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ORIGINAL ARTICLE

Effect of a high-fat meal on the relative bioavailability of H3B-6527, a novel FGFR4 inhibitor, in healthy volunteers

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Abstract

Purpose This Phase I study estimated the effect of a high-fat meal on the pharmacokinetics (PK) of H3B-6527, a covalent inhibitor of the fibroblast growth factor receptor (FGFR) 4 in clinical development for hepatocellular carcinoma and intrahepatic cholangiocarcinoma.

Methods In this randomized, single center, single-dose, open-label, 2-period crossover study 12 healthy male volunteers, aged 18–55 years old, received a single 200-mg dose of H3B-6527 (capsule) following an overnight fast or a high-fat breakfast. PK samples were collected serially up to 36 h postdose. H3B-6527 concentrations were measured using a validated high-performance liquid chromatography tandem mass spectrometry method. PK data were analyzed using a noncompartmental approach based on a mixed-effects model. The safety and tolerability of H3B-6527 were also assessed.

Results H3B-6527 plasma exposure increased after a high-fat meal with fed/fasted ratios of the geometric means (90% confidence interval) of 174% (102–298%) for C_{max} and 246% (146–415%) for AUC_{0-t}. Food delayed and prolonged absorption of H3B-6527, with a fed/fasted ratio for t_{max} of 200% (137–263%). PK variability was lower under the fed condition, as illustrated by the CV% for C_{max} and AUC_{0-t} of 41.9–54.5% (fed) versus 64.3–70.4% (fasted).

Conclusions A single 200 mg dose of H3B-6527 was safe and generally well tolerated when administered to healthy adult males. A high-fat meal significantly increased exposure to H3B-6527, from 1.5- to 2.5-fold in the systemic circulation, compared to administration under fasted conditions. Food delayed and prolonged absorption of H3B-6527. In general, lower inter-subject variability was observed in the fed state in healthy volunteers.

Trial registration ClinicalTrials.gov.: NCT03424577.

Keywords H3B-6527 · FGFR4 inhibitor · Phase I · Pharmacokinetics · Food-effect

Introduction

The fibroblast growth factor (FGF)19 is a driver oncogene in hepatocellular carcinoma (HCC) [1]. FGF19 is a gut secreted endocrine hormone that acts in the liver through the fibroblast growth factor receptor (FGFR)4 to regulate bile acid synthesis [2]. Transgenic mice overexpressing FGF19 form liver tumors and genetic ablation of FGFR4 prevents tumor formation [3]. Thus, targeting FGFR4 could have therapeutic benefit in HCC with altered FGF19 signaling.

H3B-6527 is a highly selective and orally available small molecule inhibitor FGFR4. H3B-6527 is a targeted covalent inhibitor with an acrylamide group that forms a covalent bond via Michael addition with the Cys552 on FGFR4, present in the hinge region of the ATP-binding pocket, unique within the FGFR family [4]. A functional biochemical assay demonstrated robust inhibition of the target kinase FGFR4 by H3B-6527 with an IC_{50} value of < 1.2 nM, and at least 250-fold selectivity over FGFR1-3, translating to inhibition of proliferation and leading to apoptosis in a HCC cell line by inhibiting FGFR4 signaling [4]. In addition, oral treatment of H3B-6527 inhibited tumor growth in a dose-dependent manner and caused tumor regressions in the Hep3B HCC xenograft model and patient-derived xenograft models of HCC grown in immunocompromised mice.

Liver cancer is the second leading cause of cancer-mortality and the 16th absolute cause of death worldwide [5]. The high incidence and poor prognosis associated with advanced HCC together with the lack of effective systemic

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therapies warrant the development of new therapies for this indication [6]. H3B-6527 is currently undergoing evaluation in a global multicenter Phase I clinical trial in FGF19-positive HCC and intrahepatic cholangiocarcinoma (ICC) (ClinicalTrials.gov Identifier: NCT02834780).

H3B-6527 is a weak base (measured pKa 7.8) exhibiting a pH-dependent solubility profile, with higher solubility in low-pH solutions (data on file, H3 Biomedicine, MA, USA). Food may impact the pharmacokinetics (PK) of small molecules resulting in clinically significant consequences, as food could delay gastric emptying, stimulate bile flow, change the gastrointestinal pH, increase splanchnic blood flow, change luminal metabolism of a drug substance, and/or physically or chemically interact with its dosage form [7]. This pilot clinical pharmacology study was designed to estimate the effect of a high-fat meal on the relative bioavailability of H3B-6527, when administered as a 200-mg free-base capsule (the highest strength capsule formulation). The secondary objective was to assess the safety and tolerability of single-dose H3B-6527 under fed and fasted conditions in healthy male volunteers. This study is the first report of H3B-6527 PK in humans.

Methods

H3B-6527 capsules

For this study, H3B-6527 capsules were size zero (0) hypromellose shell capsules containing 200 mg of H3B-6527 drug substance. The 200-mg capsule was selected for this preliminary food-effect study since it was the highest capsule strength used in a parallel Phase 1 study in HCC and ICC subjects.

Study design

H3B-6527-A001-001 was a single center, randomized, single-dose, open-label, 2-period crossover study conducted in healthy male volunteers. Volunteers were randomly assigned to 1 of 2 possible treatment sequences ($n = 6$ per sequence). As recommended by the Food and Drug Administration (FDA), a minimum of 12 subjects completed both treatments [7]. H3B-6527 200-mg capsule was administered as an oral single dose on 2 occasions and capsules were swallowed whole. Each subject received a single dose of H3B-6527 under each treatment: (1) after fasting for at least 10 h, or, (2) after consuming a high-fat breakfast (approximately 800–1000 kcal, with fat contributing to 50–60% of the total caloric content of the meal), with a 4-day washout period between each treatment. The standard high-fat meal including dairy consisted of 2 eggs fried in butter, 2 slices of bacon, 2 slices of white bread toast, 2 pats of butter, 4 ounces of hash brown potatoes, and 8 fluid ounces of whole milk. In fed state, subjects started the high-fat breakfast meal 30 min prior to the administration of H3B-6527, and consumed the entire meal in 30 min or less. H3B-6527 capsules were administered with 240 mL (8 fluid ounces) of water. For both conditions, no food was allowed for at least 4 h after dosing. Water was allowed as desired except for 1 h before and 1 h after the start of drug administration. While subjects were confined in the clinic, they received standardized meals scheduled at approximately the same time in each period of the study. On dosing days, a low-fat lunch (< 30% fat), an afternoon snack, dinner, and an evening snack were supplied at approximately 4, 7, 10, and 13 h, respectively, after dosing. Grapefruit, starfruit, Seville oranges, or their products were not permitted for 7 days prior to the first dose and throughout the study. Alcohol and caffeinated beverages were not permitted for 72 h prior to dosing and throughout the study. Subjects were confined to the clinic from check-in on Day − 1 through the end-of study visit on Day 9.

Study subjects

Eligible volunteers were non-smoking healthy male adults aged 18–55 years old with a body mass index (BMI) of 18 to ≤ 29 kg/m^2. As potential gender difference in H3B-6527 PK was not yet assessed, enrolment in this pilot study was limited to male subjects since the numbers of participants may not have been sufficient to result in enough power to discern any gender differences in outcomes accurately. Subjects without a successful vasectomy who were partners of women of childbearing potential were required to use a medically effective method of contraception during the study period through 30 days after the last dose of study drug. No sperm donation was allowed during the study period or for 30 days after study drug discontinuation. Key exclusion criteria included evidence or history of clinically relevant disease; drug or alcohol misuse within 6 months prior to screening or a positive urine drug test at Screening or Baseline; use of prescription drugs or over-the-counter (OTC) medication within 2 weeks prior to first dose, intake of herbal preparations/supplements within 7 days prior to the first dose, and any condition that may affect drug absorption, increase risk, or interfere with interpretation of results.

All volunteers were screened within 28 days of receiving the first dose of study drug. Medical histories as well as prior (within 28 days of first dose of study drug) and concomitant medications were reviewed. Physical examinations including ophthalmic examinations, clinical laboratory tests, vital signs, 12-lead electrocardiograms (ECGs), and urinary drug screens were performed.

Informed consent was obtained from all individual participants included in the study before any screening procedures. The study protocol was reviewed and approved by

the Institutional Review Board at the study site (Worldwide Clinical Trials Early Phase Services, LLC). This study was conducted in accordance with the International Conference on Harmonisation Guidelines for Good Clinical Practice and the Declaration of Helsinki.

Sampling and bioanalysis

PK blood samples for determining plasma concentrations of H3B-6527 were collected before dosing and at 1, 2, 3, 4, 8, 12, 16, 24, and 36 h after dosing in each treatment period. Approximately 5 mL of whole blood for each PK time point was collected into pre-chilled (on wet ice) sodium heparin vacutainers, mixed by inversion and centrifuged within 30 min of blood collection, at 1300 RCF for approximately 10 min at 4 °C. Plasma was transferred in a storage tube within 30 min of centrifugation. The tubes were capped, labeled, and stored at − 20 °C until analysis. Plasma concentrations of H3B-6527 were determined using a validated high-performance liquid chromatography/tandem mass spectrometry (LC-MS/MS) method. The lower and upper limits of quantitation were 0.100 ng/mL and 100 ng/mL, respectively, for the analysis of 0.1 mL of plasma. Incurred sample reproducibility was evaluated for this study for ≥ 10% of the samples.

Pharmacokinetic and statistical analysis

The PK analysis included subjects who received H3B-6527 in each treatment (fasted and fed) and who had sufficient evaluable plasma concentration data to derive at least one primary PK parameter in each treatment. Concentration–time data for H3B-6527 were analyzed by noncompartmental methods using Phoenix™ WinNonlin® (Version 6.3, Certara, L.P.). Plasma concentrations of H3B-6527 were tabulated by treatment (fasted and fed) and summarized at each nominal time using descriptive statistics as appropriate. Concentration–time data that are below the limit of quantification (BLQ) were treated as zero in summary statistics. During the PK analysis, BLQ concentrations were treated as zero from time-zero until the time of the first quantifiable concentration; embedded BLQ concentrations and terminal BLQs (BLQs occurring after the last quantifiable concentration) were treated as "missing". Actual sample times were used in the PK analysis. The PK parameters included the area under the plasma concentration–time curve from time 0 to time of last measurable concentration (AUC_{0-t}), maximum observed plasma concentration (C_{max}), and time of maximum observed plasma concentration (t_{max}). If data permitted, the area under the plasma concentration–time curve extrapolated to infinity (AUC_{0-inf}) and the terminal elimination half-life ($t_{½}$) were also derived. For $t_{½}$ determination (1) at least 3 time points (of which the first time point must be greater than t_{max}) with quantifiable plasma concentrations were required for the calculation of λ_z; (2) the duration of time over which λ_z is estimated was at least twice the subsequently estimated $t_{½}$; and (3) the adjusted regression coefficient (R^2adj) was ≥ 0.85. The effect of the high-fat meal on AUC_{0-t}, AUC_{0-inf}, and C_{max} of H3B-6527 was evaluated using a linear mixed-effect model with fixed effects for sequence, period, and treatment (fed or fasted) and a random effect of subject. AUC_{0-t}, AUC_{0-inf}, and C_{max} values were logarithmically transformed prior to being analyzed using the linear mixed-effect model. The ratios of geometric means (fed over fasted comparison) and associated 2-sided 90% confidence intervals for AUC_{0-t}, AUC_{0-inf}, and C_{max} were presented. The ratio of least squares means (fed over fasted conditions) and associated 2-sided 90% confidence intervals for untransformed t_{max} were also determined.

Safety and tolerability

Safety assessments for all subjects ($n = 13$) included monitoring and recording all AEs [including serious adverse events (SAEs)], clinical laboratory assessments, vital signs measurements, 12-lead ECG results, and ophthalmic and physical examinations findings. Clinical laboratory tests were performed by a Clinical Laboratory Improvement Amendments (CLIA) certified laboratory. AEs were assessed using the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE), Version 4.03.

Results

Thirteen subjects were randomly assigned to a treatment sequence, and 12 healthy volunteers completed the study. Data from one subject were excluded from the PK analysis due to early termination after receiving only the fed treatment. All subjects were men with a mean (range) age of 36.8 (20–53) years, and a mean (range) BMI of 25.5 (23.4–28.0) kg/m^2 (Table 1).

Pharmacokinetics

Mean plasma time-concentration profile of H3B-6527 following administration of a single 200-mg capsule under fasted or fed state is shown in Fig. 1. All the predose plasma concentrations of H3B-6527 were below the limit of quantitation (BLQ, < 0.100 ng/mL), indicating that the 4-day washout between administrations was adequate. The first quantifiable concentrations of H3B-6527 were observed at 1 h (the first postdose sample) for all subjects under fasted state, but a 1 h lag was observed for 3 out of the 12 subjects under fed conditions.

Table 1 Subject characteristics

Parameter	All subjects ($n=13$)
Age (years) mean (range)	36.8 (20–53)
Ethnicity*n* (%)	
Hispanic or Latino	8 (61.5)
Not Hispanic of Latino	5 (38.5)
Race*n* (%)	
White	8 (61.5)
Black or African American	4 (30.8)
Asian	1 (7.7)
Weight (kg) mean (range)	77.3 (68.4–90.4)
Height (cm) mean (range)	174 (168–180)
BMI (kg/m^2) mean (range)	25.5 (23.4–28.0)

BMI body mass index, *n* number of subjects

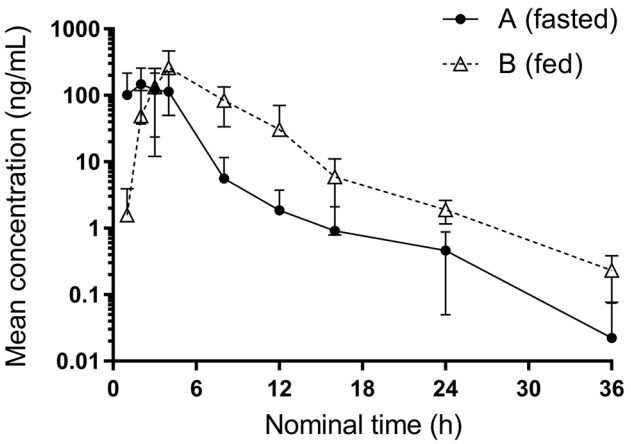

Fig. 1 Mean (±standard deviation) plasma-concentration over time profile of H3B-6527 under fasted (**a**) versus fed (**b**) conditions

A higher H3B-6527 C_{max} was observed at later times under fed conditions, compared with overnight fasting. The mean H3B-6527 C_{max} was 306 ng/mL at a median t_{max} of 4.00 h under fed conditions, and 199 ng/mL at a median t_{max} of 2.00 h under fasted conditions (Table 2). The later t_{max} under fed conditions (ranging from 3 to 12 h) suggests that food decreased the absorption rate of H3B-6527 after administration of H3B-6527 capsules. This observation is supported by a time delay between drug administration and the onset of drug absorption (t_{lag}), which ranged from 0 to 1 h in fed state, but was 0 h for all subjects under fasted conditions. Quantifiable plasma concentrations of H3B-6527 were in general observed through 24 h in the fasted treatment, but reached 36 h for all subjects in fed state. There were no missing concentration–time data in the PK analysis. Thus, a high-fat meal did not only decreased the rate of absorption of H3B-6527, but also extended the duration of absorption.

Overall systemic exposure to H3B-6527 was higher under fed conditions, compared to fasted state (Fig. 2). The mean AUC_{0-t} was 1340 h × ng/mL under fed conditions, and 691 h × ng/mL after fasting. In general, PK variability was lower under fed conditions, as illustrated by the CV% of 54.5% under fed state versus 64.3% after fasting for C_{max}, and 41.9% (fed) compared to 70.4% (fasted) for AUC_{0-t}.

The terminal rate constant λ_z could not be estimated for 7 of the 12 subjects after administration of 200 mg H3B-6527 under fasted conditions, as for one subject only 2 time points had quantifiable plasma concentration after C_{max}, while the R^2adj and λ_z acceptance criteria were not met for 4 and 2 subjects, respectively. Terminal half-life ($t_{1/2}$) were reported for 5 subjects in the fasted treatment but for all 12 subject in the fed treatment, nevertheless, mean values were comparable at 4.28 h (fed) and 5.59 h (fasted). The mean percent of AUC_{0-inf} based on extrapolation was less than 1% for both treatments ($n=5$ fasted, $n=12$ fed), indicating that the 36-h sampling schedule was adequate for characterizing the exposure to H3B-6527.

The fed/fasted ratios of the geometric means (90% confidence interval) were 174% (102–298%) for C_{max}, and 246% (146–415%) for AUC_{0-t} (Table 3), suggesting significantly higher exposure to H3B-6527 under fed conditions, compared to the fasted state. An approximate 2-h delay in t_{max} was observed when H3B-6527 capsules are administered with a high-fat meal, with a fed/fasted ratio (90% confidence interval) for t_{max} of 200% (137–263%).

Table 2 Pharmacokinetic parameters of 200 mg H3B-6527 single dose under fasted and fed conditions

Parameter	H3B-6527 fasted				H3B-6527 Fed			
	n	Mean	SD	CV%	*n*	Mean	SD	CV%
t_{max} (h)[a]	12	2.00 (1.00–4.00)			12	4.00 (3.00–12.00)		
C_{max} (ng/mL)	12	199	128	64.3	12	306	167	54.5
AUC_{0-t} (h × ng/mL)	12	691	487	70.4	12	1340	563	41.9
AUC_{0-inf} (h × ng/mL)	5	883	422	47.8	12	1350	563	41.8
AUC_{Extrap} (%)	5	0.46	0.27	58.1	12	0.12	0.08	64.9
$t_{½}$ (h)	5	5.59	1.14	20.3	12	4.28	0.77	18.0
t_{last} (h)	12	25.0	6.18	24.7	12	36.0	0	0

[a]t_{max} median (range) is reported

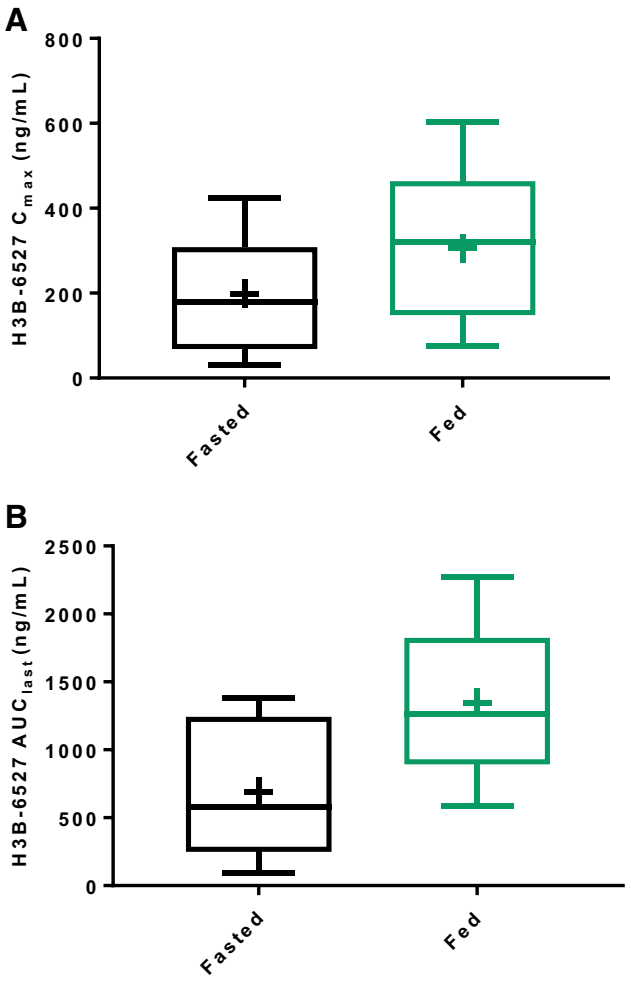

Fig. 2 **a** Box plot comparing H3B-6527 C_{max} for 200 mg H3B-6527 under fasted and fed conditions; **b** box plot comparing H3B-6527 AUC_{0-t} for H3B-6527 under fasted and fed conditions. Full line = median; plus (+) sign = average; Box = Upper and lower quartiles; Whiskers = 5% and 95% percentiles

Table 3 Statistical analysis of the natural log-transformed systemic exposure of H3B-6527 comparing 200 mg H3B-6527 under fed and fasted conditions

Dependent variable	Geometric mean[a]		Ratio (%)	90% confidence interval	
	Fed	Fasted	Fed/fasted	Lower	Upper
ln (C_{max})	259	149	174	102	298
ln (AUC_{0-t})	1235	501	246	146	415
ln (AUC_{0-inf})	1236	818	151	71	320

[a]Geometric mean for H3B-6527 fed and H3B-6527 fasted based on Least Squares Mean of log-transformed parameter values

Safety and tolerability

There were no SAEs. Three subjects experienced four treatment-emergent AEs during the study. Two AEs, a grade 2 viral infection and a grade 1 upper respiratory tract infection, were reported by two subjects following the fed condition of H3B-6527, 200 mg. The Investigator assessed both AEs as not related to study treatment. Two AEs, a grade 1 xeroderma and a grade 1 skin abrasion, were reported by one subject following the fasted condition. The Investigator assessed the event of xeroderma as related to study treatment and the event of skin abrasion as not related to study treatment. Of note, one of the AEs (viral infection; not related to study treatment) led to a subject discontinuation. There were no clinically significant values or changes in laboratory test results, ophthalmic examinations, vital signs, or 12-lead ECGs; none of the AEs were noted during these safety evaluations.

Discussion

This study presents the first pharmacokinetic data for H3B-6527 in healthy adult male volunteers. A single dose of the 200-mg H3B-6527 capsule formulation was safe and generally well tolerated when administered under fed and fasted conditions. No adverse events were serious or severe, and there were no clinically significant values or changes in laboratory test results, ophthalmic examinations, or electrocardiograms. Based on the geometric mean ratios (%), a high-fat meal significantly increased exposure to H3B-6527, from 1.5- to 2.5-fold in the systemic circulation, compared to administration under fasted conditions. After an overnight fast, H3B-6527 exhibited a fairly rapid oral absorption, as judged by the achievement of peak plasma concentrations at approximately 2 h postdose. The approximate 2-h delay in t_{max} following a meal suggests that food slowed the absorption rate of H3B-6527 capsules, although the duration of absorption was extended. H3B-6527 was rapidly cleared from the body with a plasma elimination half-life of approximately 4–6 h at a 200-mg dose, without impact from the high-fat meal. In general, lower inter-subject variability was observed in this healthy population for both C_{max} and AUC under fed conditions, compared with variability observed after an overnight fast.

One limitation of the current study is that it was conducted only in male healthy volunteers, however, a population PK analysis will be performed at a later stage of H3B-6527 development to assess any potential gender difference. Another limitation is that, to date, no data are available on other food conditions (e.g., moderate or low-fat) or food taken in other timeframes. Such studies may be done at a later time, using the H3B-6527 formulation planned for use in registrational trials.

An early assessment of food-effect is expected to facilitate rational dose selection for oncology efficacy and safety trials. The higher plasma exposure observed in this study for the capsule formulation of H3B-6527 when administered under the fed state might be the optimal condition to inhibit FGFR4 in the treatment of liver cancer. This study will help guide subsequent H3B-6527 clinical trial design, including potential combination trials with compounds required to be taken with food.

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Compliance with ethical standards

Conflict of interest All authors declare that they have no conflicts of interest.

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