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CLINICAL TRIAL REPORT

Effects of Food on the Pharmacokinetics and Safety of HA121-28 Tablet, a Novel Multi-Targeting Tyrosine Kinase Inhibitor, in Healthy Chinese Subjects: A Phase I Clinical Trial

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Purpose: HA121-28, a novel multi-targeting tyrosine kinase inhibitor, has dual efficacy against tumor growth and neovascularization. The objectives of this study were to assess the effect of high-fat and high-calorie food on the pharmacokinetic (PK) profile and safety of HA121-28 tablet in healthy subjects.

Patients and Methods: A single-dose, randomized, open-label, two-period, crossover-designed phase I clinical trial was conducted. Subjects received 200 mg HA121-28 in the fasted state or with high-fat and high-calorie breakfast. The effects of high-fat and high-calorie food on the PK profile and safety of HA121-28 were evaluated by using noncompartmental analysis and whole-process safety assessment.

Results: Twenty subjects were successfully completed the trial. The geometric mean ratios (GMRs) for the peak concentration in plasma (C_{max}), area under the curve from zero to the time point (AUC_{last}), and area under the curve from zero to infinite (AUC_{inf}) postprandially versus fasted were 108.45% (98.51% – 119.40%), 105.23% (100.25% – 110.47%), and 104.14% (97.41% – 111.34%), respectively. The majority of reported adverse events were graded as either level 1 or 2 in severity and recovered spontaneously without any interventions.

Conclusion: The exposure of HA121-28 was not significantly affected by the high-fat and high-calorie food. The clinical application of HA121-28 tablet can be recommended for use in both fasted and postprandial states.

Keywords: HA121-28, ##Food effects, pharmacokinetics, safety, tyrosine kinase inhibitor

Introduction

HA121-28, a novel, oral small molecule, multi-targeting tyrosine kinase inhibitor (TKI), has dual efficacy against tumor growth and neovascularization. Based on preclinical pharmacological investigations, HA121-28 is earmarked for indications such as *RET* fusion non-small cell lung cancer (NSCLC), medullary thyroid carcinoma (MTC), and biliary tract cancer, among other advanced solid tumors.

The *RET* gene, encoding a receptor tyrosine kinase proto-oncogene, plays a crucial role in fundamental cellular processes such as signal transduction, proliferation, and differentiation.[1,2] However, aberrations such as mutations or fusions in the *RET* gene can lead to its hyperactivation, initiating and driving tumor formation and progression by regulating the downstream pathways.[2–4] Studies indicate that the *RET* fusion rate ranges from approximately 1% to 2% in NSCLC, with a notable increase seen in epidermal growth factor receptor/anaplastic lymphoma kinase/Kirsten rat

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sarcoma viral oncogene (EGFR/ALK/KRAS)-negative lung adenocarcinoma patients, reaching 16%. In MTC, the incidence of *RET* fusion even increases to approximately 20%.[5–8]

For patients harboring *RET* mutations, specific targeted therapies have emerged as pivotal treatment strategies. The TKIs selpercatinib and pralsetinib were approved by the U. S. Food & Drug Administration (FDA) for the treatment of advanced *RET* fusion-positive lung cancer in 2020 based on the promising results of several clinical trials.[9] However, resistance is still a major challenge in *RET* fusion-positive lung cancer patients treated with RET TKIs.[6] Multi-targeting strategies might be an option.

Above targeting *RET* fusion, as a multi-targeting TKI, HA121-28 also targets EGFR, vascular endothelial growth factor receptor (VEGFR), and fibroblast growth factor receptor (FGFR) among others. These supplementary targets engagements further potentiate anti-tumor efficacy and may avoid drug resistance caused by simply targeting *RET* fusion. Moreover, the inhibition of angiogenesis by HA121-28 reduces the tumor blood supply, depriving tumor cells of oxygen and nutrients, thereby impeding tumor growth and dissemination. These attributes render it a promising candidate for the treatment of various cancers. Currently, HA121-28 is undergoing investigation in several clinical trials (NCT03994484, NCT04784520, NCT05117658, and NCT04787328).

Food effect studies represent a pivotal component in clinical trials for novel drugs.[10] Interactions between drugs and food may exert substantial influence on the safety and efficacy of pharmaceutical agents, especially for oral oncology drugs.[11] The co-administration of medication with food has the potential to modulate drug absorption and systemic exposure, thereby eliciting alterations in both safety and efficacy profiles. Specifically, food can affect drug absorption by altering gastric pH, gastrointestinal motility, or enzymatic activity, all of which can influence the rate and extent of drug absorption.[12,13] Additionally, the composition of a meal (eg, fat content, protein, or carbohydrate levels) can interact with drug properties, such as solubility or permeability, potentially affecting bioavailability.[14–16] As a result, evaluating the effect of food on the pharmacokinetics (PK) of a novel drug has emerged as a paramount endeavor, crucial for safeguarding the clinical utility and efficacy of therapeutics, while optimizing therapeutic regimens tailored to dietary considerations. This evaluation is particularly important for drugs with narrow therapeutic windows, complex absorption profiles, or those that rely on specific transporters or enzymes that may be modulated by food intake. A thorough understanding of the effect of food on the PK parameters and safety of HA121-28 is critical not only for optimizing dosing strategies but also for informing clinical administration guidelines. Therefore, the present study was designed to assess the impact of food on the PK profiles and safety of HA121-28 in healthy subjects.

Materials and Methods

Ethics Approval

This study was designed and conducted in accordance with the Declaration of Helsinki, Good Clinical Practice guidelines, and applicable FDA guidance. The clinical trial was approved by the Ethics Committee of West China Hospital, Sichuan University (Chengdu, China) and was registered at www.clinicaltrials.gov as NCT05072535. All subjects signed informed consent forms prior to screening.

Study Design

In this study, a single-dose, randomized, open-label, two-period, crossover clinical trial with the aim of evaluating the effect of food on the PK of HA121-28 was conducted. Eligible subjects (Table S1) were admitted to the clinical research unit at West China Hospital, Sichuan University, one day prior to drug administration. Following each treatment cycle, subjects underwent the required assessments and biological sample collection. The subjects were randomly assigned in a 1:1 ratio to Group A and Group B. Each subject underwent two treatment periods (fed and fasted) and received a single oral dose of 200 mg of HA121-28 on Day 1 of each period. After the first dosing, all subjects underwent a 35-day washout period before the initiation of the subsequent dosing period. In Group A, subjects first received HA121-28 under a high-fat and high-calorie fed condition followed by the fasting dosing period after the washout period. Conversely, subjects in Group B received HA121-28 under the fasting condition first, followed by the high-fat and high-calorie fed dosing period after the washout (Figure 1). The standardized high-fat and high-calorie breakfast consisted of

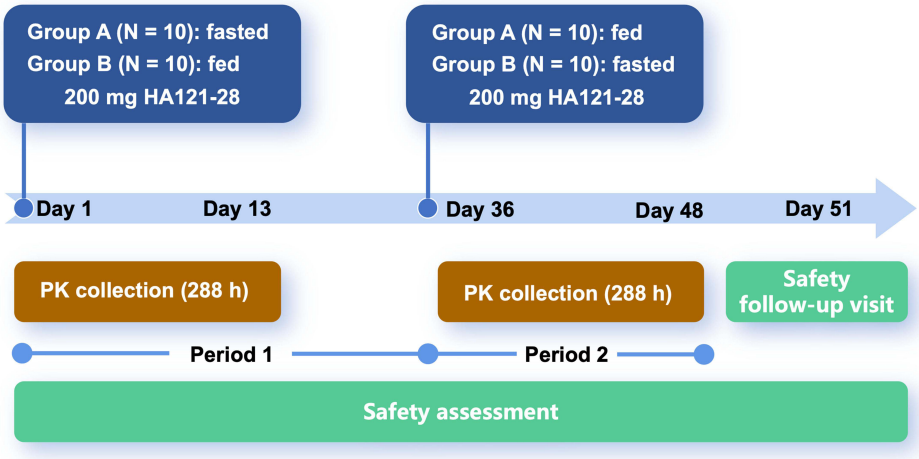

Figure 1 The schematic of study.

approximately 900 kcal, of which approximately 17% of the energy originated from protein, approximately 28% from carbohydrates, and 55% from fat.

Fasted conditions: Subjects received HA121-28 tablet with 240 mL of water following an overnight fast of at least 10 h. No food was allowed for at least 4 h post-dose. Water was not allowed up to 1 h before and 1 h after drug administration (except for medicated drinking water).

Fed conditions: Subjects received HA121-28 with 240 mL of water 30 minutes ± 3 minutes after the start of a high-fat and high-calorie breakfast, following an overnight fast of at least 10 h. No food was allowed for at least 4 h post-dose. Water was not allowed up to 1 h before and 1 h after drug administration (except for medicated drinking water).

Within the range of 25 to 600 mg, HA121-28 demonstrated predominantly linear PK in terms of the key parameters such as the peak concentration in plasma (C_{max}), area under the curve from zero to the time point (AUC_{last}), and area under the curve from zero to infinite (AUC_{inf}), along with a favorable safety profile. No dose-limiting toxicity (DLT) events were observed at or below the 600 mg dose level. The formulation size of HA121-28 tablets in this study was 200 mg. Additionally, studies of vandetanib, a drug with a similar structural target to the HA121-28, have demonstrated that it is safe and well-tolerated in healthy subjects within a dosing range of 300 to 1200 mg. Most clinical studies of vandetanib in healthy subjects used a dose of 300 mg.[17] In conclusion, considering the linearity of PK, 200 mg of HA121-28 was selected as the dosing regimen in healthy subjects for safety reasons.

Study Population

A total of twenty health subjects between 18 and 45 years of age (inclusive), with body mass index (BMI) within 18.0–26.0 kg/m^2 (inclusive) were enrolled in this study. Subjects who provided the informed consent were rigorously screened according to the inclusion and exclusion criteria (the inclusion and exclusion criteria are shown in Table S1).

Pharmacokinetic Evaluation and Parameters

Venous blood samples were collected from Day 1 and Day 36 before (−30 min to 0 h) and 1 h ± 2 min, 2 h ± 5 min, 4 h ± 5 min, 8 h ± 10 min, 12 h ± 10 min, 24 h ± 30 min, 36 h ± 30 min, 48 h ± 30 min, 72 h ± 30 min, 96 h ± 30 min, 120 h ± 1 h, 144 h ± 1 h, 168 h ± 2 h, 192 h ± 2 h, 216 h ± 2 h, 240 h ± 2 h, 264 h ± 3 h, 288 h ± 3 h after the administration of HA121-28. Approximately 3 mL of blood was put into a labeled EDTA-K2 anticoagulant vacuum blood collection tube, and the time of blood collection was recorded in the sample collection list.

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Safety Assessment

The safety assessment of the food effect study included recording adverse events (AEs), treatment-emergent adverse events (TEAEs), serious adverse events (SAEs) and the results of clinical laboratory tests (routing blood tests, blood biochemistry, routine urine tests, and coagulation function), 12-lead electrocardiogram (ECG) tests, vital sign tests, and routine physical examination. All details were recorded, including comprehensive descriptions of the AEs, TEAEs, SAEs and associated symptoms, the timing of occurrence, severity (graded in accordance with NCI-CTCAE 5.03 guidelines), potential causes, correlation with the investigation drug, duration, treatments administered, and final outcomes.

Bioanalytical Methods

Plasma concentrations of HA121-28 were determined using a methodologically validated liquid chromatography-mass spectrometry/mass spectrometry (LC-MS/MS) method. The linear range of the plasma drug concentration standard curve was 2.00–2000 ng/mL, and the lower limit of quantification was 2.00 ng/mL. The accuracy was within ±15.0% with a precision < 15%. The selectivity, recovery, matrix effect, and stability of the assay were also met the requirements of the FDA guideline for bioanalytical validation.[18]

Data and Statistical Analysis

The full analysis set (FAS) encompasses all enrolled participants who have administered with HA121-28 at least once. The FAS served as the cohort for demographic and baseline characteristic analyses. The safety set (SS) comprises all enrolled subjects who have received HA121-28 at least once and for whom safety assessment data are available. The SS was used for safety analysis, with adverse events and adverse reaction incidence calculated based on the number of subjects in the SS. The PK parameter set (PKPS) included subjects who had at least one evaluable PK parameter. Subjects were excluded if they had serious protocol violations, pre-administration concentrations exceeding 5% of C_{max}, concomitant drug use during the trial, or any other conditions that could affect PK parameters calculation of HA121-28.

The main PK parameters of the food effect study were as follows: C_{max}, AUC_{last}, AUC_{inf}, time to reach peak concentration in plasma (T_{max}), terminal half-life ($t_{1/2}$), volume of distribution ($V_{z/F}$), total body clearance for extra-vascular administration ($CL/_F$), terminal elimination phase rate constant (λ_z), etc. The PK parameters were calculated by a non-compartmental analysis by Phoenix WinNonlin software (version: 8.3.1, Certara, USA, Inc., Princeton, New Jersey) and the log-transformed PK parameter calculations were performed using mixed-effects model. SAS® (version 9.4, SAS Institute Inc., Cary, North Carolina) was used for the statistical analysis.

In accordance with the FDA guidance, it is recommended to enroll a minimum of 12 subjects in a trial to assess the effects of food on drugs.[19] The least squares mean differences between the fed and fasted conditions and their 90% confidence intervals (CIs) were estimated by the linear mixed-effects model. The 90% CIs of geometric mean ratios (GMRs) were further assessed to determine whether they fell in the range of 80% – 125% to evaluate the effect of food on the PK of the HA121-28 tablet. The significance level of the hypothesis test using a two-sided test was 0.05.

Results

Subjects Characteristics

Twenty subjects were enrolled in the FAS dataset, with 14 were male (70.0%) and 6 were female (30.0%). The mean age was 26.5 ± 5.46 years, with a mean BMI of 22.29 ± 1.901 kg/m². The demographic characteristics of the particulars in each arm of the study are outlined in Table 1.

PK Assessment and Food Effect on HA121-28

Based on the PKCS, the study on food effects delineated the mean (Mean ± SD) plasma drug concentration-time profiles under fasted and postprandial conditions, as depicted in Figure 2. Following oral administration of HA21-28 postprandially, the concentration-time curve was similar to that observed under fasting conditions, with no significant differences in C_{max}, T_{max}, and λ_z (Table 2). The median T_{max} in both groups remained consistent at 8.00 h, indicating that food intake does not influence the absorption rate of HA121-28. The arithmetic means for $t_{1/2}$ under fasting and fed conditions were

Table 1 Baseline Demographic of Subjects

	A[a] (N=10)	B[a] (N=10)	Total (N=20)
Age (years)			
Mean (SD)	25.3 (5.36)	27.6 (5.60)	26.5 (5.46)
Median	25.0	26.0	25.5
Min, Max	18, 36	23, 42	18, 42
Sex			
Male (%)[b]	8 (80.0)	6 (60.0)	14 (70.0)
Female (%)[b]	2 (20.0)	4 (40.0)	6 (30.0)
Height (cm)			
Mean (SD)	169.15 (7.960)	164.96 (7.467)	167.06 (7.813)
Median	170.45	166.95	167.70
Min, Max	155.4, 180.1	148.9, 173.6	148.9, 180.1
Weight (kg)			
Mean (SD)	64.40 (7.021)	60.12 (7.514)	62.26 (7.410)
Median	62.60	61.70	61.95
Min, Max	52.7, 74.2	45.8, 70.8	45.8, 74.2
BMI (kg/m^2)			
Mean (SD)	22.53 (1.960)	22.05 (1.914)	22.29 (1.901)
Median	22.60	21.40	21.65
Min, Max	20.0, 25.9	19.6, 25.8	19.6, 25.9

Notes: [a] A, administration commenced on Day 1 under fasting conditions, with subsequent dosing initiated on Day 36 following a high-fat and high-calorie diet. B, dosing was initiated postprandially on Day 1, transitioning to fasting conditions on Day 36 for the second cycle. [b] The computation of percentages (%) is predicated upon the total number of individuals within each cohort's full analysis set.
Abbreviations: BMI, body mass index; SD, standard deviation.

103 h and 97.6 h, respectively, with corresponding arithmetic means for λ_z at 0.00668 h^{-1} and 0.00718 h^{-1}, demonstrating that drug elimination is unaffected in the presence of food. As shown in Table 3, the 90% CI of GMRs for C_{max}, AUC_{last}, and AUC_{inf} under postprandial versus fasting conditions were 108.45% (98.51% – 119.40%), 105.23% (100.25% – 110.47%), and 104.14% (97.41% – 111.34%), respectively. Thus, the PK characteristics of HA121-28 administered under fed and fasted conditions closely resemble each other, with food exerting no influence on the PK profile of HA121-28.

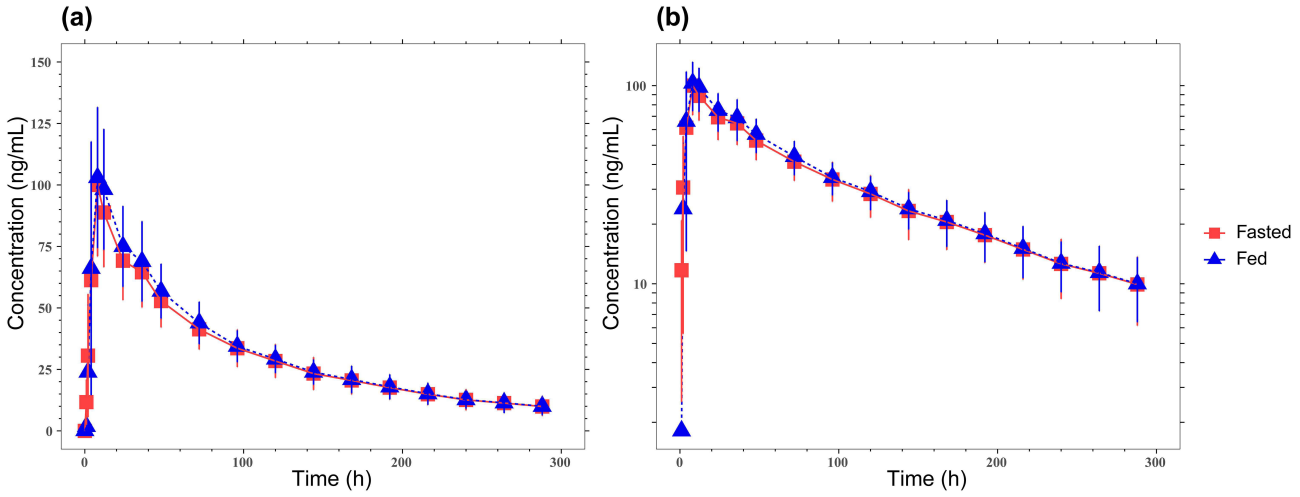

Figure 2 The mean plasma concentration-time curves of fasting or fed state. (**a**) Linear mean plasma concentration-time plot. (**b**) Semi-logarithmic mean plasma concentration-time plot. Error bars in the plots represent SD.

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Table 2 The Pharmacokinetic Parameters of HA121-28 on Fasted and Fed

Parameter[a]	Fasted (N = 20)	CV (%)	Fed (N = 20)	CV (%)
C_{max} (ng/mL)	102 (29.5)	29.8	110 (32.2)	27.5
AUC_{last} (ng*h/mL)	8880 (1990)	21.9	9300 (1820)	19.6
AUC_{inf} (ng*h /mL)	10300 (2580)	24.3	10,400 (2040)	19.5
T_{max} (h)	8.00 (4.00, 24.00)		8.00 (4.00, 12.00)	
λ_z (1/h)	0.00668 (0.00128)	19.2	0.00718 (0.00134)	
$t_{1/2}$ (h)	103 (17.1)	16.9	97.6 (16.4)	19.7
CL/F (L/h)	20.6 (4.73)	24.2	19.9 (3.77)	19.5
V_z/F (L)	3010 (661)	21.3	2760 (539)	31.2

Notes: [a] Data are presented as mean (standard deviation); T_{max} is shown as median (minimum, maximum).

Abbreviations: C_{max}, peak concentration in plasma; AUC_{last}, area under the curve from zero to the time point; AUC_{inf}, area under the curve from zero to infinite; T_{max}, time of peak concentration in plasma; λ_z, terminal elimination phase rate constant; $t_{1/2}$, terminal half-life; CL/F; total body clearance for extravascular administration; V_z/F volume of distribution; CV, coefficient of variation.

Table 3 Analysis of Food Effect on HA121-28

Parameter	Geometric Mean (Fasted, N = 20)	Geometric Mean (fed, N = 20)	GMRs% (Fed/Fasted)	90% CIs (%)	CV (%)
C_{max} (ng/mL)	98.3	107	108.45	(98.51, 119.40)	17.7
AUC_{last} (ng*h /mL)	8680	9130	105.23	(100.25, 110.47)	8.9
AUC_{inf} (ng*h /mL)	10000	10,400	104.14	(97.41, 111.34)	10.8

Abbreviations: C_{max}, peak concentration in plasma; AUC_{last}, area under the curve from zero to the time point; AUC_{inf}, area under the curve from zero to infinite; GMRs, geometric mean ratio; CV, coefficient of variation; 90% CIs, 90% confidence intervals.

Safety Assessment

In this study, the majority of adverse events were categorized as grade 1 to 2, without any interventions required. Only one subject (5.0%) experienced grade 3 (increased aspartate aminotransferase level) and grade 4 (increased creatine phosphokinase level) TEAEs. Both grade 3 and grade 4 TEAEs were deemed unrelated to the investigational drug. There was no occurrence of SAEs or TEAEs leading to permanent discontinuation, suspension of medication, premature withdrawal, or fatality. There were 9 cases (45.0%) experienced a total of 15 times adverse events. Specifically, within the fasting periods, adverse events occurred in 5 cases totaling 6 times, while in the postprandial periods, there were 6 cases with 9 times. Further details are listed in Table 4.

Discussion

This study was a phase I clinical study with a single-center, single-dose, randomized, open-label, two-cycle, double-crossover design to evaluate the effect of food on the PK characteristics of HA121-28 tablet and to provide information for the design of dosing regimens and administration indications in later clinical trials.

When administered following a high-fat and high-calorie diet, as opposed to under fasting conditions, the arithmetic mean C_{max} of HA121-28 increased by approximately 7.8%, while the AUC_{last} and AUC_{inf} incremented of approximately 4.7% and 0.97%, respectively. Both fasting and postprandial median T_{max} values occurred at 8.00 h. Thus, our findings suggest that a high-fat and high-calorie diet does not significantly impact the PK profile of HA121-28. From a PK perspective, adjusting the administration of HA121-28 based on dietary intake may not be imperative in clinical practice. Despite the C_{max}, AUC_{last}, and AUC_{inf} of HA21-28 being slightly elevated under high-fat and high-calorie fed conditions compared to fasting conditions, these increase remains within acceptable ranges. It suggests that high-fat and a high-calorie diet has negligible influence on the PK profiles of HA121-28. When administered to healthy Chinese subjects, HA121-28 exhibit a good safety profile, with no significant increase in adverse reactions attributed to a high-fat and high-calorie diet. As a quinazoline compound, the solubility of HA121-28

Table 4 Summary of Adverse Events and Treatment-Emergent Adverse Events (%)[a]

	Fasted (N=20)		Fed (N=20)	
	Instance	**Occurrence**	**Instance**	**Occurrence**
Adverse events[b]	5 (25.0)	6	6 (30.0)	9
Laboratory findings	1 (5.0)	2	4 (20.0)	5
Alanine aminotransferase increased	0	0	1 (5.0)	1
Electrocardiogram QT prolonged	0	0	0	0
Aspartate aminotransferase increased	0	0	0	0
Blood bilirubin increased	0	0	1 (5.0)	1
Transaminases increased	0	0	1 (5.0)	1
Urinary occult blood positive	1 (5.0)	1	0	0
Creatine phosphokinase increased	1 (5.0)	1	2 (10.0)	2
Gastrointestinal disorders	1 (5.0)	1	0	0
Diarrhea	0	0	0	0
Abdominal pain	0	0	0	0
Upper abdominal pain	1 (5.0)	1	0	0
Respiratory, thoracic and mediastinal disorders	0	0	0	0
Epistaxis	0	0	0	0
Cardiac disorders	2 (10.0)	2	2 (10.0)	4
Ventricular pre-excitation	0	0	0	0
Ventricular extrasystoles	1 (5.0)	1	1 (5.0)	1
Arrhythmia	0	0	1 (5.0)	1
First degree atrioventricular block	1 (5.0)	1	1 (5.0)	2
Skin and subcutaneous tissue disorders	1 (5.0)	1	0	0
Rash	1 (5.0)	1	0	0
Vascular diseases	0	0	0	0
Hypertension	0	0	0	0
Treatment-emergent adverse events	7 (35.0)	8	8 (40.0)	17
Laboratory findings	3 (15.0)	4	4 (20.0)	11
Alanine aminotransferase increased	0	0	2 (10.0)	2
Electrocardiogram QT prolonged	0	0	0	0
Aspartate aminotransferase increased	0	0	1 (5.0)	1
Blood bilirubin increased	0	0	1 (5.0)	1
Transaminases increased	0	0	1 (5.0)	1
Urinary occult blood positive	1 (5.0)	1	0	0
Creatine phosphokinase increased	1 (5.0)	1	3 (15.0)	3
Alpha-hydroxybutyrate dehydrogenase increased	0	0	1 (5.0)	1
Urinary leukocytes positive	2 (10.0)	2	0	0
Abnormal ST segment on electrocardiogram	0	0	1 (5.0)	1
Lactate dehydrogenase increased	0	0	1 (5.0)	1
Gastrointestinal disorders	1 (5.0)	1	0	0
Diarrhea	0	0	0	0
Abdominal pain	0	0	0	0
Upper abdominal pain	1 (5.0)	1	0	0
Cardiac disorders	2 (10.0)	2	3 (15.0)	5
Ventricular pre-excitation	0	0	0	0
Palpitation	0	0	0	0
Intraventricular block	0	0	1 (5.0)	1
Ventricular extrasystole	1 (5.0)	1	1 (5.0)	1
Arrhythmia	0	0	1 (5.0)	1
First degree atrioventricular block	1 (5.0)	1	1 (5.0)	2

(*Continued*)

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Table 4 (Continued).

	Fasted (N=20)		Fed (N=20)	
	Instance	**Occurrence**	**Instance**	**Occurrence**
Respiratory, thoracic and mediastinal disorders	0	0	0	0
Epistaxis	0	0	0	0
Ear diseases	0	0	0	0
Tinnitus	0	0	0	0
Skin and subcutaneous tissue disorders	1 (5.0)	1	0	0
Rash	1 (5.0)	1	0	0
Vascular diseases	0	0	0	0
Hypertension	0	0	0	0
Eye and its accessory organs diseases	0	0	0	0
Floaters	0	0	0	0
Musculoskeletal disorders	0	0	1 (5.0)	1
Anchylosis	0	0	1 (5.0)	1

Notes: [a] Calculate the percentage with the number of subjects in each group as the denominator.[b] Adverse events that were considered to be possibly, probably or definitely related to study medication.

in lipids could be increased due to its hydrochloride salt. Quinazoline compounds typically exhibit favorable lipid solubility, with aromatic amine and heterocyclic oxygen moieties increasing their molecular lipophilicity.[20,21] Thus, following a high-fat and high-calorie diet, increased lipid concentrations may facilitate drug dissolution in lipid-rich environments, consequently amplifying systemic exposure.[22]

Safety analyses revealed that adverse reactions were predominantly related to hepatotoxicity and cardiotoxicity. HA121-28, which contains benzene and nitrogen-containing rings, harbors constituents that could play a pivotal role in its pharmacological effects, particularly concerning hepatotoxicity. These structural elements are crucial because they may undergo metabolic transformations, especially through oxidative reactions, leading to the generation of reactive intermediates or metabolites that could induce hepatotoxic effects.[23,24] The majority of these AEs were mild (grade 1 or 2) and did not necessitate intervention, suggests that the investigational drug has a relatively favorable safety profile regarding the frequency and severity of AEs. In both fasting and fed conditions, laboratory abnormalities were noted, including increases in alanine aminotransferase, creatine phosphokinase, and aspartate aminotransferase. These increases were generally mild and isolated to specific individuals. Cardiac disorders were another notable category of TEAEs including mild ventricular extrasystoles and first-degree atrioventricular block. Importantly, no serious arrhythmias or fatal events occurred, which further supports the safety of the investigational drug in relation to cardiovascular health. A small number of subjects experienced gastrointestinal disorders such as upper abdominal pain. These symptoms were generally mild and occurred more frequently in the fasting group (1 subject, 1 occurrence). This could potentially be related to the fasting condition itself rather than the study medication, as gastrointestinal distress can sometimes be exacerbated by fasting.[25] A significant finding in this study is the absence of any adverse events leading to permanent discontinuation, suspension of medication, premature withdrawal, or fatality under single administration. This aspect of the results supports for the drug's potential future use in broader populations. Further studies should aim to confirm these findings in larger and more diverse populations, particularly to assess the long-term safety profile. Although this study focused on a single administration, future research incorporating multiple administration would be necessary to comprehensively assess the pharmacokinetic profile over time, as well as the potential changes in drug-food interactions with repeated dosing.

In brief, HA121-28 tablet can be administrated for both fasting and postprandial circumstances. Nonetheless, subsequent confirmatory clinical studies mandated careful attention to the PK accumulation, hepatotoxicity and cardiotoxicity under multiple-dose.

Conclusion

Food had no effect on the PK profile of HA121-28 tablet. Clinical application of HA121-28 tablet can be recommended for fasting and postprandial use. 200 mg of HA121-28 tablet was given as a single dose in Chinese healthy subjects, with a favorable safety profile and no serious adverse events occurred.

Ethics Statement

The clinical trial was approved by the Ethics Committee of West China Hospital, Sichuan University (Chengdu, China) and was registered at www.clinicaltrials.gov as NCT05072535. All subjects signed informed consent forms prior to screening.

Date Availability Statement

The authors confirm that the data supporting the findings of this study are available within the article and its supplementary material. Data requests should be addressed by e-mail to the corresponding author.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

All authors declare no competing interests in this work.

References

1. Plaza-Menacho I, Burzynski GM, de Groot JW, Eggen BJ, Hofstra RM. Current concepts in RET-related genetics, signaling and therapeutics. *Trends Genet*. 2006;22(11):627–636. doi:10.1016/j.tig.2006.09.005
2. Eng C. RET proto-oncogene in the development of human cancer. *J Clin Oncol*. 1999;17(1):380–393. doi:10.1200/JCO.1999.17.1.380
3. Guo Q, Cheng ZM, Gonzalez-Cantu H, et al. TMEM127 suppresses tumor development by promoting RET ubiquitination, positioning, and degradation. *Cell Rep*. 2023;42(9):113070. doi:10.1016/j.celrep.2023.113070
4. Mulligan LM. RET revisited: expanding the oncogenic portfolio. *Nat Rev Cancer*. 2014;14(3):173–186. doi:10.1038/nrc3680
5. Addeo A, Miranda-Morales E, den Hollander P, et al. RET aberrant cancers and RET inhibitor therapies: current state-of-the-art and future perspectives. *Pharmacol Ther*. 2023;242:108344. doi:10.1016/j.pharmthera.2023.108344
6. Lin JJ, Gainor JF. Selective targeting of RET fusions in lung cancer. *J Clin Oncol*. 2023;41(2):410–412. doi:10.1200/JCO.22.01644
7. Elisei R, Ciampi R, Matrone A, et al. Somatic RET indels in sporadic medullary thyroid cancer: prevalence and response to selpercatinib. *J Clin Endocrinol Metab*. 2022;107(8):2195–2202. doi:10.1210/clinem/dgac325
8. Gild ML, Clifton-Bligh RJ, Wirth LJ, Robinson BG. Medullary thyroid cancer: updates and challenges. *Endocr Rev*. 2023;44(5):934–946. doi:10.1210/endrev/bnad013
9. Wang Z, Xing Y, Li B, Li X, Liu B, Wang Y. Molecular pathways, resistance mechanisms and targeted interventions in non-small-cell lung cancer. *mol Biomed*. 2022;3(1):42. doi:10.1186/s43556-022-00107-x
10. Vinarov Z, Butler J, Kesisoglou F, Koziolek M, Augustijns P. Assessment of food effects during clinical development. *Int J Pharm*. 2023;635:122758. doi:10.1016/j.ijpharm.2023.122758
11. Farha M, Masson E, Tomkinson H, Mugundu G. Food effect study design with oral drugs: lessons learned from recently approved drugs in oncology. *J Clin Pharmacol Apr*. 2019;59(4):463–471. doi:10.1002/jcph.1351
12. Williams L, Hill DP Jr, Davis JA, Lowenthal DT. The influence of food on the absorption and metabolism of drugs: an update. *Eur J Drug Metab Pharmacokinet*. 1996;21(3):201–211. doi:10.1007/BF03189714

13. Omachi F, Kaneko M, Iijima R, Watanabe M, Itagaki F. Relationship between the effects of food on the pharmacokinetics of oral antineoplastic drugs and their physicochemical properties. *J Pharm Health Care Sci*. 2019;5(1):26. doi:10.1186/s40780-019-0155-1
14. Koziolek M, Alcaro S, Augustijns P, et al. The mechanisms of pharmacokinetic food-drug interactions - A perspective from the UNGAP group. *Eur J Pharm Sci*. 2019;134:31–59. doi:10.1016/j.ejps.2019.04.003
15. Roy R, Marakkar S, Vayalil MP, et al. Drug-food interactions in the era of molecular big data, machine intelligence, and personalized health. *Recent Adv Food Nutr Agric*. 2022;13(1):27–50. doi:10.2174/2212798412666220620104809
16. Boullata JI, Hudson LM. Drug-nutrient interactions: a broad view with implications for practice. *J Acad Nutr Diet*. 2012;112(4):506–517. doi:10.1016/j.jada.2011.09.002
17. Martin P, Oliver S, Kennedy SJ, et al. Pharmacokinetics of vandetanib: three phase I studies in healthy subjects. *Clin Ther*. 2012;34(1):221–237. doi:10.1016/j.clinthera.2011.11.011
18. US Food and Drug Administration. Bioanalytical method validation guidance for industry. 2018, Available from https://www.fda.gov/media/70858/download. Accessed June 16, 2021.
19. US Food and Drug Administration. Guidance for industry: assessing the effects of food on drugs in INDs and NDAs–clinical pharmacology considerations; 2022. Available from: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/assessing-effects-food-drugs-inds-and-ndas-clinical-pharmacology-considerations. Accessed 1 June 2024.
20. Alagarsamy V, Chitra K, Saravanan G, Solomon VR, Sulthana MT, Narendhar B. An overview of quinazolines: pharmacological significance and recent developments. *Eur J Med Chem*. 2018;151:628–685. doi:10.1016/j.ejmech.2018.03.076
21. El-Malah A, Malebari AM, Khayyat AN, Mohammad KA, Gineinah MM, Mahmoud Z. Design, synthesis, and antiproliferative activities of novel substitutedhydrazone/triazolo-linked quinazoline derivatives. *J Mol Struct*. 2024;1306:137822. doi:10.1016/j.molstruc.2024.137822
22. Kambayashi A, Shirasaka Y. Food effects on gastrointestinal physiology and drug absorption. *Drug Metab Pharmacokinet*. 2023;48:100488. doi:10.1016/j.dmpk.2022.100488
23. Ritchie TJ, Macdonald SJF. Heterocyclic replacements for benzene: maximising ADME benefits by considering individual ring isomers. *Eur J Med Chem*. 2016;124:1057–1068. doi:10.1016/j.ejmech.2016.10.029
24. Ritchie TJ, Macdonald SJF, Peace S, Pickett SD, Luscombe CN. The developability of heteroaromatic and heteroaliphatic rings - do some have a better pedigree as potential drug molecules than others? *Medchemcomm*. 2012;3(9):1062–1069. doi:10.1039/c2md20111a
25. Lukic S, Mijac D, Filipovic B, et al. Chronic abdominal pain: gastroenterologist approach. *Dig Dis*. 2022;40(2):181–186. doi:10.1159/000516977