ORIGINAL ARTICLE

The Prostate WILEY

Phase I clinical trial of HC-1119 soft capsule in Chinese healthy adult male subjects: Pharmacokinetics and safety of single-dose proportionality and effects of food

Haiping Ma PhD[1] | Weidong Xu MSc[2] | Jin Ni PhD[1] | Naping Zhao PhD[1] |
Shouyan Tang BSc[3] | Song Li MSc[3] | Tingting Cai[1] | Jianping Xiu[1] |
Xin Kang MSc[1] | Shen Gao BSc[1] | Li Zhang PhD[1,4] ⬥ | Tie Zhou MD, PhD[3]

[1]Department of Phase I Clinical Trial, Clinical Research Unit, Changhai Hospital, Naval Medical University, Shanghai, China

[2]Department of Urology, Changzheng Hospital, Naval Medical University, Shanghai, China

[3]Department of Urology, Changhai Hospital, Naval Medical University, Shanghai, China

[4]Department of Pharmacy, The Second Hospital of Anhui Medical University, Hefei, China

Correspondence
Li Zhang, PhD, Department of Phase I Clinical Trial, Clinical Research Unit, Changhai Hospital, Naval Medical University, 168 Changhai Road, Shanghai 200433, China.
Email: lizhangpaper@163.com

Tie Zhou, MD, PhD, Department of Urology, Changhai Hospital, Naval Medical University, 168 Changhai Road, Shanghai 200433, China.
Email: wenzhoutie@163.com

Abstract

Background: Preclinical studies showed that HC-1119, a deuterated version of enzalutamide, could competitively inhibit androgen binding to androgen receptor by blocking the transmission of androgen receptor signaling pathway as enzalutamide, inducing apoptosis of prostate cancer cells and reducing the proliferation of prostate cancer cells. Animal pharmacokinetic studies also show that deuterization of enzalutamide as HC-1119 could retain the basic properties of mother drug, increases the stability of compounds to metabolic enzymes and the drug exposure in vivo, prolong the half-life and reduce the production of metabolites, which may lead to a better efficacy and safety of HC-1119 compared with enzalutamide.

Methods: To evaluate the pharmacokinetics and safety of HC-1119 and the effects of food on pharmacokinetics in healthy adult Chinese men after single-dose administration of HC-1119. A total of 47 Chinese healthy adult male subjects received HC-1119 soft capsule at a single oral dose of 40, 80, or 160 mg followed on fasting or 160 mg after high-fat meal respectively. HC-1119 prototype and its metabolites M1 and M2 in plasma were collected individually in a total 23 time points. Pharmacokinetics were determined by sensitive LC/MS/MS for dose-proportionality study.

Results: In subjects taking HC-1119 soft capsules on fasting, C_{max} of HC-1119 prototype increased dose-dependently. Either C_{max} and $AUC_{0-\infty}$ of M1 or C_{max} of M2 showed statistically significant difference. Dose-proportionality evaluation showed linear pharmacokinetic characteristics in C_{max} of HC-1119 prototype, C_{max} and $AUC_{0-\infty}$ of M2 in dose range of 40–160 mg. C_{max} of HC-1119 was significantly different between the two groups as 160 mg HC-1119 on fasting or after a high-fat

diet respectively, while the other parameter were not. HC-1119 and its metabolites M1 and M2 showed a linear dynamic trend.

Conclusions: HC-1119 is expected to have lower clinical dose than the similar drug enzalutamide. The absorption of HC-1119 and the main pharmacokinetic parameters of HC-1119 and its metabolites M1 and M2 were not affected by high-fat diet. The clinical application of HC-1119 soft capsule in the later stage can be recommended for both fasting and postprandial. The safety and tolerance were good in this population.

KEYWORDS

Chinese healthy adult male, deuterated enzalutamide, dose-proportionality, food effect, pharmacokinetics

1 | INTRODUCTION

With an estimated almost 1.4 million new cases and 375,000 deaths worldwide, prostate cancer is the second most frequent cancer and the fifth leading cause of cancer death among men in 2020, and the incidence rates continue to increase in China.[1,2] Androgen deprivation therapy remains the gold standard for prostate cancer. Unfortunately, nearly all patients will develop resistance to androgen blockade leading to castration-resistant prostate cancer (CRPC) within 2–3 years.[3–5]

Oral enzalutamide (Xtandi®), a second generation androgen receptor inhibitor, is indicated for the treatment of CRPC in numerous countries worldwide, with specific indications in this patient population varying between individual countries. Oral enzalutamide 160 mg once daily is an effective and generally well tolerated treatment in a broad spectrum of patients with CRPC, including in nonmetastatic and metastatic disease and in chemotherapy-naive and -experienced metastatic CRPC.[6] Enzalutamide has improved outcomes for metastatic castration-resistant prostate cancer (mCRPC) and prolonged patients' lives significantly.[7] According to highlights of prescribing of Food and Drug Administration, In four placebo-controlled trials (AFFIRM, PROSPER, PREVAIL, and ARCHES), the most common adverse reactions (≥10%) that occurred more frequently (≥2% over placebo) in the XTANDI-treated patients were asthenia/fatigue, back pain, hot flush, constipation, arthralgia, decreased appetite, diarrhea, and hypertension. Adverse reactions of enzalutamide including seizure, posterior reversible encephalopathy syndrome (PRES), hypersensitivity, ischemic heart disease, falls and fractures are warned and required precaution.[8]

Deuterated drugs have attracted more and more attention in clinical studies for its expected efficacy improvement. The deuterium content in the substituted compound is much higher than in nature, it can be regarded as a new IND candidate. The substitution of carbon-hydrogen bonds (C–H) with deuterium bonds (C–D) on a specific metabolic molecule site can slow down drug metabolism, improving pharmacokinetics and reduce toxic metabolites.[9–12]

HC-1119 is the first and exclusive deuterated form of enzalutamide designed and owned by Sichuan HISCO Pharmaceutical Co., Ltd with N-methyl in enzalutamide replaced by tri-deuterated methyl (Figure 1). Preclinical studies showed that HC-1119 could competitively inhibit androgen binding to androgen receptor by blocking the transmission of androgen receptor signaling pathway as enzalutamide, inducing apoptosis of prostate cancer cells and reducing the proliferation of prostate cancer cells. Animal pharmacokinetic studies also show that deuterization of enzalutamide as HC-1119 could retain the basic properties of mother drug, increases the stability of compounds to metabolic enzymes and the drug exposure in vivo, prolong the half-life and reduce the production of metabolites, which may lead to a better efficacy and safety of HC-1119 compared with enzalutamide.[13,14]

According to the previous results, it is expected that the dose of HC-1119 will be significantly reduced compared with enzalutamide for mCRPC, and the safety of HC-1119 may be improved due to lower dose; Sichuan HISCO Pharmaceutical Co., Ltd. sponsored the clinical trial approved by the former China Food and Drug Administration (Class 1 innovative drugs IND registration, Approval No.: 2016L07045) which conducted at Phase I Clinical Research Unit (Phase I—CRU) in Changhai Hospital, Shanghai. In this report, we
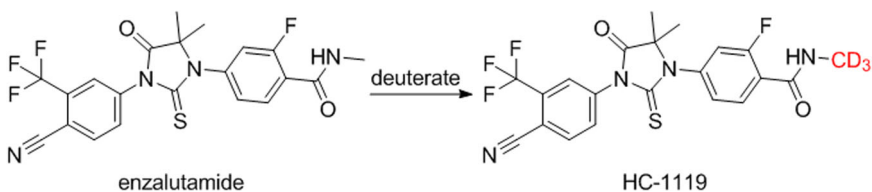

FIGURE 1 Chemical structure of enzalutamide and HC-1119 [Color figure can be viewed at wileyonlinelibrary.com]

present the results from the completed pharmacokinetics and safety evaluation of HC-1119 soft capsule in healthy adult Chinese subjects. These results will provide strong support for ongoing clinical trials and future new drug application.

2 | MATERIALS AND METHODS

2.1 | Study population

A total of 47 subjects between 18 and 45 years of age (inclusive), with body mass index (BMI) within 19.0–26.0 kg/m^2 (inclusive) were enrolled in this study. Subjects were in good general health as determined by medical history, physical examination, vital signs, 12-lead electrocardiogram (ECG) and clinical laboratory measurements. The study candidates matched with the exclusion criteria in the study protocol will be excluded such as a history of heart, liver, lung, kidney, respiratory, nervous, skeletal muscle, endocrine, digestive system diseases or other serious diseases; clinical drug allergy history or specific allergic disease history, especially those who are allergic to any ingredient used in the investigational product; History of convulsion, loss of consciousness, or transient ischemic attack, or any condition prone to epilepsy within 12 months before the trial will not be enrolled. Any drug abuse or urine drug screening positive, smokers or smokers who smoked more than 10 cigarettes (or the same amount of tobacco) a day in the 3 months before the trial, or who could not give up smoking during the whole study period, or who had a history of alcoholism or regular drinking within 6 months before the trial will not be enrolled; Patients with positive results of alcohol breath test, blood donation or blood loss of more than 400 ml within 3 months before the test, patients who took any clinical trial drugs or participated in any clinical trials within 3 months before the trial, and those who had special dietary requirements like excessive tea, coffee and/or caffeinated drinks, grapefruit or grapefruit containing products. Positive human immunodeficiency virus antibody, hepatitis B surface antigen or hepatitis C virus antibody, Treponema pallidum antibody, and those candidates may be unable to complete the study due to other reasons. Additionally, subjects will be refrained from strenuous exercise from 48 h before Day 1 and during the period of confinement at the clinical research unit throughout the study. Concomitant medications were not allowed for the subjects. Any concomitant medications that occurred during the study were coded using World Health Organization Drug Dictionary released in September 2016 for the description of its frequency and percentage. The trial complies with the ethical principles of the Declaration of Helsinki, which is consistent with good clinical practice, applicable regulatory requirements and corresponding regulations. The study was in compliance with the respective protocol reviewed and approved by an independent institutional review board (Changhai Hospital, Shanghai, China). All subjects provided written informed consent form (ICF) before entering the study. The trial was registered on ClinicalTrials.gov (NCT01695044) and chinadrugtrials.org.cn (CTR20171334).

2.2 | Study designs

The study was an open-label, parallel experiment design, and was conducted in a single trial center from October 24th, 2017 to January 15th, 2018 with a Day 15 to Day 2 as a 14-day screening phase and up to 23 points observation phase. The end-of-study assessments were to be performed on Day 50 or upon early withdrawal. The total study duration was approximately 50 days.

HC-1119 was provided as 40 mg soft capsule. In this study, HC-1119 was administered at doses of 40, 80, 160 mg on fasted and 160 mg after meal, indicating groups as A, B, C, and D, respectively. which were 40 mg (group A, fasting), 80 mg (group B, fasting), 160 mg (group C, fasting), and 160 mg (group D, after meal). A total of 36 healthy male subjects were enrolled in groups A, B, C with 12 subjects in each group, and 11 for group D. The subjects were admitted to the Phase I—CRU after the investigators confirmed the admission criteria and the written ICF. They were assigned the enrolling numbers consecutively. HC-1119 was given according to the dose cohorts and was taken orally after a light dinner and overnight fasting allowing water consumption ad libitum. Subjects in A, B, C were fasted for at least 10 h before and 4 h after HC-1119 administration in the study. Subjects in D were restricted to the protocol-specific standardized high-fat meal consisted of approximately 58 g of fat and approximately 923.94 kcal 30 min before dosing. Water consumption was restricted from 1 h predose through 1 h postdose. The HC-1119 soft capsules were administered with non-carbonated water around 37℃. The upper body kept upright within 2 h after taking the capsules. Standard diets for identical lunches and dinners were provided at 4 and 10 h (not before 6 h postlunch) after taking the capsules, respectively. Subjects were confined to Phase I—CRU until finishing collection of 72 h (Days 2–4) pharmacokinetic sample the following days. In addition, subjects visited CRU on Day 5 for PK sampling, safety evaluation before discharge, and on Days 8, 11, 15, 22, 29, 36, 50 as safety follow-up period of each dose cohort for study procedures accordingly.

After dosing of each cohort, the safety data were reviewed and assessed as not having any safety concerns such as clinically significant adverse event indicative of drug intolerance; clinically significant finding by physical examination, 12-lead ECG, or vital signs; or clinically significant change in laboratory parameters.

2.3 | Pharmacokinetic evaluation and parameters

Blood samples were collected for the measurement of HC-1119 and its major metabolites M1 (amide hydrolysis) and M2 (N-demethylation) in plasma by sampling venous blood 4 ml at each time points. Samples were collected from the peripheral vein via an indwelling catheter or direct venipuncture in case of clot block. The pharmacokinetic sampling time points were predose 0 h (within 30 min before dosing), postdose 10, 20, 30, 45 min, 1, 2, 3, 4, 6, 12, 24 h (Day 2), 48 h (Day 3), 72 h (Day 4), 96 h (Day 5), 168 h (Day 8), 240 h (Day 11), 336 h (Day 15), 504 h (Day 22), 672 h (Day 29), 840 h

(Day 36), 1176 h (Day 50, approximate 7 half-lives of the HC-1119 prototype).

The following pharmacokinetic parameters were calculated from plasma concentration-time data by noncompartmental analysis using WinNonlin 8.0: C_{max} were maximum plasma concentration, t_{max} were time to reach C_{max}, $t_{1/2}$ were apparent plasma terminal elimination half-life, AUC_{0-t} were area under the plasma concentration-time curve from 0 to the last quantifiable plasma concentration, $AUC_{0-\infty}$ were area under the plasma concentration-time curve from 0 to infinite time. Additionally, CL/F (clearance of parent drug), Vd/F (apparent volume of distribution of parent drug), and MRT (mean residence time) after extravascular administration were also determined in this study.

2.4 | Bioanalytical method

All study samples were analysed within the established stability using fully validated bioanalytical methods in the laboratories of Shanghai Xihua Scientific Co. Ltd. Concentrations of HC-1119 and its metabolites M1, M2 in human ethylenediaminetetraacetic acid-K_2 plasma were determined by a validated liquid chromatography-tandem mass spectrometric detection, with the main instruments including Shimadzu liquid chromatography LC-20ADXR and ESI ion source combined with AB company's mass spectrometer Triple Quard 6500. The concentrations of HC-1119, M1 and M2 in plasma were quantified under multiple reaction monitoring (MRM) mode. The concentration range of HC-1119 was 4.00–6000 ng/ml and the concentration range of M1 and M2 was 1.00–1500 ng/ml. The precision of the assay was less than 15%, as indicated by the coefficient of variation (%CV), and the accuracy was within ±15% of the actual concentration. The stability investigation results show that HC-1119 and its metabolites M1 and M2 are stable in human plasma under −80°C (−60°C to −90°C) storage for 223 days.

2.5 | Data and statistical analysis

For the fasting dose-proportionality study, linear relationship of AUC (AUC_{0-t} $AUC_{0-\infty}$) and C_{max} with dose were performed using Phoenix WinNonlin (Version8.0) with the power function model and constructed confidence interval. For 160 mg dosing between the fasting and postprandial groups, the pharmacokinetic parameters of HC-1119 and metabolites M1 and M2 in plasma were logarithmically transformed and compared. SAS 9.4® was used for all statistical calculations, tables, and plots. SAS 9.4® was used for confidence interval testing. Pharmacokinetics analysis sets (PKAS) included all subjects who received the investigational drug after screening and had no major protocol violation that affected the pharmacokinetic evaluation, and who had evaluable pharmacokinetic data.

Sample size determination: according to Technical Guidelines for Clinical Pharmacokinetics Research on Chemical Drugs, 8–12 subjects are generally required for each dose group. A total of 47 subjects were enrolled in this study which was sufficient for the point estimates of ratio of AUC (AUC_{0-t} $AUC_{0-\infty}$) fall within 90%–111% of the true value with 90% confidence. This sample size was also sufficient for the point estimate of the ratio of C_{max} to fall within 86%–116% of the true value with 90% confidence using an estimated intra-participant coefficient of variation of 31% for C_{max}.

2.6 | Safety evaluations

Safety measures included the collection of data on all adverse events, adverse reactions, serious adverse events, serious adverse reactions, physical examination, 12-lead ECG, vital signs and laboratory tests. All the safety data were tabulated descriptively. Adverse events were coded using the current version of MedDRA at the beginning of coding. Adverse events that occurred before the first medication were not included in the analysis. Adverse events were grouped according to the doses. Adverse events, adverse reactions, serious adverse events, serious adverse responses, important adverse events, adverse events leading to withdrawal, and adverse responses leading to withdrawal were summarized by system organ classification and preferred term. If there are multiple adverse events in the same subject, it is recorded as one case when calculating the adverse events incidence.

3 | RESULTS

3.1 | Subjects' demographic and baseline characteristics

A total of 47 subjects (12 cases in group A, 12 cases in group B, 12 cases in group C and 11 cases in group D) completed the experiment and were included in the full analysis set (FAS), safety analysis set (SS) and PKAS. In the FAS, 44 subjects were Han nationality and 3 subjects were other nationalities. The age range of groups A, B, C and D was 19–28, 18–30, 18–38, and 18–26 years old, respectively. BMI ranged from 20.6 to 25.7, 19.6 to 23.4, 19.4 to 25.4, and 19.3 to 25.9 kg/m², respectively (Table 1). All the 47 subjects took the medicine and completed the study, and no subjects fell off.

TABLE 1 Demographic and baseline characteristics of subjects, $n = 12$ or 11[a], mean ± SD

Group	Age (year)	Height (cm)	BMI (kg/m²)
A	21.5 ± 2.71	173.8 ± 8.40	23.13 ± 1.777
B	20.8 ± 4.20	174.7 ± 7.57	21.36 ± 1.070
C	25.2 ± 5.95	171.8 ± 6.02	22.26 ± 2.184
D	20.4 ± 2.11	174.3 ± 6.05	22.75 ± 2.29

Abbreviation: BMI, body mass index.

[a] A, 40 mg on fasting, $n = 12$; B, 80 mg on fasting, $n = 12$; C, 160 mg on fasting, $n = 12$; D, 160 mg after meal, $n = 11$.

3.2 | Pharmacokinetics of 40, 80, or 160 mg HC-1119 soft capsules on fasting

The main pharmacokinetic parameters of HC-1119 after single oral administration of 40, 80, or 160 mg HC-1119 soft capsules in A/B/C group were shown in Table 2. The C_{max} of HC-1119 prototype drug in each dose group has statistically significant difference ($p < 0.001$). Further multiple comparisons showed that the C_{max} of HC-1119 were significantly different between groups, indicating that the C_{max} increased with the increase of dosage.

3.3 | Pharmacokinetic characteristics of metabolites M1 and M2 administered 40, 80, or 160 mg orally on fasting

Enzalutamide is primarily eliminated by hepatic metabolism. The major metabolites are the carboxylic acid metabolite (M1, inactive with respect to mCRPC) and N-desmethyl enzalutamide (M2). M2 is an active metabolite of similar potency to enzalutamide and is thought to contribute to the pharmacologic effects.[15,16] Deuteration stabilizes enzalutamide by blocking the generation of M1 and M2 (Figure 2).[17]

The pharmacokinetic parameters of metabolite M1 were compared between groups. The results showed that the C_{max} and $AUC_{0-\infty}$ of metabolite M1 has statistically significant difference ($p < 0.001$), and the Cl/F of metabolite M1 were statistically different ($p < 0.05$). The C_{max} and $AUC_{0-\infty}$ of metabolite M1 increased with the increase of dose. The pharmacokinetic parameters of metabolite M2 were compared between groups. The C_{max} of metabolite M2 has statistically significant increases ($p < 0.001$) with the increase of dose (Figure 3).

3.4 | Evaluation of dose-proportionality of 40, 80, or 160 mg on fasting

Using Phoenix winonlin 8.0 and SAS software, the linear relationship between AUC (AUC_{0-t} $AUC_{0-\infty}$) and C_{max} of HC-1119 and its metabolites M1 and M2 in plasma after a single oral administration of 40 mg, 80 mg or 160 mg of HC-1119 soft capsules on an empty stomach was evaluated by using the software Phoenix winonlin 8.0 and SAS.

Linear evaluation of pharmacokinetic characteristics of fasting 40, 80, 160 mg doses was carried out. In the fasting group, the confidence interval method was used to evaluate the pharmacokinetic parameters C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$. The conclusion are shown in Table 3. The pharmacokinetic parameters of HC-1119, within the dose range of 40–160 mg, the 95% confidence interval of the slope β of the linear equation of C_{max} is 0.92–1.14, which completely falls within the judgment interval 0.74–1.26, indicating that C_{max} is linear with dose Kinetic characteristics.

The pharmacokinetic parameters of metabolite M2, within the dose range of 40–160 mg, the 95% confidence interval of the slope β of the linear equation of C_{max} is 0.77–1.08, which completely falls within the judgment interval of 0.74–1.26, indicating that C_{max} is proportional to the dose Linear kinetic characteristics, the 95% confidence interval of the slope β of the linear equation of $AUC_{0-\infty}$ is 0.84–1.10, which completely falls within the judgment interval 0.84–1.16, indicating that $AUC_{0-\infty}$ and dose have linear kinetic characteristics.

In summary, the C_{max} of the prototype drug HC-1119 in healthy people is linear in the dose range of 40–160 mg, the C_{max} and $AUC_{0-\infty}$ of the metabolite M2 are linear in the dose range of 40–160 mg.

TABLE 2 The pharmacokinetic parameters of HC-1119 after single oral administration of 40, 80, or 160 mg HC-1119 soft capsules on fasting, $n = 12$[a], mean ± SD

PK parameters	A	B	C
C_{max} (ng/ml)	1479.17 ± 219.605	3098.33 ± 584.774	6215.00 ± 1326.962
AUC_{0-t} (h·ng·ml^{-1})	150793.9 ± 27914.63	333528.8 ± 61538.58	748835.4 ± 96855.49
$AUC_{0-\infty}$ (h·ng·ml^{-1})	152350.7 ± 28197.16	335305.8 ± 61651.48	758527.4 ± 104410.16
T_{max} (h)[b]	1.000 (0.75, 3)	1.500 (0.5, 3)	1.000 (0.75, 3)
$t_{1/2}$ (h)	139.92 ± 35.190	115.34 ± 24.304	159.03 ± 56.614
CL/F (ml/h)	271.8 ± 56.00	247.3 ± 54.00	214.6 ± 29.67
Vd/F (ml)	53779.7 ± 12707.16	40322.0 ± 7929.20	48202.0 ± 14028.23
MRT (h)	186.01 ± 42.057	168.70 ± 33.797	222.38 ± 61.350

Abbreviation: MRT, mean residence time.
[a]A, 40 mg on fasting; B, 80 mg on fasting; C, 160 mg on fasting.
[b]T_{max} (h), median (min, max).

FIGURE 2 The pathway by which M1 and M2 are generated for enzalutamide or HC-1119

Enzalutamide R=CH$_3$
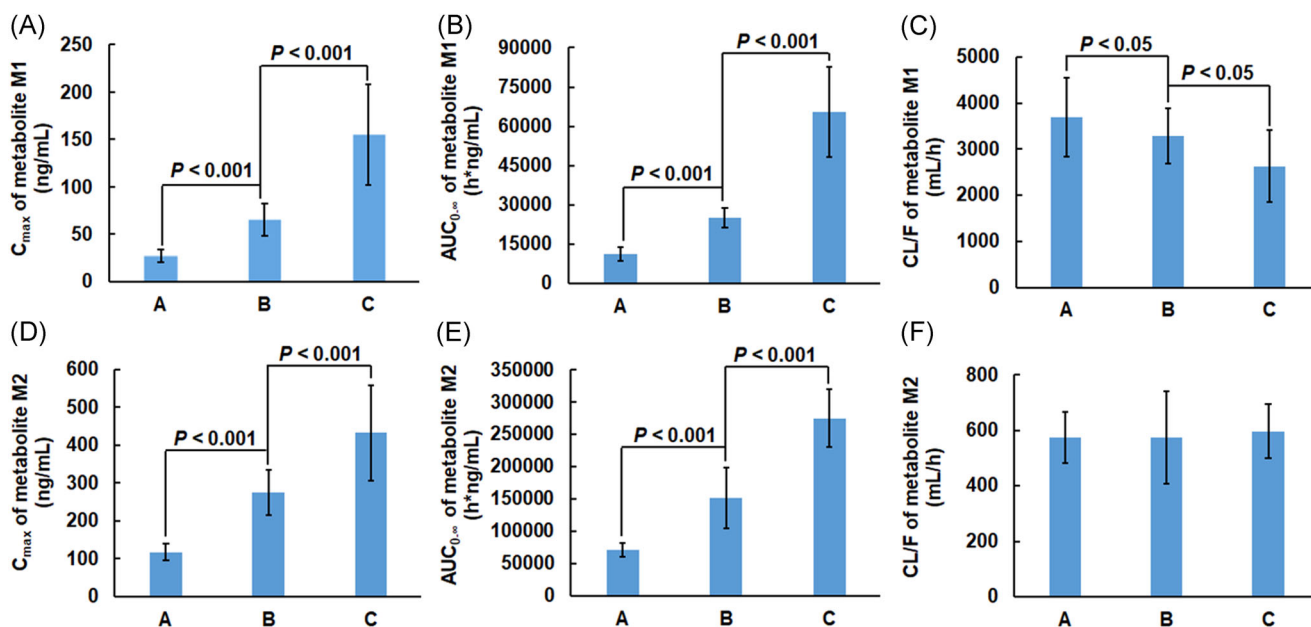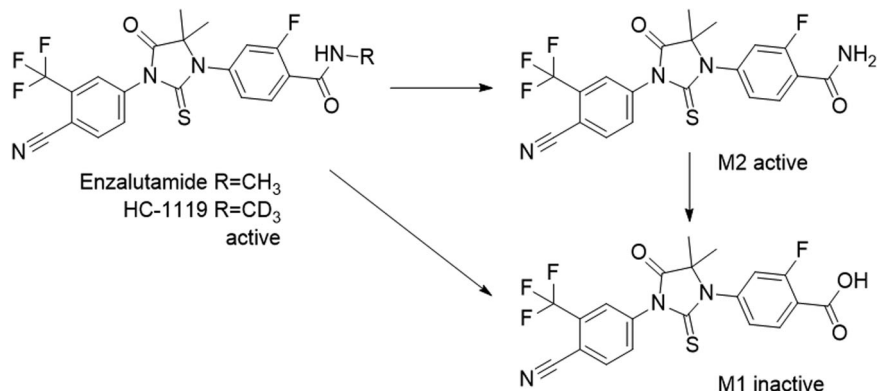HC-1119 R=CD$_3$
active

M2 active

M1 inactive

FIGURE 3 The pharmacokinetic parameters of metabolites M1 and M2 after single oral administration of 40, 80, or 160 mg on fasting, $n = 12$. A, 40 mg on fasting. B, 80 mg on fasting. C, 160 mg on fasting. (A) C$_{max}$ of metabolite M1. (B) AUC$_{0-\infty}$ of metabolite M1. (C) Cl/F of metabolite M1. (D) C$_{max}$ of metabolite M2. (E) AUC$_{0-\infty}$ of metabolite M2. (F) Cl/F of metabolite M2 [Color figure can be viewed at wileyonlinelibrary.com]

TABLE 3 Evaluation of pharmacokinetic characteristics of HC-1119 and metabolite M1 and M2 after single oral administration of 40, 80, or 160 mg on fasting by confidence interval method

Compound detected	Pharmacokinetic parameters[a]	β	95% Confidence interval	θ$_L$	θ$_H$	Judgment interval
HC-1119	C$_{max}$ (ng/ml)	1.03	(0.92, 1.14)	0.70	1.43	(0.74, 1.26)
	AUC$_{0-t}$ (h·ng·ml^{-1})	1.16	(1.06, 1.27)	0.80	1.25	(0.84, 1.16)
	AUC$_{0-\infty}$ (h·ng·ml^{-1})	1.16	(1.06, 1.27)	0.80	1.25	(0.84, 1.16)
Metabolite M1	C$_{max}$ (ng/ml)	1.24	(1.05, 1.42)	0.70	1.43	(0.74, 1.26)
	AUC$_{0-t}$ (h·ng·ml^{-1})	1.27	(1.13, 1.42)	0.80	1.25	(0.84, 1.16)
	AUC$_{0-\infty}$ (h·ng·ml^{-1})	1.25	(1.12, 1.39)	0.80	1.25	(0.84, 1.16)
Metabolite M2	C$_{max}$ (ng/ml)	0.92	(0.77, 1.08)	0.70	1.43	(0.74, 1.26)
	AUC$_{0-t}$ (h·ng·ml^{-1})	0.96	(0.83, 1.09)	0.80	1.25	(0.84, 1.16)
	AUC$_{0-\infty}$ (h·ng·ml^{-1})	0.97	(0.84, 1.10)	0.80	1.25	(0.84, 1.16)

[a]All pharmacokinetic parameters are logarithmically transformed.

PK parameters	HC-1119	Metabolite M1	Metabolite M2
C_{max} (ng/ml)	4827.27 ± 1161.130	130.29 ± 48.642	463.09 ± 128.365
AUC_{0-t} (h·ng·ml^{-1})	711817.3 ± 200586.27	53992.5 ± 13449.55	259821.1 ± 39341.72
$AUC_{0-\infty}$ (h·ng·ml^{-1})	715703.8 ± 200270.98	55760.8 ± 13213.89	269934.7 ± 40313.88
T_{max} (h)[a]	2.000 (0.75, 4)	48.000 (24, 168)	240.000 (168, 336)
$t_{1/2}$ (h)	131.42 ± 41.084	215.28 ± 76.959	202.96 ± 50.892
CL/F (ml/h)	237.9 ± 59.12	3037.2 ± 803.24	608.8 ± 121.75
Vd/F (ml)	45160.9 ± 19069.27	965392.0 ± 483623.29	178513.7 ± 58699.85
MRT (h)	194.58 ± 49.151	333.97 ± 56.135	402.52 ± 63.053

TABLE 4 The pharmacokinetic parameters of HC-1119, metabolite M1 and M2 after single oral administration of 160 mg HC-1119 soft capsules after meal, n = 11, mean ± SD

Abbreviation: MRT, mean residence time.

[a]T_{max} (h), median (min, max).

3.5 | Effects of food on pharmacokinetics of HC-1119

The main pharmacokinetic parameters of HC-1119, metabolite M1 and metabolite M2 were shown in Table 4.

Take 160 mg on an empty stomach and after a high-fat meal the pharmacokinetic parameters of HC-1119, metabolites M1 and M2 in plasma were compared with those of fasting (group C) and post-prandial (group D) after logarithmic transformation. The results showed that the difference of C_{max} of HC-1119 was statistically significant, and the pharmacokinetic parameters of M1/M2 compound were not statistically significant. The results showed that high-fat diet did not affect the absorption degree of HC-1119, AUC and the main pharmacokinetic parameters of its metabolites M1 and M2, but decreased the C_{max} of HC-1119. Therefore, the clinical application of HC-1119 soft capsules in the later stage can be recommended for both fasting and postprandial. The specific results are shown in Table 5.

TABLE 5 Pharmacokinetic parameters of HC-1119, metabolite M1 and M2 after single oral administration of 160 mg HC-1119 soft capsules on fasting or after meal, n = 12 or 11[a]

Compound detected	Pharmacokinetic parameters[b]	Statistics	p value
HC-1119	C_{max} (ng/ml)	t value: 2.78	0.011
	AUC_{0-t} (h·ng·ml^{-1})	t value: 0.86	0.403
	$AUC_{0-\infty}$ (h·ng·ml^{-1})	t value: 0.92	0.370
Metabolite M1	C_{max} (ng/ml)	t value: 1.22	0.237
	AUC_{0-t} (h·ng·ml^{-1})	t value: 1.25	0.227
	$AUC_{0-\infty}$ (h·ng·ml^{-1})	t value: 1.35	0.190
Metabolite M2	C_{max} (ng/ml)	t value: −0.57	0.575
	AUC_{0-t} (h·ng·ml^{-1})	Chi-Square: 0.64	0.424
	$AUC_{0-\infty}$ (h·ng·ml^{-1})	t value: 0.24	0.815

[a]160 mg on fasting, n = 12, group C. 160 mg after meal, n = 11, group D.
[b]All pharmacokinetic parameters are logarithmically transformed.

3.6 | Safety of single dose HC-1119 soft capsules orally

Among the 47 subjects, 22 cases (44 times) of adverse events occurred, with the incidence rate of 46.8%; 5 cases (5 times) of important adverse events (any adverse events that lead to the use of targeted medical measures) occurred, with the incidence rate of 10.6%; 6 cases (17 times) of adverse reactions (adverse events that are certainly related, probably related, or possibly related to the drug), the incidence rate was 12.8%; There were no serious adverse events, serious adverse reactions, adverse events leading to shedding and adverse reactions leading to shedding (Table 6).

There were 5 cases (11 times) of adverse events and 4 cases (4 times) of important adverse events in group A, the incidence rate was 41.7% and 33.3%, respectively. Important adverse events included upper respiratory tract infection (3 cases, 3 times) and lip pain (1 case, 1

time). 3 cases (3 times) of adverse events occurred in group B, the incidence rate was 25.0%. There were 7 cases (17 times) of adverse events, 5 cases (14 times) of adverse reactions and 1 case (1 time) of important adverse event in group C, the incidence rate was 58.3%, 41.7% and 8.3%, respectively. In group C (Table S2), One case subject reported twice serum total bilirubin and serum conjugated bilirubin increased and an increase of serum unconjugated bilirubin. Two subjects reported increase of serum total bilirubin, serum conjugated bilirubin and serum unconjugated bilirubin each, and serum triglycerides of one of them also increased. Important adverse event occurred in group C was toothache (1 case, 1 time). There were 7 cases (13 times) of adverse events and 1 case (3 times) of adverse reactions in group D, the incidence rate was 63.6% and 9.1%, respectively. In one case, serum total bilirubin, serum conjugated bilirubin and serum unconjugated bilirubin increased. No adverse reactions occurred in groups A and B, and no important adverse events occurred in groups B and D.

TABLE 6 Summary of adverse events classified by system organs and preferred terms, times, cases (ratio%)[a]

	A (n = 12)[b]	B (n = 12)[b]	C (n = 12)[b]	D (n = 11)[b]	Total (n = 47)
Adverse events (AE)	11, 5 (41.7)	3, 3 (25.0)	17, 7 (58.3)	13, 7 (63.6)	44, 22 (46.8)
Important adverse events[c]	4, 4 (33.3)	0, 0	1, 1 (8.3)	0, 0	5, 5 (10.6)
Infections and infestations	3, 3 (25.0)	0, 0	0, 0	0, 0	3, 3 (6.4)
Upper respiratory tract infection	3, 3 (25.0)	0, 0	0, 0	0, 0	3, 3 (6.4)
Gastrointestinal diseases	1, 1 (8.3)	0, 0	1, 1 (8.3)	0, 0	2, 2 (4.3)
Toothache	0, 0	0, 0	1, 1 (8.3)	0, 0	1, 1 (2.1)
Lip pain	1, 1 (8.3)	0, 0	0, 0	0, 0	1, 1 (2.1)
Adverse reactions[c]	0, 0	0, 0	14, 5 (41.7)	3, 1 (9.1)	17, 6 (12.8)
Various inspections	0, 0	0, 0	14, 5 (41.7)	3, 1 (9.1)	17, 6 (12.8)
Elevated serum total bilirubin	0, 0	0, 0	4, 3 (25.0)	1, 1 (9.1)	5, 4 (8.5)
Elevated serum conjugated bilirubin	0, 0	0, 0	4, 3 (25.0)	1, 1 (9.1)	5, 4 (8.5)
Elevated serum unconjugated bilirubin	0, 0	0, 0	3, 3 (25.0)	1, 1 (9.1)	4, 4 (8.5)
Elevated serum triglycerides	0, 0	0, 0	2, 2 (16.7)	0, 0	2, 2 (4.3)
Elevated alanine aminotransferase	0, 0	0, 0	1, 1 (8.3)	0, 0	1, 1 (2.1)
Serious adverse event (SAE)	0, 0	0, 0	0, 0	0, 0	0, 0
Serious adverse reactions	0, 0	0, 0	0, 0	0, 0	0, 0
Adverse events leading to shedding	0, 0	0, 0	0, 0	0, 0	0, 0
Adverse reactions leading to shedding	0, 0	0, 0	0, 0	0, 0	0, 0

[a]Calculate the percentage with the number of subjects in each group as the denominator.

[b]A, 40 mg on fasting. B, 80 mg on fasting. C, 160 mg on fasting. D, 160 mg after meal.

[c]Important adverse events refer to any adverse events that lead to the use of targeted medical measures (such as drug withdrawal, dose reduction, and symptomatic treatment) in addition to serious adverse events. Adverse reactions refer to adverse events that are certainly related, probably related, or possibly related to the drug.

4 | DISCUSSION AND CONCLUSION

Deuterium (^{2}H) is one of the most widely used isotopes of hydrogen which is stable and nonradioactive. Deuterium and Hydrogen exhibit almost identical physical and chemical properties. Deuterium-modified or -deuterated compounds retain the potency and selectivity of their hydrogen analogs.[18,19] Therefore, the deuterated derivatives are expected to show the same physical and chemical properties as their parent chemicals including solubility, melting point and target receptor protein affinity. HC-1119 is a trideuterated derivative of enzalutamide with C-H bonds on N-methyl replaced by C-D bonds.

More energy is needed to break the C–D bond than the C–H bond cleavage. Thus, the metabolic process of the deuterated compounds under the catalysis of cytochrome P450, monoamine oxidase or aldehyde oxidase will be slowed down when the C-H bond participates in the rate determining step of the metabolic pathway.[19,20] This is the most expected isotopic effect for deuterated enzalutamide to carry higher resistance to enzyme oxidation.

In preclinical pharmacokinetic studies, HC-1119 showed similar ADME characteristics as enzalutamide. The plasma protein binding rate, metabolic species difference, metabolic pathway, metabolites,

tissue distribution of rats, permeability of blood-brain barrier and permeability of cells were evaluated to be similar to its mother drug. The C_{max} and the T_{max} of HC-1119 and enzalutamide were similar in mice, rats and dogs. The AUC_{0-24h} of HC-1119 in mice, ras and dogs was 1.41, 1.49, and 1.16 times that of enzalutamide. The $t_{1/2}$ of HC-1119 in mice, ras and dogs was 1.14, 2.03, and 1.21 times that of enzalutamide.[13]

We found in this study that, for healthy volunteers, the C_{max} of HC-1119 prototype and its metabolites M1 and M2 showed linear proportionality in the dose range of 40–160 mg on fasting. C_{max} and $AUC_{0-\infty}$ of metabolite M2 showed linear characteristics in the dose range of 40–160 mg in healthy subjects. For dosing 160 mg HC-1119 soft capsules either on fasting or after a high-fat diet, the C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ were compared between the two groups by logarithmic transformation. The results showed that the C_{max} of HC-1119 was significantly different, and the pharmacokinetic parameters of other compounds were not statistically significant. In a comparison of the pharmacokinetics and safety of enzalutamide in subjects from Moldova and Bulgaria with hepatic impairment and matched healthy subject, all subjects received a single oral dose of 160 mg enzalutamide under fasting conditions. The C_{max} of enzalutamide in three matched healthy controls were 3.8, 3.8, and 4.6 μg/ml. The

$AUC_{0-\infty}$ were 245.8, 224.8, 319.4 h·µg·ml^{-1}. The $t_{1/2}$ were 115.3, 108.3, 111.6 h.[16] In group C of our study, the C_{max}, $AUC_{0-\infty}$ and $t_{1/2}$ of HC-1119 were 6.2 µg/ml, 758.5 h·µg·ml^{-1}, and 159 h, respectively (Table 2). Compared with enzalutamide, HC-1119 prototype showed longer half-life and higher exposure. The results showed that deuteration could retain the basic properties of its mother drug without changing the metabolic pathway and prolong the half-life and reduce the generation of metabolites resulting in higher exposure in vivo. These could help HC-1119 to carry a better efficacy and safety than enzalutamide.

In the lowest dosing group A, the incidence of adverse events was higher than that of group B. There were three cases of upper respiratory tract infection what didn't occurred in other groups, probably because this clinical trial was carried out in winter, so upper respiratory tract infection was not a dose-dependent adverse event. The research doctor judged that they were irrelevant to the HC-1119. It is worth noting that there were more clinically significant laboratory findings and ECG abnormalities in the highest dosing groups C and D, although they were mild. In this study, the severity of all adverse events is grade 1, with a low incidence of adverse reactions, no serious adverse events, no serious adverse reactions, no important adverse events, no adverse events leading to shedding and no adverse reactions leading to shedding. In a clinical trial of 25 healthy subjects received a single oral dose of 160 mg enzalutamide under fasting conditions, one control subject experienced a serious AE of hypertensive crisis (NCI-CTCAE grade 2) that was considered possibly related to enzalutamide.[16] In our study, adverse reactions of enzalutamide such as fatigue, back pain, hot flush, constipation, arthralgia, decreased appetite, diarrhea, hypertension and seizure didn't occur. The result indicated that HC-1119 was well tolerated in Chinese healthy adult men in the evaluated dose range and the specific dosing with high-fat meal.

A study included 64 patients (48–99 years) showed that age did not significantly influence exposure to the active compounds enzalutamide and N-desmethyl enzalutamide. Exposure to the inactive metabolite carboxylic acid enzalutamide was significantly higher in older patients.[21] Older patients (>85 years and 65–85 years) treated with enzalutamide are at increased risk of cardiac, infectious, metabolic, and respiratory disorders when compared with younger patients (<65).[22] In this clinical trial, the average age of subjects in four groups ranged from 20 to 25 years old (18–38 years) , younger than the average patient likely to receive enzalutamide or HC-1119 and mentioned before. It should be noted that only a few subjects with limited ranges of age and bodyweight values were included. Therefore, further research including older and lighter or heavier subjects should be considered, with special attention to adverse events in older patients.

According to the ClinicalTrial.gov database, there are 6 clinical trials of HC-1119 are registered, confirming the pre marketing research and development stage of HC-1119. Our study as NCT03776968 was a first-in-human trial conducted to observe the pharmacokinetics and food effects of HC-1119 in Chinese healthy adult male subjects. The pharmacokinetic results in this study are of great significance to the clinical pharmacology of deuterated enzalutamide, which is helpful to understand the bridging strategy and promote the development of deuterated drugs. HC-1119, as a deuterated enzalutamide, is expected to fill a real gap in the pharmaceutical market.

In conclusion, HC-1119 was well tolerated in Chinese healthy adult men over in the evaluated dose range and the specific dosing with high-fat meal. HC-1119 is expected to have lower dosage than enzalutamide, which is a promising better choice for clinical treatment of prostate cancer. To prove that HC-1119 has higher safety and more clinical benefits than enzalutamide, head-to-head clinical trials in patients are needed.

CONFLICT OF INTERESTS

The authors declare that there are no conflict of interests.

AUTHOR CONTRIBUTIONS

Li Zhang, Tie Zhou, and Shen Gao: designed this research; all authors performed this research; **Naping Zhao**: performed data analysis; **Haiping Ma, Weidong Xu, and Jin Ni**: wrote the paper; **Li Zhang**: critically revised the manuscript.

DATA AVAILABILITY STATEMENT

The data that supports the findings of this study are available in the supplementary material of this article.

ORCID

Li Zhang http://orcid.org/0000-0003-1094-2192

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