal conditions are presented in Table 2.

Safety Evaluation

The incidences of AEs were similar under different conditions, with 12 (66.7%, 12/18), 15 (83.3%, 15/18), and 12 (70.6%, 12/17) subjects under fasted, low-fat meal, and high-fat meal conditions, respectively. Only 1 subject in the condition of low-fat meal experienced a CTCAE grade 2 headache. All other AEs were CTCAE grade 1. All AEs have resolved by the end of the study. The most common (top 5 overall incidences) AEs were headache (39.6%, 21/53), blood fibrinogen decreased (22.6%, 12/53), head discomfort (9.4%, 5/53), dizziness (9.4%, 5/53), and protein urine presence (7.6%, 4/53). Data under different food conditions are shown in Table 3. No SAEs or AEs leading to permanent discontinuation were reported in this study. No clinically significant abnormalities in other tolerability assessments (laboratory parameters, vital signs, physical examination, 12-lead ECGs) were reported in this study.

Discussion

SCC244 is a potent, and highly selective oral inhibitor of c-Met and shows significant antitumor activity to NSCLC and other tumors. Preliminary dose-finding trials showed that SCC244 was well tolerated with manageable toxicities over the dose of 25 mg to 400 mg QD and the recommended Phase II dose (RP2D) was 300 mg QD. However, with poor aqueous solubility but sufficient permeability, SCC244 is a Biopharmaceutics Classification System (BCS) Class II drug substance, whose bioavailability often depends on the luminal gastrointestinal conditions. Current literature indicates

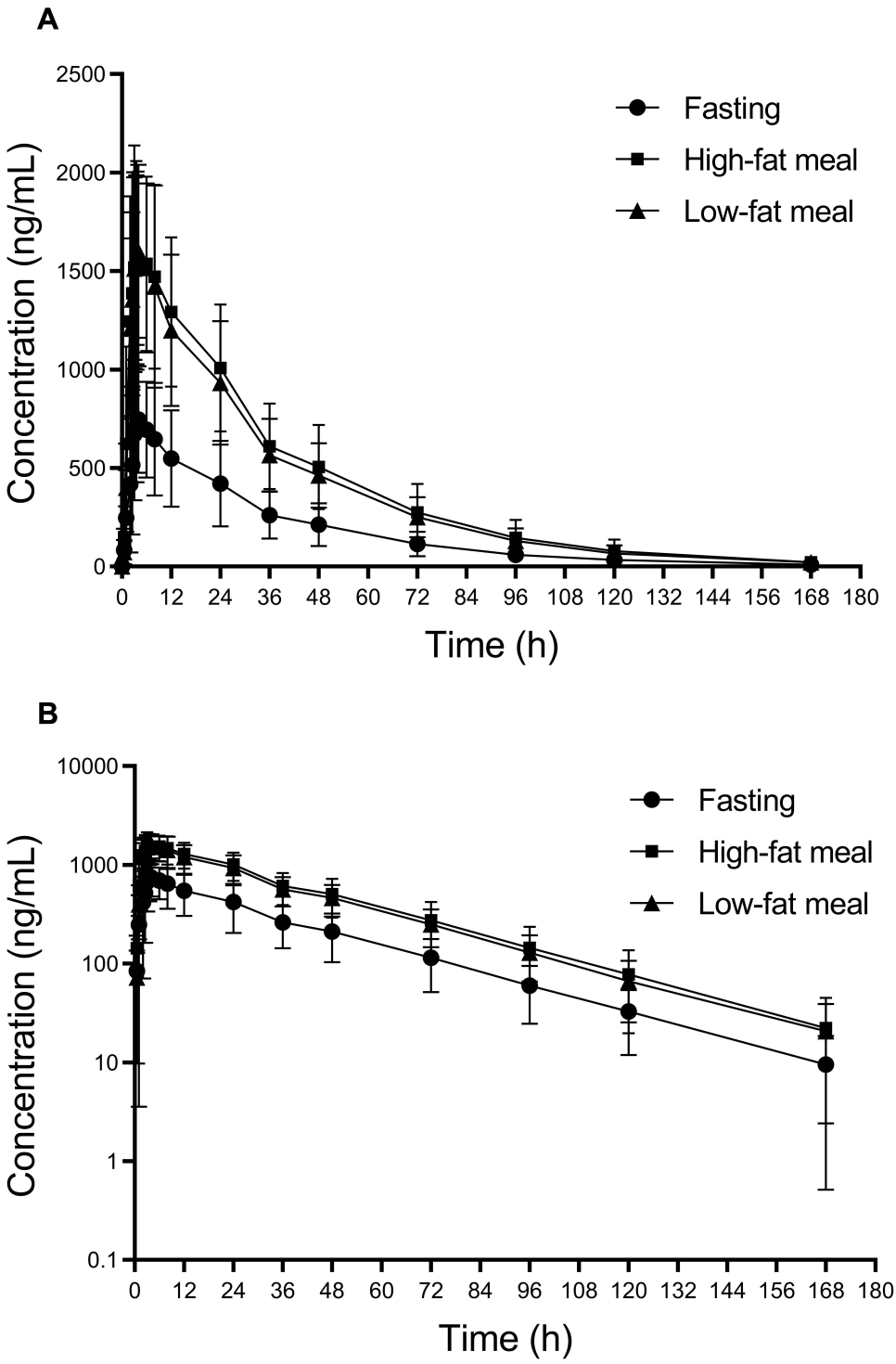

Figure 2 Mean (SD) plasma SCC244 concentration-time curves on linear scale (**A**), and log-linear scale (**B**) after single oral 300mg dose in the high-fat/high-calorie meal, low-fat meal and fasted states.

that oral targeted therapies, such as tyrosine kinase inhibitors (TKIs), are highly lipophilic and often show pH-dependent solubility. Therefore, the intake of these drugs with food can result in decreased or increased systemic drug exposure,[11] leading to poor efficacy, clinical benefit, or toxicity.[12–14]

Table 1 Evaluation results of Geometric Mean Ratio of PK Parameters Under High-Fat Meal Condition and Low-Fat Meal Condition Vs Fasting Condition - Bioavailability Analysis Set

PK Parameter	Fasting (n=17)	High-Fat Meal (n=17)	Low-Fat Meal (n=17)	Ratio (90% CI) of High-Fat Meal vs Fasting (n=17)	Ratio (90% CI) of Low-Fat Meal vs Fasting (n=17)
C_{max}, ng/mL	824.2	1605.3	1604.1	194.8% (174.3–217.7%)	194.6% (174.1–217.5%)
AUC_{0-t}, h·ng/mL	24799.8	58,867.7	54,347.8	237.4% (208.7–270.0%)	219.2% (192.7–249.3%)
AUC_{0-inf}, h·ng/mL	25322.2	59,746.0	55,282.0	235.9% (207.5–268.3%)	218.3% (192.0–248.3%)

Table 2 Effect of Food on the Pharmacokinetics of SCC244

PK Parameter	Fasting (n=18)	High-Fat Meal (n=17)	Low-Fat Meal (n=18)
C_{max}, ng/mL	868.7 (297.5)	1729.8 (527.9)	1748.9 (528.9)
%CV (C_{max})	34.3	30.5	30.2
T_{max}, h	4.0 (2.5–8.0)	4.0 (2.0–12.0)	4.0 (2.0–8.0)
$t_{1/2}$, h	26.1 (6.3)	24.7 (5.0)	25.6 (5.4)
AUC_{0-t}, h·ng/mL	27204.8 (12,017.4)	64,123.3 (22,312.2)	59,552.9 (18,751.2)
%CV (AUC_{0-t})	44.2	34.8	31.5
AUC_{0-inf}, h·ng/mL	27727.0 (12,195.2)	65,089.9 (22,968.6)	60,508.0 (19,103.4)
%CV (AUC_{0-inf})	44.0	35.3	31.6
CL/F, L/h	12.8 (5.5)	5.7 (4.2)	6.3 (5.8)
V/F, L	461.5 (173.6)	192.6 (111.2)	217.9 (148.6)

Note: Data are given as mean (SD), while T_{max} are given as median (range).

Table 3 Top 5 Incidences of AEs Under Fasting Condition, High-Fat Meal Condition and Low-Fat Meal Condition

AEs	Fasting (n=18) % (n)	High-Fat Meal (n=17) % (n)	Low-Fat Meal (n=18) % (n)	Total (n=53) % (n)
Headache	27.8% (5)	47.1% (8)	44.4% (8)	39.6% (21)
Blood fibrinogen decreased	16.7% (3)	23.5% (4)	27.8% (5)	22.6% (12)
Head discomfort	5.6% (1)	11.8% (2)	11.1% (2)	9.4% (5)
Dizziness	16.7% (3)	0% (0)	11.1% (2)	9.4% (5)
Protein urine presence	16.7% (3)	0% (0)	5.6% (1)	7.6% (4)

Note: Data are given as percent (absolute number).

In the present study, we found that the bioavailability of SCC244 was significantly impacted when a single 300 mg oral dose was administrated by meals. The exposures of SCC244 under high-fat and low-fat conditions were both higher than that under fasted conditions with the mean C_{max}, AUC_{0-t}, and AUC_{0-inf} approximately doubled. There was no significant difference between high-fat and low-fat meal groups, indicating that under low-fat meal condition, the influence of food on drug absorption has already reached its maximum. Increasing calories or fat content of food composition does not further increase drug absorption. As a weak base drug, the solubility of SCC244 declines greatly when the pH is higher than 1.2. Food increases the gastric pH and SCC244 may be less soluble in this gastric fluid. However, the increased bioavailability under both high-fat and low-fat meal conditions in the current study suggests that pH is not the main factor for SCC244 absorption. It was reported that bile salt secretion increases from approximately 4–6 mmol/L to 10–20 mmol/L after meal,[15] which is sufficient to solubilize 300 mg (0.65 mmol) dose of SCC244. By incorporation into micelles formed by bile salts, the solubility and permeability of SCC244 into enterocytes are increased, which would result in improved bioavailability. In addition, delay in gastric emptying rate[16] and increase of

splanchnic blood flow may also enhance the uptake of SCC244 into circulation. In the current study, inter-subject variabilities in SCC244 C_{max} and AUC were decreased in both high-fat and low-fat states.

It has been reported that, among oral TKIs, the strongest effect of high-fat meal is a 3.7-fold increase reported for 960mg single dose vemurafenib.[17] Lapatinib bioavailability increased 80% and 161% with a low-fat and high-fat meal, respectively.[18] Low-fat and high-fat meal can increase the bioavailability of regorafenib by 36% and 48%, respectively.[19] In contrast, crizotinib and vandetanib bioavailability are unaffected by food.[20,21] Currently, for the drug whose oral bioavailability can be increased by food, like lapatinib, whether it should be taken with food is still controversial.[11] Some suggested that a lower dose taken in the fed state might be sufficient to achieve therapeutic concentration compared with fasted state. Thus, medical costs can be reduced and adverse gastrointestinal reactions might be diminished. Others, however, argued that extrapolating the effects of standardized meal to daily practice in patients with cancer is complicated and may lead to therapeutic risks.

Whereas the C_{max} and AUC for SCC244 increased when the drug was administered with food, the mean $t_{1/2}$ values were not affected. This finding suggests that food affects the bioavailability of SCC244 mainly by altering the gastrointestinal absorption-related mechanisms, and has no apparent systemic effects. Therefore, the decrease in SCC244 CL/F values in fed groups was probably the result of increase in the total bioavailability of SCC244 and not its total body clearance. Furthermore, there were no significant differences in median T_{max} values between the three groups, which indicated that food affects the extent but not the rate of SCC244 absorption. This may be due to the use of solid dispersion technology by hot melt extrusion in SCC244 tablets manufacturing, which can increase the dissolution rate of poorly water-soluble drugs.[22–24] Furthermore, in the fed state, water co-administered with drug does not mix very well with the chyme but rapidly emptied from the stomach along the stomach wall.[25] This may result in faster absorption of certain amount of drug than it would be in the case of the slower gastric emptying.[26]

Findings from the safety evaluation were similar under three meal conditions (fasting, low-fat meal, and high-fat meal). The majority of AEs were CTCAE grade 1 and all were resolved by the end of the study. In general, the safety of the single oral dose of SCC244 300 mg under different meal conditions in healthy Chinese male subjects was acceptable in this study.

There were several limitations in this study and should be clarified. First of all, the findings in this study were based on a single dose of SCC244 in healthy subjects, and the number of subjects is relatively small. It is not possible to draw the final conclusions. Secondly, dietary habits vary from patient to patient, and even the same patient has different daily food composition. In addition, even a low-fat meal of 400 to 500 calories may be too much for patients with advanced cancer, who often experience loss of appetite and adverse gastrointestinal events. Therefore, further study should be carried out to assess the reliability, consistency, and safety of routine use of food to improve SCC244 bioavailability for chronic therapy. Finally, female subjects were not enrolled in this study. Preliminary data suggested that the PK profiles of SCC244 were similar in male and female patients. Given that the primary objective of the study was to investigate the effect of food on PK, the influencing factors should be reduced as far as possible. Therefore, this study enrolled only healthy male subjects.

Conclusions

Overall, the exposures of SCC244 under high-fat and low-fat conditions were both higher than that under fasted condition when a single 300 mg oral dose was administrated. However, the meal did not affect the rate of absorption (T_{max}) and systemic clearance and elimination ($t_{1/2}$) of SCC244. The safety of a single oral dose of SCC244 300 mg under different meal conditions was acceptable in this study.

Data Sharing Statement

The original contributions presented in the study are included in the article, and further inquiries can be directed to the corresponding author.

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Disclosure

Lei Ma and Juan Chen are employees of Haihe Biopharma Co., Ltd. The authors have indicated that they have no other conflicts of interest with regard to the content of this article.

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