Pharmacokinetics and Safety of Enzalutamide in Healthy Chinese Male Volunteers

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ABSTRACT

Purpose: This open-label, single-dose study evaluated the pharmacokinetic profiles of enzalutamide and its major metabolites and the safety of enzalutamide in healthy, Chinese male volunteers.

Methods: Fourteen volunteers (median age, 28.5 years) received a single oral dose of enzalutamide (160 mg) under fasting conditions on day 1 and were followed for 50 days. Pharmacokinetic profiles were obtained for enzalutamide and its major metabolites, carboxylic acid metabolite (M1; inactive metabolite) and *N*-desmethyl enzalutamide (M2; active metabolite), on day 1 up to 1176 hours (49 days). Safety data were also collected.

Findings: Enzalutamide plasma concentration rapidly increased (median T_{max}, 1.5 hours) followed by a slow decrease (mean $t_{½}$, 90.7 hours). M1 and M2 plasma concentrations increased gradually with a median T_{max} of 72.0 and 121 hours, respectively. M1 and M2 mean metabolite-to-parent ratios were 0.2 and 1.3, respectively. Mean $AUC_{0-\infty}$ of enzalutamide plus M2 was 828 μg h/mL versus 368 μg h/mL for enzalutamide alone. Mean $t_{½}$, maximum concentration, and T_{max} of enzalutamide plus M2 were comparable with those of enzalutamide. Drug-related treatment-emergent adverse events were reported in 4 men (28.6%): 1 each of upper respiratory tract infection, chest discomfort, increased blood bilirubin, and decreased white blood cell count. No deaths or serious treatment-emergent adverse events were observed.

Implications: The pharmacokinetic profiles of enzalutamide, M1, M2, and enzalutamide plus M2 in healthy Chinese men were generally consistent with those in white men. No new safety concerns were found. Chinese Clinical Trial Registration identifier: CTR20150635. (*Clin Ther*. 2019;41:261–268)

Keywords: enzalutamide, pharmacokinetics, prostate cancer, prostatic neoplasms.

INTRODUCTION

Enzalutamide is an androgen receptor inhibitor that prevents androgen ligand and androgen receptor binding, androgen receptor nuclear translocation, and androgen receptor–mediated DNA binding.[1] Enzalutamide, currently approved for use in >95 countries, initially received US Food and Drug Administration approval in 2012[2] for the treatment of patients with metastatic castration-resistant prostate cancer (mCRPC) who previously received docetaxel based on the results of the AFFIRM Phase III study.[3] Building on the results of the AFFIRM study, enzalutamide has received US Food and Drug Administration approval for the treatment of men with chemotherapy-naïve mCRPC[4] and, subsequently, men with nonmetastatic castration-resistant prostate cancer[5] based on the results of the PREVAIL and PROSPER Phase III studies, respectively. In the AFFIRM and PREVAIL trials, enzalutamide prolonged overall survival and radiographic progression-free survival versus placebo in men with mCRPC.[3,4] In PROSPER, a significant improvement in metastasis-free survival, defined as time to radiographic progression or death, with enzalutamide versus placebo was observed in men with nonmetastatic castration-resistant prostate

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cancer, and further analysis of overall survival is awaited.[5] As per the latest available data, an estimated 60,300 Chinese men were diagnosed with prostate cancer in 2015, and, as such, prostate cancer represents a substantial health concern in China.[6]

Two major metabolites for enzalutamide have been identified in human plasma. The carboxylic acid metabolite (M1) is an inactive metabolite, whereas *N*-desmethyl enzalutamide (M2) is an active metabolite, with primary pharmacodynamics and potency similar to those of enzalutamide.[7] Compared with the plasma concentration of enzalutamide at steady state, the concentration of M1 is 25% lower, whereas M2 is approximately the same.[7] Studies performed *in vitro* report that enzalutamide is metabolized by the cytochrome P450 enzymes 2C8 and 3A4/5, both of which play a role in the formation of the active metabolite.[8] In humans, enzalutamide is primarily eliminated by hepatic metabolism.[7] After oral administration of ^{14}C-enzalutamide to healthy volunteers, 84.6% of the dose was recovered through day 77 after dosing: 71.0% was recovered in urine (primarily M1, with trace quantities of enzalutamide and M2) and 13.6% was recovered in feces.[7] Renal excretion is therefore a minor elimination pathway for unchanged parent enzalutamide and the active metabolite M2.

Importantly, previous studies on the pharmacokinetic profiles of enzalutamide and its major metabolites were conducted in white men.[7,8] Considering that variability in body size might alter enzalutamide exposure and that the median weight of white men previously reported[8] was higher than that of the healthy Chinese male volunteers reported here, it is reasonable that the pharmacokinetic profile of enzalutamide might vary among populations based on body size. The pharmacokinetic profile of enzalutamide may therefore not be applicable to all male populations. Further studies in special populations are necessary to advance our understanding of the pharmacokinetic and safety profile of enzalutamide.

This study evaluated the pharmacokinetic and safety profiles of enzalutamide and its 2 major metabolites in healthy Chinese male volunteers.

METHODS

Study Design

This open-label, single-dose, single-center study of enzalutamide enrolled healthy Chinese male volunteers. The investigators and all parties involved conducted the study in adherence to the Declaration of Helsinki and the Drug Administration Law of the People's Republic of China, as well as Good Clinical Practice promulgated by the China Food and Drug Administration. All study volunteers provided written informed consent before any study-related screening procedures took place.

Study inclusion criteria included the following: Chinese men aged 18 to 40 years; normal body mass index (19−25 kg/m^2); weight of ≥50 kg at screening; no preexisting heart, liver, kidney, gastrointestinal tract, or nervous system disease; and no history of drug allergy. Study exclusion criteria included the following: known or suspected hypersensitivity to enzalutamide or any of the constituents of the formulation used; any liver function tests with results above the upper limit of normal and that the investigator considered to be of clinical significance; a history of seizures; use of prescribed or over-the-counter drugs, including vitamins, natural and herbal remedies, and food supplements, from 14 days before admission until the end-of-study visit; use of all concomitant medication during the study except for the occasional use of acetaminophen (paracetamol); and abnormal pulse rate and/or blood pressure.

Sample Size and Analysis Set

No formal statistical sample size calculation has been performed. The intended sample size of 12 healthy study volunteers was based on Chinese regulations, which specify that a sample size of 8−12 participants per dose group is sufficient for a pharmacokinetic study with single-dose administration[9]; 14 volunteers were enrolled considering the possible dropout during the long trial period. All study volunteers who received enzalutamide and from whom samples for drug concentrations were collected for at least 1 time point were included in the pharmacokinetic analysis set. All study volunteers who received enzalutamide were included in the safety analysis set.

Study Treatment

Study volunteers received a single oral dose of enzalutamide (160 mg) under fasting conditions on day 1 and were followed for 50 days. Study volunteers were admitted to the study center for

4 days (day –1 to day 3) and continued with outpatient visits from day 4 until day 50. No fluid intake was allowed from 4 hours before dosing until 1 hour after dosing, except for water accompanying drug intake (approximately 240 mL). No food intake was allowed until 4 hours after dosing. Study volunteers were able to freely withdraw from the study treatment and/or study. The study investigator was also able to freely terminate a study volunteer's involvement at any time if the volunteer's clinical condition warranted it.

Sample Collection and Bioanalysis Method

Blood samples (3 mL) for enzalutamide, M1, and M2 were collected from the brachial vein in collection tubes that contained dipotassium ethylenediaminetetraacetic acid before dosing and at 0.5, 0.75, 1, 1.5, 2, 3, 4, 6, 8, 12, 24, 36, 48, 72, 120, 168, 264, 336, 432, 504, 600, 672, 768, 840, 936, 1008, 1104, and 1176 hours after dosing. All study volunteers who received the study drug had an end-of-study visit 7 to 10 days after the last blood sampling for pharmacokinetic analysis or early termination.

Plasma concentrations of enzalutamide, M1, and M2 were measured at WuXi AppTec (Shanghai, China) using a validated LC-MS/MS method, which was originally validated at inVentiv Health[10] and then transferred to WuXi. Briefly, 50 μL of plasma was mixed with 25 μL of internal standard solution, which contained $^{13}CD_3$ analogs of enzalutamide and its metabolites, and analytes were extracted by liquid–liquid extraction using *tert*-butyl methyl ether. The extracted samples were injected onto HPLC Cadenza CD-C18 columns (3 μm, 2 × 30 mm; Imtakt Co, Kyoto, Japan) and then detected by mass spectrometer API 4000 (AB SCIEX, Foster City, California). Monitoring parent and product ions were 465.2 and 229.2 m/z for enzalutamide, 452.2 and 196.1 m/z for M1, and 451.2 and 178.4 m/z for M2, respectively. The lower limit of quantification was 0.02 μg/mL for all three analytes (enzalutamide, M1, and M2), and intra-assay and interassay precision (relative SD) and accuracy (percentage of bias) of each of the three analytes were <10%. The quantification range for each analyte was 0.02 to 50 μg/mL when 50 μL of plasma was used.

Data Handling

Missing data were not imputed or used for analyses. Concentrations below the quantification limit were treated as zero in the analyses.

Pharmacokinetic Analysis

Full pharmacokinetic profiles were obtained for enzalutamide, M1, and M2 up to 1176 hours (49 days) after intake of enzalutamide and were estimated using plasma concentrations of enzalutamide and its metabolites. Because M2 is the pharmacologically active metabolite of enzalutamide, pharmacokinetic parameters were also presented for the sum of the concentration of enzalutamide plus M2. Noncompartmental methods were used to calculate pharmacokinetic parameters, which included the following.

For enzalutamide, the following parameters were measured: $AUC_{0-\infty}$, AUC_{0-last}, T_{max}, C_{max}, k_e, $t_{1/2}$, apparent volume of distribution during the terminal phase after extravascular dosing, apparent body clearance after extravascular dosing, mean residence time from the time of dosing up to infinity ($MRT_{0-\infty}$), and percentage of $AUC_{0-\infty}$ attributable to extrapolation from the last time point with quantifiable concentration to time infinity. For M1 and M2, the following parameters were measured: $AUC_{0-\infty}$, AUC_{0-last}, t_{max}, C_{max}, k_e, $t_{1/2}$, $MRT_{0-\infty}$, and metabolite-to-parent ratio. For enzalutamide plus M2, $AUC_{0-\infty}$, AUC_{0-last}, t_{max}, C_{max}, and $t_{1/2}$ were measured. Pharmacokinetic parameters were estimated by noncompartmental analysis methods in Phoenix WinNonlin version 6.3 (Certara USA, Inc, Princeton, New Jersey).

Safety Assessments

Safety assessments were performed through the recording of adverse events (AEs), clinical laboratory tests, physical examinations, 12-lead ECGs, and vital signs. AEs were defined as such if observed after administration of enzalutamide, and collection of AEs began when a volunteer signed the informed consent form and continued until the completion of the end-of-study visit. All observed and spontaneously reported AEs were recorded, and the severity of AEs was graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 4.03.

Statistical Analysis

Descriptive statistics were used to summarize continuous variables. The coefficient of variation and geometric mean were also presented for concentrations and pharmacokinetic parameters. The number and percentages of study volunteers were used to summarize categorical variables. All data processing, summarization, and analyses were performed using SAS Drug Development version 4.5 and SAS version 9.4 (SAS Institute Inc, Cary, North Carolina).

RESULTS

Baseline Demographic Characteristics

Fourteen healthy male volunteers were enrolled and received a single oral dose of enzalutamide 160 mg under fasting conditions (median age, 28.5 years [range, 24–36 years]; median body mass index, 21.5 kg/m^2 [range, 19.9–24.0 kg/m^2]) (Figure 1 and Table I). Two study volunteers withdrew during the study period (Figure 1). All study volunteers were included in the safety and pharmacokinetic populations (Figure 1).

One volunteer deviated from the protocol on day 31 of the study after receiving an excluded concomitant treatment (traditional herbal medicines). Because this volunteer provided samples for the evaluation of at least 1 time point after receiving the excluded concomitant treatment, he was still included in the safety and pharmacokinetic populations.

Pharmacokinetics

After the single dose of oral enzalutamide, enzalutamide plasma concentrations had a median T_{max} of 1.50 hours (range, 0.75–3.0 hours) followed by a mean (SD) $t_{1/2}$ of 90.7 (55.3) hours (Figure 2A and Table II). Plasma concentrations of M1 and M2 had a median T_{max} of 72.0 hours (range, 24.0–265 hours) and 121 hours (range, 120–265 hours), respectively (Figure 2B and C and Table II). The mean (SD) $t_{1/2}$ of M1 and M2 was 201 (38.9) hours and 162 (29.0) hours, respectively (Table II).

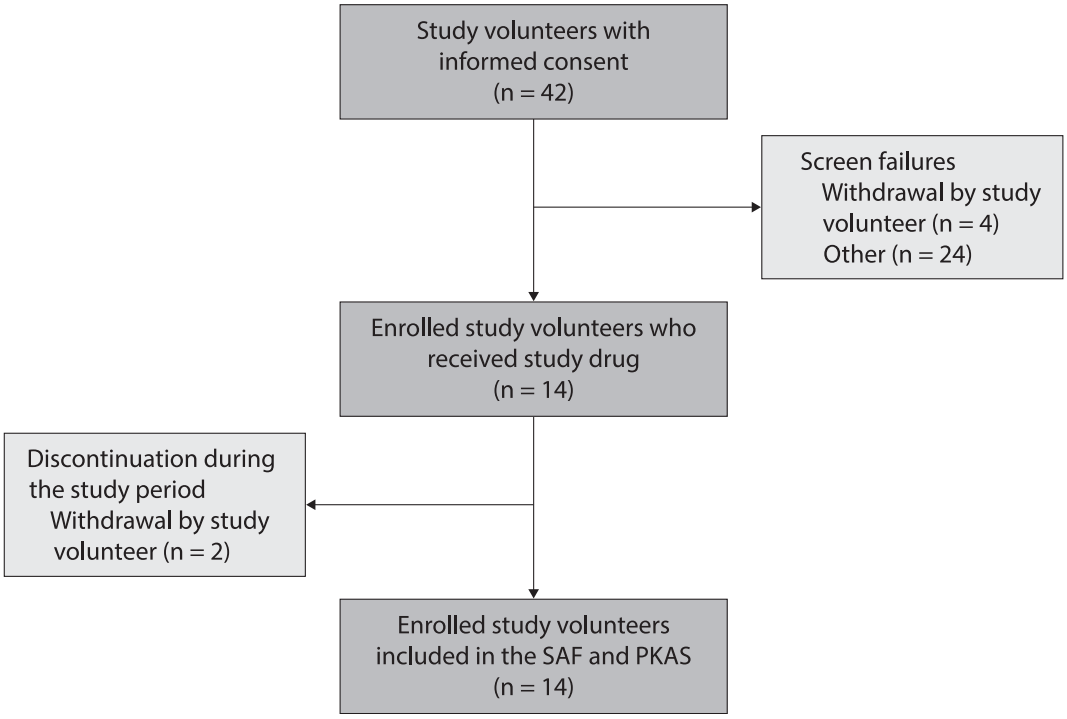

Figure 1. Disposition of study volunteers and analysis sets. Only the primary reason for discontinuation was collected. PKAS = pharmacokinetic analysis set; SAF = safety analysis set.

Table I. Demographic and other baseline characteristics.

Characteristic	Enzalutamide (N = 14)
Male, no. (%)	14 (100)
Age at the time of informed consent, median (range), y	28.5 (24–36)
Asian, no. (%)	14 (100)
Height at screening, median (range), cm	171.6 (164.8–179.7)
Weight at screening, median (range), kg	64.2 (55.4–77.5)
BMI at screening, median (range), kg/m^2	21.5 (19.9–24.0)
No past medical conditions, no. (%)	14 (100)
No present medical conditions, no. (%)	14 (100)
Smoking history at screening, no. (%)	10 (71.4)
Never used tobacco	2 (14.3)
Current tobacco user	2 (14.3)
Former tobacco user	
Never used alcohol, no. (%)	14 (100)
Never abused drugs, no. (%)	14 (100)

BMI = body mass index.

The median T_{max} of the sum of enzalutamide and M2 (1.3 hours [range, 0.8–3.0 hours]) was similar to that of enzalutamide, whereas its mean (SD) $t_{1/2}$ (155 [27.9] hours) was similar to that of M2 (Figure 2D and Table II).

The mean (SD) C_{max} of enzalutamide, M1, and M2 was 6.48 (0.987) μg/mL, 0.208 (0.0823) μg/mL, and 1.08 (0.258) μg/mL, respectively. The mean (SD) C_{max} of the sum of enzalutamide and M2 was comparable with that of enzalutamide (6.52 [1.05] μg/mL) (Table II). The mean (SD) metabolite-to-parent ratios of M1 and M2 were 0.206 (0.0827) and 1.32 (0.318), respectively (Table II). The mean (SD) $AUC_{0-\infty}$ of enzalutamide, M1, and M2 was 368 (67.5) μg·h/mL, 72.9 (28.3) μg·h/mL, and 459 (92.4) μg·h/mL, respectively (Table II). The mean (SD) $AUC_{0-\infty}$ of the sum of enzalutamide and M2 was 828 (112) μg·h/mL.

Adverse Events

Treatment-emergent AEs were reported in 7 of the 14 study volunteers (50.0%). The most common (occurring in ≥2 volunteers) were upper respiratory tract infection and scratch (2 volunteers each [14.3%]). For 4 study volunteers (28.6%), the treatment-emergent AE was considered possibly or probably related to enzalutamide. Study drug–related treatment-emergent AEs included chest discomfort, upper respiratory tract infection, increased blood bilirubin, and decreased white blood cell count (1 volunteer each [7.1%]). Increased blood bilirubin (mean bilirubin, 13.61 μmol/L at screening and 13.5 μmol/L at end-of-study visit) and decreased white blood cell count (mean count, 5.79×10^9/L at baseline and 5.51×10^9/L at end-of-study visit) were not deemed clinically significant. No deaths, AEs of special interest, serious treatment-emergent AEs, or treatment-emergent AEs of grade ≥3 severity were reported.

Laboratory tests did not find any potentially clinically significant changes from baseline for liver enzymes (ie, total bilirubin, alkaline phosphatase, alanine aminotransferase, and aspartate aminotransferase), hematologic parameters (ie, hemoglobin, hematocrit, red blood cells, white blood cells, neutrophils, lymphocytes, monocytes, eosinophils, basophils, platelets, prothrombin time, international normalized ratio, and activated partial thromboplastin time), urinalysis parameters (ie, urine pH, protein, glucose, blood, leukocytes, urobilinogen, bilirubin, ketones, and nitrite), or other biochemistry parameters throughout the study. Vital signs (blood pressure, pulse rate, and body temperature) remained at or near baseline values during the study.

DISCUSSION

This study assessed the pharmacokinetic properties of enzalutamide and its 2 major metabolites, as well as the safety properties of enzalutamide, after a single oral administration of 160 mg in nonelderly, healthy Chinese male volunteers under fasting conditions. The single dose of enzalutamide 160 mg was rapidly absorbed and eliminated slowly, with a median T_{max} of 1.50 hours and a mean $t_{1/2}$ of 90.7 hours. In

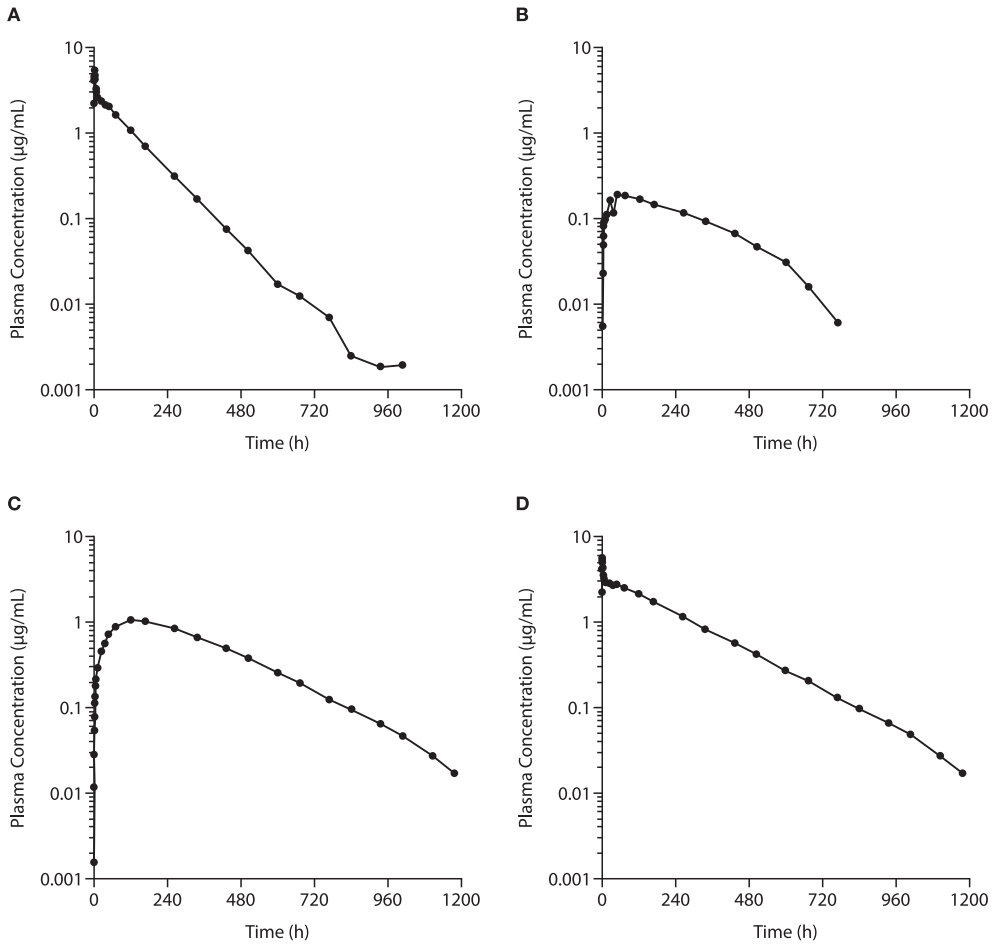

Figure 2. Semilog scale plot of mean plasma concentration–time profiles for (A) enzalutamide, (B) carboxylic acid metabolite of enzalutamide (M1), (C) *N*-desmethyl enzalutamide (M2), and (D) enzalutamide plus M2. Concentrations below the lower limit of quantification (0.02 μg/mL) are set to zero. If ≥1 values at a given time point are below the quantification limit, the mean value may be <0.02 μg/mL.

contrast, the plasma concentration of the 2 major metabolites M1 and M2 gradually increased after oral administration of enzalutamide. The long elimination half-life for enzalutamide and both of its major metabolites suggests significant accumulations of these analytes at steady state. The rapid increase and the concentration levels for the sum of enzalutamide and its active moiety, M2, were comparable with those of enzalutamide alone, whereas its longer elimination time was comparable with that of M2.

Similar to reports from earlier studies where healthy volunteers were administered enzalutamide 160 mg orally,[7,11] no clinically relevant safety concerns were reported in this study. Importantly, no deaths, serious AEs, AEs resulting in discontinuation, or grade ≥3 AEs were reported in this study. Furthermore, no clinically significant changes from baseline were found in clinical laboratory parameters and vital signs.

In a mass balance and biotransformation study that enrolled healthy white male volunteers (n = 6), enzalutamide administered as a single dose of 160 mg under fasting conditions had previously found a rapid increase followed by a slower decrease in plasma concentration after dosing (median T_{max} of

Table II. Pharmacokinetic parameters of enzalutamide, M1, M2, and the sum of enzalutamide and M2.*

	Parameter										
Analyte	$AUC_{0-\infty}$, µg·h/mL (n = 12)	AUC_{0-last}, µg·h/mL (n = 12)	T_{max}, h (n = 14)†	C_{max}, µg/mL (n = 14)†	k_e, l/h (n = 12)	$t_{1/2}$, h (n = 12)	V_z/F, L (n = 12)	CL/F, L/h (n = 12)	$MRT_{0-\infty}$, h (n = 12)	$AUC_{0-\infty}$, % extrapolated (n = 12)	MPR (n = 12)
Enzalutamide	368 (67.5)	364 (67.1)	1.50 (0.750–3.00)	6.48 (0.987)	0.00918 (0.00318)	90.7 (55.3)	55.7 (29.1)	0.445 (0.0668)	115 (35.3)	1.16 (0.479)	–
M1	72.9 (28.3)	63.5 (25.5)	72.0 (24.0–265)	0.208 (0.0823)	0.00356 (0.000674)	201 (38.9)	–	–	321 (67.6)	13.0 (4.30)	0.206 (0.0827)
M2	459 (92.4)	451 (87.8)	121 (120–265)	1.08 (0.258)	0.00437 (0.000600)	162 (29.0)	–	–	331 (64.9)	1.77 (1.25)	1.32 (0.318)
Sum of enzalutamide and M2	828 (112)	819 (108)	1.25 (0.750–3.00)	6.52 (1.05)	–	155 (27.9)	–	–	–	–	–

M1 = carboxylic acid metabolite of enzalutamide; M2 = *N*-desmethyl enzalutamide; MPR = metabolite-to-parent ratio; MRT = mean residence time; $MRT_{0-\infty}$ = MRT from the time of dosing up to infinity.*Values expressed as mean (SD), with the exception of T_{max}, which is reported as median (range).
† n = 12 for M1, M2, and sum of enzalutamide and M2.

1.8 hours [range, 1−3 hours] and mean $t_{1/2}$ of 69.8 hours, respectively).[7] Compared with enzalutamide, M1 and M2 had slower increases in plasma concentration after dosing, with median T_{max} in plasma of 96 hours and 132 hours, respectively.[7] Although the study duration and sampling time points used to assess the pharmacokinetic profiles in healthy white male volunteers differ from those used in the present study and despite weight differences between the white and Chinese study groups, results between the 2 study populations were generally consistent. Finally, no new safety concerns for treatment with enzalutamide were reported in this cohort of healthy Chinese men.

CONCLUSIONS

Our results indicate that the pharmacokinetic profiles of enzalutamide, M1, M2, and the sum of enzalutamide and M2 in healthy Chinese men were generally consistent with those previously reported in white men, and no clinically relevant safety concerns were reported. Taken together, the pharmacokinetic and safety profiles suggest that enzalutamide 160 mg is an appropriate dose in the Chinese male population.

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CONFLICTS OF INTEREST

Peggy Wu, MSc, is an employee of Astellas Pharma China Inc. Risa Fukushi, MSc, and Shunsuke Yamada, MEng, are employees of Astellas Pharma Inc. As study sponsor, Astellas Pharma China Inc was involved in the design and conduct of the study, the collection, management, analysis, and interpretation of the data, and the review and approval of the manuscript. The authors have indicated that they have no other conflicts of interest regarding the content of this article.

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