

# Pharmacokinetic Interaction of Finasteride With Tamsulosin Hydrochloride: An Open-Label, Randomized, 3-Period Crossover Study in Healthy Chinese Male Volunteers

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## ABSTRACT

**Purpose:** The primary aim of this study was to evaluate whether there was clinically significant pharmacokinetic (PK) interaction between finasteride and tamsulosin in healthy Chinese male subjects.

**Methods:** This was an open-label, randomized, 3-period, crossover study. Subjects received single and multiple doses of 5 mg finasteride alone, single and multiple doses of 0.2 mg tamsulosin hydrochloride sustained-release capsule alone, and single and multiple doses of 5 mg finasteride with 0.2 mg tamsulosin hydrochloride, in an order determined by a computerized randomization schedule. Blood samples were collected up to 48 hours after dosing on study day 1 and up to 24 hours after dosing on study day 9 for determination of plasma concentrations with a validated LC-MS/MS method. Pharmacokinetic parameters were estimated via noncompartmental methods. Tolerability was evaluated by monitoring adverse events, laboratory assays, vital signs, and 12-lead ECG.

**Findings:** Fifteen subjects were enrolled, and 14 completed the study. The geometric mean ratios (GMRs) (90% CIs) of  $AUC_{\tau,ss}$  and  $C_{max,ss}$  values of finasteride at steady state between coadministration of finasteride and tamsulosin hydrochloride and finasteride alone were 1.14 (1.05–1.23) and 1.06 (0.99–1.14), respectively. The GMRs (90% CIs) for  $AUC_{0-t}$  and  $C_{max}$  values of finasteride for a single dose of coadministration of finasteride and tamsulosin hydrochloride and finasteride alone were 1.02 (0.94–1.11) and 1.06 (1.01–1.11), respectively. The GMRs (90% CIs) for  $AUC_{\tau,ss}$  and  $C_{max,ss}$  values of tamsulosin at steady state for coadministration of finasteride and tamsulosin hydrochloride and tamsulosin hydrochloride alone were 1.18 (1.05–1.33) and 1.23 (1.06–1.43),

respectively. The GMRs (90% CIs) for  $AUC_{0-t}$  and  $C_{max}$  values of tamsulosin for a single dose of coadministration of finasteride and tamsulosin hydrochloride and tamsulosin hydrochloride alone were 1.04 (0.97–1.10) and 1.04 (0.98–1.11), respectively. Statistical analyses confirmed that the 90% CIs for these PK parameters were within the predefined not clinically significant PK drug-drug interaction effect boundaries (0.5–2.0) in this study. If comparing the findings with narrower boundaries (0.8–1.25), the conclusion may not be supportive for tamsulosin hydrochloride. During the study, a total of 4 adverse events were reported in 3 subjects including allergic reaction, abnormal findings on an ECG, a slight increase in alanine aminotransferase, and a positive result on glucose urine test.

**Implications:** Both finasteride and tamsulosin hydrochloride were well tolerated. Coadministration of finasteride and tamsulosin hydrochloride seems unlikely to lead to a clinically significant PK drug-drug interaction, after a single dose and at steady state. (*Clin Ther.* 2014;■:■■■–■■■) © 2014 Elsevier HS Journals, Inc. All rights reserved.

**Key words:** drug-drug interaction, finasteride, healthy subjects, pharmacokinetics, tamsulosin hydrochloride.

## INTRODUCTION

Benign prostatic hyperplasia (BPH) is a chronic disease that affects as many as 50% of men by the age of

Accepted for publication October 23, 2014.

<http://dx.doi.org/10.1016/j.clinthera.2014.10.021>

0149-2918/\$ - see front matter

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50 years, and the incidence of BPH becomes higher with increasing age. If no timely treatment is given, it will lead to some serious complications such as kidney stones, urinary tract infection, and renal insufficiency. Medical therapy for BPH consists primarily of 5 $\alpha$ -reductase inhibitors (5 $\alpha$ RI) such as finasteride and dutasteride and  $\alpha_1$  receptor antagonists ( $\alpha_1$  blockers) such as tamsulosin hydrochloride, terazosin, and doxazosin. Because 5 $\alpha$ RI and  $\alpha_1$  blockers have complementary mechanisms of action, it is plausible that 5 $\alpha$ RI combined with  $\alpha_1$  blockers could have an increased or even synergistic effect in the treatment of BPH. Recently, some clinical studies<sup>1,2</sup> and clinical practice showed that combination therapy with 5 $\alpha$ RI and  $\alpha_1$  blockers can provide significantly greater benefit than 5 $\alpha$ RI or  $\alpha_1$  blockers alone. In China, the instructions for tamsulosin hydrochloride administration specifically mentions that for the patient with BPH, a 5 $\alpha$ -reductase inhibitor (such as finasteride\* manufactured by Hangzhou MSD Pharmaceutical CO., LTD) should be added to the tamsulosin hydrochloride treatment regimen.

Finasteride is a 5 $\alpha$ -reductase inhibitor that prevents the conversion of testosterone to dihydrotestosterone. The pharmacokinetic (PK) properties of finasteride in healthy adult subjects have been reported.<sup>3,4</sup> After oral administration, finasteride is rapidly absorbed, and  $C_{max}$  is generally reached within 1 to 2 hours. Finasteride is extensively metabolized in the liver, primarily via the cytochrome P-450 3A4 enzyme subfamily. Two metabolites, the t-butyl side-chain monohydroxylated and monocarboxylic acid metabolites, were identified that have no more than 20% of the 5 $\alpha$ -reductase inhibitory activity of finasteride. After an oral dose of <sup>14</sup>C-labeled finasteride in a man, a mean of 39% of the dose is excreted in the urine in the form of metabolites and 57% is excreted in the feces. The  $t_{1/2}$  in plasma was reported to be 6 hours in healthy young Western subjects. A longer  $t_{1/2}$  and greater AUC were observed in subjects 70 years of age and older than in subjects 45 to 60 years of age.

Tamsulosin hydrochloride is a selective  $\alpha_1$ -adrenoceptor antagonist that causes smooth muscles in the bladder neck and prostate to relax, resulting in an improvement in urine flow rate and a reduction in symptoms of BPH. The PK properties of tamsulosin in healthy adult subjects have also been reported.<sup>5</sup>

Tamsulosin exhibits linear kinetics with doses ranging from 0.1 to 1.0 mg after single and multiple dosing, achieving steady-state concentrations by the fifth day of once-daily dosing. Food has effect on the oral bioavailability of tamsulosin. When tamsulosin hydrochloride is administered with food, the time to  $C_{max}$  ( $T_{max}$ ) is prolonged, and AUC and  $C_{max}$  are decreased. Tamsulosin is extensively metabolized by cytochrome P-450 enzymes including CYP3A4 and CYP2D6 in the liver, and <10% of the dose is excreted in urine unchanged. The  $t_{1/2}$  in plasma of a sustained-release capsule formulation is longer (9–13 hours in healthy subjects, 14–15 hours in BPH patients) than that of an intravenous or oral immediate-release formulation.

CYP enzyme induction or inhibition of the drug is one of the main reasons for a drug-drug interaction. Limited available information showed that strong inhibition of CYP2D6 (paroxetine) and CYP3A4 (ketoconazole) can lead to increased exposure of tamsulosin.<sup>6</sup> However, the available data regarding the PK interaction between finasteride and tamsulosin in healthy subjects or BPH patients is very rare. Only 1 available article suggested that coadministration of 5 mg finasteride once daily and 0.2 mg tamsulosin once daily did not affect the steady-state pharmacokinetics of the 2 agents.<sup>7</sup> According to the requirements of US Food and Drug Administration in China, before an international multiple-center Phase III study examining the safety and efficacy of coadministration of finasteride and tamsulosin hydrochloride in patients with BPH could be conducted, it is necessary to confirm the lack of a clinically significant PK drug-drug interaction between the 2 agents and to support the dose used of the 2 agents in the international multicenter Phase III study. Therefore, the aims of the current study were to evaluate the effect of coadministration of finasteride and tamsulosin hydrochloride on the PK parameters of finasteride and tamsulosin after single and multiple dose administration, to determine whether there is any clinically significant PK drug-drug interaction between finasteride and tamsulosin, and to assess the tolerability of the finasteride and tamsulosin hydrochloride in Chinese subjects.

## METHODS

This open-label, randomized, 3-period, cross-over study was conducted at Clinical Pharmacology Center of Zhongshan Hospital in Shanghai, China. The

\*Trademark: Proscar<sup>®</sup> (Hangzhou MSD Pharmaceutical CO., LTD).

clinical study protocol was approved by the Medical Ethics Committee at Zhongshan Hospital. All procedures were performed in accordance with the Good Clinical Practice guidelines as well as the Declaration of Helsinki and its amendments. All subjects provided written informed consent before being screened for eligibility.

Finasteride, 5-mg tablets (batch no. 320888, manufactured by Hangzhou MSD Pharmaceutical CO., LTD) and tamsulosin hydrochloride sustained release 0.2-mg capsules (batch no. H0801, manufactured by Astellas Pharma China, Inc) were used in this study. All study drugs were provided by the sponsor (Merck Sharp & Dohme Corp) at no cost.

### Study Subjects

Eligible subjects were Chinese men 18 to 55 years of age, with a body mass index between 18 and 24 kg/m<sup>2</sup>. All subjects were healthy, as confirmed by medical history, physical examination, semirecumbent vital sign measurements (heart rate, blood pressure, tympanic temperature, and respiratory rate), orthostatic vital sign measurement (heart rate and blood pressure), 12-lead ECG, and laboratory safety tests including chemistry, hematology, and urinalysis. Volunteers who had any medical history that might affect drug absorption, distribution, metabolism, and/or excretion, such as a history of gastrectomy or any disorder of the pancreas, liver, or kidney, were excluded. Subjects were excluded if they had an estimated creatinine clearance of  $\leq 70$  mL/min based on the Cockcroft-Gault equation. Subjects who had diastolic blood pressure  $< 50$  mm Hg or systolic blood pressure  $< 95$  mm Hg, or had a history of symptomatic orthostatic hypotension of orthostatic hypotension were excluded. Subjects were excluded if they took a strong inhibitor of CYP3A4 or CYP2D6, such as grapefruit juice, boceprevir, clarithromycin, and bupropion and/or strong inducers of CYP3A4 such as carbamazepine and phenytoin at  $\sim 2$  weeks before administration of the initial dose of the study drug. Subjects were instructed to abstain from using any drug including over-the-counter and herbal products and grapefruit juice for 2 weeks before the study began and during the study period; they were also asked to abstain from the use of alcohol- and caffeine-containing food and beverages for 24 hours before the first administration until discharge.

### Study Design

This study was a 3-period full cross-over study that had 6 treatment arms given 3 treatments (ABC, ACB, BAC, BCA, CAB, CBA). Each treatment period was separated by a 5-day wash-out interval. As subjects were enrolled in the study, they were assigned unique consecutive numbers and were randomized to treatment group according to a computer-generated allocation schedule. For tamsulosin hydrochloride, although the recommended dose in many Western countries is 0.4 mg, 0.2 mg is the more common dose used in Asian countries and is the clinically approved dose in China. Therefore, the dose selected for this study was 0.2 mg. For finasteride, the dose selected for this study was 5 mg, which is the clinically approved dose in China and also has been shown to be safe. The subjects in the treatment group A received a single dose of 5 mg finasteride on day 1, followed by multiple doses of 5 mg finasteride from days 3 to 9. The subjects in the treatment group B received a single dose of 0.2-mg tamsulosin hydrochloride sustained-release capsule on day 1, followed by multiple doses of a 0.2-mg tamsulosin hydrochloride sustained-release capsule from days 3 to 9. The subjects in the treatment group C received coadministration of a single dose of 5 mg finasteride + a single dose of 0.2-mg tamsulosin hydrochloride sustained-release capsule on day 1, followed by multiple doses of 5 mg finasteride + 0.2-mg tamsulosin hydrochloride sustained-release capsule from days 3 to 9. All doses were given  $\sim 30$  minutes after a standardized breakfast (700 kcal in total). On study day 1 and day 9, subjects fasted for 4 hours with water restricted for 1 hour after dosing. After fasting 4 hours, subjects were given standardized meals (700 kcal in total).

### Blood Sampling and Assay Methods

Blood samples for determination of finasteride and tamsulosin concentrations were collected in vacutainer tubes with K<sub>2</sub> EDTA as an anticoagulant. The sampling time points were at  $\sim 30$  minutes (time 0) before dosing on study days 1, 7, 8, and 9 of each treatment period. In addition, during each treatment period, serial blood samples were collected after dosing on study day 1 at 0.5, 1, 2, 3, 4, 6, 8, 12, 24, 36, and 48 hours, and on study day 9 at 0.5, 1, 2, 3, 4, 6, 8, 12, and 24 hours. The blood samples were immediately centrifuged at 1700g ( $\sim 3000$  rpm) for 10 minutes at 4°C to separate the plasma. The separated plasma samples were transferred to

label (bar-coded) 3.6 mL Nunc CryoTubes (Sigma-Aldrich, St. Louis, Missouri) with internal thread round bottoms and stored at the study center at  $-20^{\circ}\text{C}$  until shipment to the another laboratory (WuXi AppTec Co, Ltd, Shanghai, China) where the analyses of finasteride and tamsulosin concentrations were performed.

Plasma samples were determined at WuXi AppTec Co Ltd and analyzed by LC-MS/MS methods, which were validated in terms of specificity, sensitivity, linearity, within-day and between-day precision, and accuracy tests. The standard curve ranged from 0.5 to 500 ng/mL for finasteride and 0.1 to 100 ng/mL for tamsulosin. The %CV values for within-day and between-day precision were  $<4\%$  for finasteride and tamsulosin. Accuracy expressed as bias ranged from  $-4.0\%$  to  $+1.3\%$  and  $-2.1\%$  to  $+2.7\%$  for finasteride and tamsulosin, respectively. The lower limit of quantification was 0.5 ng/mL for finasteride and 0.1 ng/mL for tamsulosin. The stability of finasteride and tamsulosin in spiked plasma samples were tested under specific test conditions including room temperature (17.5 hours), 5 freeze-thaw cycles, and specific temperature (84 days  $\leq -15^{\circ}\text{C}$ , 74.5 hours in an autosampler at  $8^{\circ}\text{C}$ ). The results showed finasteride and tamsulosin were stable in these test conditions.

### PK Analysis

The PK parameters for finasteride and tamsulosin after oral administration of single and multiple doses were analyzed using noncompartmental methods with Phoenix WinNolin, version 6.2.1 software (Pharsight Corporation, Mountain View, California). The actual blood sampling times were used in the PK analysis.  $C_{\max}$ ,  $T_{\max}$ , and  $C_{\max,ss}$  were obtained directly from the observed values. The  $k_e$  was determined by linear regression of the logarithm of the concentration in plasma with time over the terminal phase.  $t_{1/2}$  was calculated as  $0.693/k_e$ .  $AUC_{0-\infty}$  was determined by summing the areas from time (0) to the time of last quantifiable concentration ( $AUC_{0-t}$ ) and the extrapolated area by linear trapezoidal with linear/log interpolation method. The extrapolated area was determined by dividing the last detectable concentration by the slope of terminal log-linear phase.

### Statistical Analysis

Statistical analysis was performed using SAS version 9.3 (SAS Institute, Cary, North Carolina). Descriptive statistics were provided by treatment. Minimum, median, maximum, arithmetic mean, SD,

geometric mean, and the %CV for the geometric mean were provided and calculated for all PK parameters. The sample size of this study was calculated based on the number estimated to provide  $\geq 80\%$  power and the 90% CIs of geometric mean ratios (GMRs) fall within the prespecified no drug-drug interaction effect boundaries (0.5–2.0) at a significance level of 0.05. All conclusions in this study were made based on applying the predefined boundaries (0.5–2.0). The findings had also been compared with the narrower boundaries (0.8–1.25) for reference.

To compare the PK parameters ( $AUC_{\tau,ss}$  and  $C_{\max,ss}$ ) at steady state of finasteride after multiple doses of coadministration of finasteride and tamsulosin hydrochloride in treatment group C with the corresponding PK parameters at steady state of finasteride after multiple dose of finasteride alone in treatment group A, the log-transformed individual  $AUC_{\tau,ss}$  and  $C_{\max,ss}$  values were compared using linear mixed-effect models with period and treatment as fixed effects, and subjects as the random effect. Treatment effects ( $AUC_{\tau,ss}$  and  $C_{\max,ss}$ ) were presented as ratios and 90% CIs of the GMRs for coadministration of finasteride and tamsulosin hydrochloride to finasteride alone, respectively. A similar method was used to compare the PK parameters ( $AUC_{0-t}$  and  $C_{\max}$ ) of finasteride after a single dose of coadministration of finasteride and tamsulosin hydrochloride in treatment group C with the corresponding PK parameters of finasteride after a single dose of finasteride alone in treatment group A. If the corresponding 90% CIs of GMRs for both  $AUC_{\tau,ss}$  and  $C_{\max,ss}$  values of finasteride at steady state for coadministration of finasteride and tamsulosin hydrochloride and finasteride alone and those for both  $AUC_{0-t}$  and  $C_{\max}$  of finasteride between a single-dose coadministration of finasteride and tamsulosin hydrochloride and a single dose of finasteride alone were completely contained within the no-effect boundaries (0.5–2.0), it could be concluded that coadministration of finasteride and tamsulosin hydrochloride after administration of a single dose and multiple doses did not have a clinically significant effect on the PK profiles of finasteride. The drug-drug interaction conclusion based on comparing the findings with narrower boundaries (0.8–1.25) are discussed in the results as a reference.

To compare the PK parameters ( $AUC_{\tau,ss}$  and  $C_{\max,ss}$ ) at steady state of tamsulosin after multiple doses of coadministration of finasteride and tamsulosin hydrochloride in treatment group C with the corresponding



PK parameters at steady state of tamsulosin after multiple doses of tamsulosin hydrochloride alone in treatment group B, the log-transformed individual  $AUC_{\tau,ss}$  and  $C_{max,ss}$  values were compared using linear mixed-effect models, with period and treatment as fixed effects and subjects as the random effect. Treatment effects ( $AUC_{\tau,ss}$  and  $C_{max,ss}$ ) were presented as ratios and 90% CIs of the GMRs of coadministration of finasteride and tamsulosin hydrochloride to tamsulosin hydrochloride alone. A similar method was used to compare the PK parameters ( $AUC_{0-t}$  and  $C_{max}$ ) of tamsulosin after a single dose of coadministration of finasteride and tamsulosin hydrochloride in treatment group C with the corresponding PK parameters of tamsulosin after a single dose of tamsulosin hydrochloride alone in treatment group B. If the corresponding 90% CIs of GMRs for both  $AUC_{\tau,ss}$  and  $C_{max,ss}$  values of tamsulosin at steady state between coadministration of finasteride and tamsulosin hydrochloride and tamsulosin hydrochloride alone and those for both  $AUC_{0-t}$  and  $C_{max}$  of tamsulosin between a single dose of coadministration of finasteride and tamsulosin hydrochloride and a single dose of tamsulosin hydrochloride alone were completely contained within the no-effect boundaries (0.5–2.0), it could be concluded that coadministration of finasteride and tamsulosin hydrochloride after single-dose and multiple-dose administration did not have a clinically significant effect on the PK profiles of tamsulosin hydrochloride. The drug-drug interaction conclusion based on comparing the findings with narrower boundaries (0.8–1.25) are discussed in the results as a reference.

### Tolerability Assessment

To assess the safety and tolerance of the finasteride and tamsulosin hydrochloride, vital signs, physical examinations, 12-lead ECG, and clinical laboratory tests were examined at predefined regular intervals throughout the study. Adverse events (AEs) were monitored throughout the study. Vital signs (blood pressure, heart rate, and body temperature) were measured at predose (within 1 hour) and 8 hours after the dose daily in each treatment period. ECGs were obtained 8 hours after dosing on day 8 of each treatment period. Clinical laboratory tests and physical examinations were performed ~1 hour before dosing on day 8 of treatment period 3. Clinical laboratory tests included hematology (erythrocytes, hemoglobin, leukocytes, platelets, and other

measures), clinical chemistries (total protein, total bilirubin, albumin, alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, glucose, creatinine, blood urea nitrogen, calcium, chloride, potassium, and sodium), and urinalysis (specific gravity, pH, glucose, blood, protein, and ketones). In addition, ~14 days after the last dose of study drug, subjects received a follow-up phone call to determine whether any AE had occurred since the subjects were discharged from the hospital.

## RESULTS

### Study Population

Fifteen healthy male subjects were enrolled in the study. The demographic details were as follows (mean [SD]: age was 26.2 (3.4) years (range, 20–31 years), weight 63.9 (5.9) kg (range, 54.4–74.5 kg), height 171.4 (6.2) cm (range, 160.9–180.6 cm), and body mass index 21.7 (1.4)  $\text{kg} \cdot \text{m}^{-2}$  (range, 19.5–23.7  $\text{kg} \cdot \text{m}^{-2}$ ). Fourteen subjects completed all 3 treatment periods. One subject dropped out of the study due to an allergic reaction after single-dose administration of 5 mg finasteride in treatment period 1.

### Pharmacokinetic Results

#### Finasteride Pharmacokinetics

After a single dose and multiple doses of 5 mg finasteride (alone or in combination with tamsulosin hydrochloride), the concentration-time profiles of finasteride were similar in the treatment groups A and C (Figure 1). After oral administration of finasteride alone or in combination with tamsulosin hydrochloride, finasteride was readily absorbed with median a  $T_{max}$  of 3 hours. Plasma concentrations of finasteride decreased relatively fast with a mean  $t_{1/2}$  of 4.99 hours for finasteride alone and 4.99 hours for finasteride coadministered with tamsulosin hydrochloride. For treatment group A, after oral administration of a single dose of 5 mg finasteride alone, the geometric mean (GM) of the finasteride  $C_{max}$ ,  $AUC_{0-t}$ , and  $AUC_{0-\infty}$  were 39.82 ng/mL, 307.53  $\text{ng} \cdot \text{h/mL}$ , and 315.81  $\text{ng} \cdot \text{h/mL}$ , respectively; after oral administration of multiple doses of 5 mg finasteride alone, the GM of the finasteride  $C_{max,ss}$  and  $AUC_{\tau,ss}$  were 43.35 ng/mL and 343.85  $\text{ng} \cdot \text{h/mL}$ , respectively. For treatment group C, after oral administration of a single dose of 5 mg finasteride in combination with 0.2 mg tamsulosin hydrochloride, the GM of the finasteride  $C_{max}$ ,  $AUC_{0-t}$ , and  $AUC_{0-\infty}$

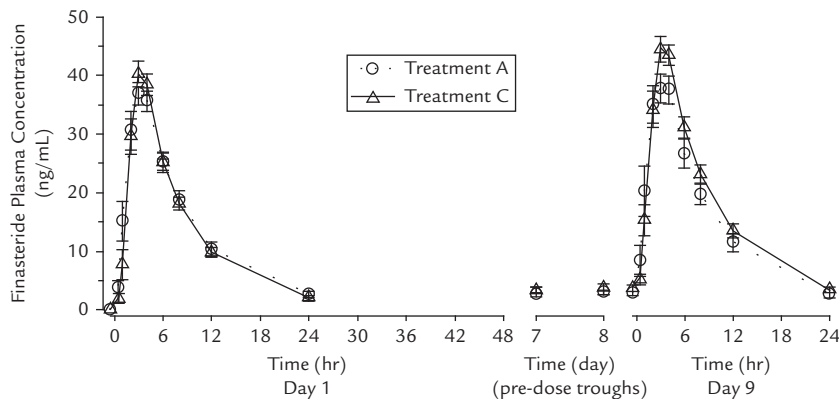


Figure 1. Arithmetic mean (SE) plasma concentration-time profiles for finasteride after administration of single (day 1) and multiple (days 3–9) oral doses of 5 mg finasteride (Proscar<sup>®</sup> [Hangzhou MSD Pharmaceutical CO., LTD]) and coadministration of 5 mg finasteride and 0.2 mg tamsulosin hydrochloride in healthy Chinese male subjects ( $n = 14$ ). Treatment group A = 5 mg finasteride; treatment group C = 5 mg finasteride + 0.2-mg tamsulosin hydrochloride.

were 42.21 ng/mL, 313.99 ng·h/mL, and 323.94 ng·h/mL, respectively; after oral administration of multiple doses of 5 mg finasteride in combination with 0.2 mg tamsulosin hydrochloride, the GM of the finasteride  $C_{max,ss}$  and  $AUC_{\tau,ss}$  were 45.98 ng/mL and 391.33 ng·h/mL, respectively. **Table I** summarizes the PK parameters for finasteride after administration of single dose and multiple doses of 5 mg finasteride alone and coadministration of 5 mg finasteride with 0.2 mg tamsulosin hydrochloride.

### Tamsulosin Pharmacokinetics

After single dose and multiple doses of 0.2 mg tamsulosin hydrochloride alone or in combination with finasteride, the concentration-time profiles of tamsulosin were similar in treatment groups B and C (**Figure 2**). After oral administration of tamsulosin hydrochloride alone or in combination with finasteride, tamsulosin was readily absorbed with a median  $T_{max}$  of 6 hours. Plasma concentrations of tamsulosin decreased relatively slowly with a mean  $t_{1/2}$  of 12.73 hours for tamsulosin hydrochloride alone and 12.94 hours for tamsulosin hydrochloride coadministered with finasteride. For treatment group B, after oral administration of a single dose of 0.2 mg tamsulosin hydrochloride alone, the GM of the tamsulosin  $C_{max}$ ,  $AUC_{0-t}$ , and  $AUC_{0-\infty}$  were 4.39 ng/mL, 62.92 ng·h/mL, and 68.90 ng·h/mL, respectively; after oral

administration of multiple doses of 0.2 mg tamsulosin hydrochloride alone, the GM of the tamsulosin  $C_{max,ss}$  and  $AUC_{\tau,ss}$  were 5.18 ng/mL and 71.90 ng·h/mL, respectively. For treatment group C, after oral administration of a single dose of 0.2 mg tamsulosin hydrochloride in combination with 5 mg finasteride, the GM of the tamsulosin  $C_{max}$ ,  $AUC_{0-t}$ , and  $AUC_{0-\infty}$  were 4.58 ng/mL, 65.23 ng·h/mL, and 70.99 ng·h/mL, respectively; after oral administration of multiple doses of 0.2 mg tamsulosin hydrochloride in combination with 5 mg finasteride, the GM of the finasteride  $C_{max,ss}$  and  $AUC_{\tau,ss}$  were 6.38 ng/mL and 84.74 ng·h/mL, respectively. **Table II** summarizes the PK parameters for tamsulosin after administration of single and multiple doses of 0.2 mg finasteride alone and coadministration of 0.2 mg tamsulosin hydrochloride with 5 mg finasteride.

### Drug-Drug Interaction Assessment

**Table III** summarizes the results of the clinically significant drug-drug interaction potential of finasteride and tamsulosin hydrochloride based on the assessment of 90% CIs of the GMRs for both  $AUC_{0-t}$  and  $C_{max}$  values after administration of a single dose as well as the 90% CIs of the GMRs for both  $AUC_{\tau,ss}$  and  $C_{max,ss}$  values after administration of multiple doses.

The GMRs (90% CIs) for both  $AUC_{\tau,ss}$  and  $C_{max,ss}$  values of finasteride at steady state for multiple doses

Table 1. Pharmacokinetic parameters of finasteride after oral coadministration of single and multiple doses of 5 mg finasteride (Proscar®)\* with 0.2 mg tamsulosin hydrochloride and administration of single and multiple doses of 5 mg finasteride (Proscar®) alone in healthy Chinese subjects (N = 14).

| Pharmacokinetic Parameters        | Finasteride With Tamsulosin Hydrochloride |                            | Finasteride Alone      |                            |
|-----------------------------------|---|----------------------------|------------------------|----------------------------|
|                                   | Study Day 1                               | Study Day 9 (Steady State) | Study Day 1            | Study Day 9 (Steady State) |
| AUC <sub>0-t</sub> , ng·h/mL      | 313.99 (280.04–352.05)                    | NA                         | 307.53 (274.20–344.91) | NA                         |
| AUC <sub>0-∞</sub> , ng·h/mL      | 323.94 (289.88–362.00)                    | NA                         | 315.81 (282.53–353.01) | NA                         |
| C <sub>max</sub> , ng/mL          | 42.21 (38.96–45.73)                       | NA                         | 39.82 (36.75–43.15)    | NA                         |
| T <sub>max</sub> , h <sup>†</sup> | 3.00 [2.00, 4.00]                         | NA                         | 3.00 [2.00, 6.00]      | NA                         |
| t <sub>1/2</sub> , h <sup>‡</sup> | 4.99                                      | NA                         | 4.99                   | NA                         |
| AUC <sub>τ,ss</sub> , ng·h/mL     | NA  | 391.33 (343.29–446.09)     | NA                     | 343.85 (301.57–392.05)     |
| C <sub>max,ss</sub> , ng/mL       | NA  | 45.98 (41.97– 50.37)       | NA                     | 43.35 (39.56– 47.51)       |

Values are geometric mean (95% CI).

NA = not applicable.

\*Trademark: Proscar® (Hangzhou MSD Pharmaceutical CO., LTD).

<sup>†</sup>Median [min, max] reported for T<sub>max</sub>.

<sup>‡</sup>Arithmetic mean.

of coadministration of finasteride and tamsulosin hydrochloride and multiple doses of finasteride alone were 1.14 (1.05–1.23) and 1.06 (0.99–1.14), respectively. The GMRs (90% CIs) for both AUC<sub>0-t</sub> and C<sub>max</sub> values of finasteride for a single dose of

coadministration of finasteride and tamsulosin hydrochloride and a single dose of finasteride alone were 1.02 (0.94–1.11) and 1.06 (1.01–1.11), respectively. The 90% CIs for both AUC<sub>τ,ss</sub> and C<sub>max,ss</sub> at steady state and the 90% CIs for both AUC<sub>0-t</sub> and C<sub>max</sub> after

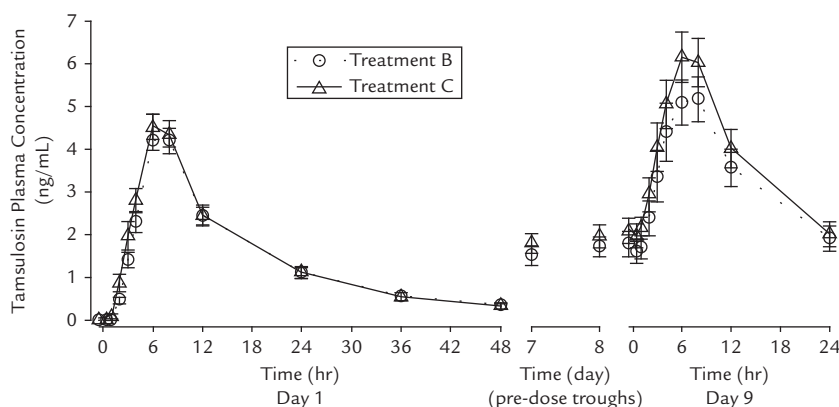


Figure 2. Arithmetic mean (SE) plasma concentration-time profiles for tamsulosin following administration of single (day 1) and multiple (day 3–9) oral doses of 0.2 mg tamsulosin hydrochloride and coadministration of 5 mg finasteride (Proscar® [Hangzhou MSD Pharmaceutical CO., LTD]) and 0.2 mg tamsulosin hydrochloride in healthy Chinese male subjects (n = 14). Treatment group B = 0.2 mg tamsulosin hydrochloride; Treatment group C = 5 mg finasteride + 0.2 mg tamsulosin hydrochloride.

Table II. Pharmacokinetic parameters of tamsulosin after oral coadministration of single and multiple doses of 5 mg finasteride (Proscar<sup>®</sup>\*) with 0.2 mg tamsulosin hydrochloride and administration of single and multiple doses of 0.2 mg tamsulosin hydrochloride alone in healthy Chinese subjects (N = 14).

| Pharmacokinetic Parameters        | Tamsulosin Hydrochloride With Finasteride |                            | Tamsulosin Hydrochloride Alone |                            |
|-----------------------------------|---|----------------------------|--------------------------------|----------------------------|
|                                   | Study Day 1                               | Study Day 9 (Steady State) | Study Day 1                    | Study Day 9 (Steady State) |
| AUC <sub>0-t</sub> , ng·h/mL      | 65.23 (54.07–78.70)                       | NA                         | 62.92 (52.15–75.91)            | NA                         |
| AUC <sub>0-∞</sub> , ng·h/mL      | 70.99 (57.58–87.51)                       | NA                         | 68.90 (55.89–84.94)            | NA                         |
| C <sub>max</sub> , ng/mL          | 4.58 (3.94–5.32)                          | NA                         | 4.39 (3.78–5.10)               | NA                         |
| T <sub>max</sub> , h <sup>†</sup> | 6.00 [3.00, 8.00]                         | NA                         | 7.00 [6.00, 8.00]              | NA                         |
| t <sub>1/2</sub> , h <sup>‡</sup> | 12.94                                     | NA                         | 12.73                          | NA                         |
| AUC <sub>τ,ss</sub> , ng·h/mL     | NA  | 84.74 (66.84–107.43)       | NA                             | 71.90 (56.71–91.15)        |
| C <sub>max,ss</sub> , ng/mL       | NA  | 6.38 (5.21–7.81)           | NA                             | 5.18 (4.23–6.35)           |

NA = not applicable.

Values are geometric mean (95% CI).

\*Trademark: Proscar<sup>®</sup> (Hangzhou MSD Pharmaceutical CO., LTD).

<sup>†</sup>Median [min, max] reported for T<sub>max</sub>.

<sup>‡</sup>Arithmetic mean.

single-dose administration were completely contained within the no-effect boundaries (0.5–2.0), suggesting that coadministration of finasteride and tamsulosin hydrochloride has no clinically significant effect on the PK profiles of finasteride, both after a single dose and at steady state. The conclusion was consistent when comparing the findings with narrower boundaries (0.8–1.25) for finasteride.

The GMRs (90% CIs) for both AUC<sub>τ,ss</sub> and C<sub>max,ss</sub> values of tamsulosin at steady state between multiple doses of coadministration of finasteride and tamsulosin hydrochloride and multiple doses of tamsulosin hydrochloride alone were 1.18 (1.05–1.33) and 1.23 (1.06–1.43), respectively. The GMRs (90% CIs) for both AUC<sub>0-t</sub> and C<sub>max</sub> values of tamsulosin for a single dose of coadministration of finasteride and tamsulosin hydrochloride and a single dose of tamsulosin hydrochloride alone were 1.04 (0.97–1.10) and 1.04 (0.98–1.11), respectively. The 90% CIs for both AUC<sub>τ,ss</sub> and C<sub>max,ss</sub> at steady state and the 90% CIs for both AUC<sub>0-t</sub> and C<sub>max</sub> after single-dose administration were completely contained within the no-effect boundaries (0.5–2.0), suggesting that coadministration of finasteride and tamsulosin hydrochloride has no clinically significant effect on the PK profiles of tamsulosin, both after a single dose and at steady

state. When comparing the findings with narrower boundaries (0.8–1.25), the findings based on the current sample size may not be supportive for tamsulosin hydrochloride at steady state.

### Tolerability

All 15 subjects enrolled in the study were included in the assessment of safety and tolerability. For single dose and multiple doses in this study, coadministration of finasteride and tamsulosin hydrochloride as individual tablets or administration of corresponding doses of finasteride or tamsulosin hydrochloride alone was safe and generally well tolerated.

Four AEs were reported during this study. These AEs occurred in 3 subjects including 1 volunteer with allergic reaction that resulted in his withdrawing from the study and abnormal findings on an ECG after oral administration of a single dose of finasteride, 1 subject with a slight increase in alanine aminotransferase after oral administration of multiple doses of finasteride, and 1 subject with positive glucose urine test result after oral administration of multiple doses of tamsulosin hydrochloride. The previous 3 AEs were assessed as related to the drug by the study physician, but the fourth AE was not considered drug-related by the study physician. All AEs were rated as mild in



Table III. The Geometric mean ratios (90 % CI<sup>\*</sup>) for pharmacokinetic parameters of both finasteride and tamsulosin after oral co-administration of single and multiple doses of 5-mg finasteride with 0.2-mg tamsulosin hydrochloride and administration of single and multiple doses of 5-mg finasteride alone, or administration of single and multiple doses of 0.2-mg tamsulosin hydrochloride alone in Chinese healthy subjects (n = 14).

| Pharmacokinetic Parameters | Finasteride + Tamsulosin Hydrochloride/<br>Finasteride Alone |                               | Finasteride + Tamsulosin Hydrochloride/<br>Tamsulosin Hydrochloride Alone |                               |
|----------------------------|--|-------------------------------|---|-------------------------------|
|                            | Study Day 1  | Study Day 9<br>(Steady State) | Study Day 1   | Study Day 9<br>(Steady State) |
| AUC <sub>0-t</sub>         | 1.02 (0.94-1.11)   | NA                            | 1.04 (0.97-1.10)  | NA                            |
| AUC <sub>0-∞</sub>         | 1.03 (0.95-1.11)   | NA                            | 1.03 (0.96-1.10)  | NA                            |
| C <sub>max</sub>           | 1.06 (1.01-1.11)   | NA                            | 1.04 (0.98-1.11)  | NA                            |
| AUC <sub>τ,ss</sub>        | NA   | 1.14 (1.05-1.23)              | NA  | 1.18 (1.05-1.33)              |
| C <sub>max,ss</sub>        | NA   | 1.06 (0.99-1.14)              | NA  | 1.23 (1.06-1.43)              |

NA = not applicable.

<sup>\*</sup>CI from mixed-effects model performed on natural log-transformed values.

intensity, and all volunteers recovered spontaneously without treatment. No clinically significant changes in clinical laboratory test results, vital signs, physical examinations, and ECGs were found in other subjects.

## DISCUSSION

Compared with the known PK data on finasteride and tamsulosin, the PK profiles of finasteride and tamsulosin when given alone in healthy Chinese subjects were mainly consistent with those in non-Chinese subjects.<sup>3-5</sup> Finasteride was rapidly absorbed and eliminated quickly after oral administration. Tamsulosin was absorbed and eliminated relatively slowly after oral administration.

Comparing the estimated CIs of the study results with the prespecified boundaries (0.5-2.0), no drug-drug interaction between finasteride and tamsulosin can be concluded. If compared with the boundaries (0.8-1.25), the conclusion of no drug-drug interaction may not be supported based on sample size in the current study.

According to the US Food and Drug Administration guidelines (drug interaction studies: study design, data analysis, implications for dosing, and labeling and recommendations), if a statement is included that no known drug-drug interaction of clinical significance exists, no effect boundaries should be

recommended that represent the interval within which a change in a systemic exposure measure is considered not clinically meaningful. There are 2 approaches to defining no effect boundaries. In approach 1: no-effect boundaries can be based on the population (group) average dose-related and/or individual concentration-response relationships derived from PK/pharmacodynamic models, and other available information for the substrate drug to define a degree of difference caused by the interaction that is of no clinical consequence. In approach 2, in the absence of no-effect boundaries defined in approach 1, the default no-effect boundaries of 0.8-1.25 can be used.

In this study, approach 1 was used to define no-effect boundaries. Tamsulosin is extensively metabolized by cytochrome P-450 enzymes including CYP3A4 and CYP2D6 in the liver, and finasteride is extensively metabolized in the liver primarily via the CYP3A4 subfamily, which indicates a potential drug-drug interaction between these 2 drugs. However, finasteride and tamsulosin have been available in China for more than a decade with satisfactory safety and efficacy profiles, and combining them confirms wide therapeutic windows for both drugs. In Asian countries, 0.2 mg tamsulosin hydrochloride is recommended as the standard regimen for the treatment of BPH patients. Many studies have shown that 0.4 mg is also safe in Asian

patients who had no response to 0.2-mg treatment,<sup>8</sup> especially those heavier patients. Long-term therapy with tamsulosin 0.4 mg once daily is also reported to be safe and well tolerated, even therapy for 3 years.<sup>9</sup> There were no apparent dose-dependent changes in drug safety from 0.2 mg to 0.4 mg.<sup>10</sup> Therefore, in our study, if there were no safety concern, it would be considered clinically acceptable even if the AUC and  $C_{\max}$  of tamsulosin after coadministration of tamsulosin hydrochloride 0.2 mg and finasteride 5 mg were slightly increased compared with those after tamsulosin hydrochloride administration alone. This was the basis for the selection of 0.5 to 2.0 as the no drug-drug interaction boundary in this study.

Because tamsulosin hydrochloride exhibits linear pharmacokinetics in adult healthy subjects and patients with BPH after single and multiple dosing with doses ranging from 0.1 to 1.0 mg, PK/pharmacodynamic evidence can be replaced with dose-response evidence to help define no-effect boundaries. Some clinical studies in the United States and Europe have shown that the 0.4- and 0.8-mg doses were similarly effective in improving symptoms or urinary flow rate.<sup>11,12</sup> Some clinical studies in Asian countries have demonstrated that there was no significant difference in improvement in urinary symptoms or urinary flow rate between the 0.2- and the 0.4-mg doses.<sup>13</sup> Although Lepor<sup>14</sup> reported that AEs were comparable in the 0.4-mg/day tamsulosin and placebo groups and were somewhat higher in the 0.8-mg/day tamsulosin group, in our study, the dose of tamsulosin was 0.2 mg, which was far less than 0.8 mg; thus, safety would not be a concern even if there were a slightly increased exposure to tamsulosin after coadministration. These results adequately proved that change in systemic exposure (AUC,  $C_{\max}$ ) within the boundaries (0.5–2.0) is not clinically different. For finasteride, the dose of 5 mg has been shown to be effective and safe. There was efficacy associated with a 1-mg dose of finasteride in the Phase III study of finasteride, strongly suggesting that even a 50% reduction in exposure from the 5-mg dose would not have a clinically meaningful change in its effect. According to the FDA guidelines (drug interaction studies: study design, data analysis, implications for dosing, and labeling and recommendations), when comparisons indicate twofold or greater increments in systemic exposure measures for substrate + interacting drug (ie, GMRs for AUC and  $C_{\max}$  are  $\geq 2.0$ ), a

clinical significance of drug-drug interaction should be presented clearly. In summary, the above rationales support why a broader boundary of 0.5–2.0 is selected in this study to address clinically significant drug-drug interaction potential.

In our study, the  $AUC_{\tau,ss}$  and  $C_{\max,ss}$  values of tamsulosin hydrochloride at steady state after multiple-dose administration were increased by 18% and 23%, respectively, when coadministered with finasteride compared with alone. These differences may be attributed to the inhibitory potential of finasteride on CYP2D6 and/or CYP3A4, resulting in the increased systemic exposure of tamsulosin. Sample size calculation and findings of this study are based on using the predefined no-effect boundaries of 0.5–2.0. If comparing the finding with the boundary 0.8–1.25, no drug-drug interaction between finasteride and tamsulosin hydrochloride is inconclusive. However, if a narrower boundary such as 0.8–1.25 were used in this study design, we would have used a larger sample size, and thus narrower CIs would have been estimated. Therefore, we could not exclude the possibility that with an increased sample size, no drug-drug interaction could be concluded. In addition, in the present study, coadministration of finasteride and tamsulosin hydrochloride was safe and well tolerated, which supports our finding that the slight increase in tamsulosin exposure has no clinical significance.

The AEs that occurred in the study were predominantly mild in intensity, and no serious AEs were reported. During the whole study, no subjects reported gastrointestinal issues, headaches, and so on, which are common in any healthy subject study, even in subjects administered placebo. The possible reason is that all doses were given ~30 minutes after a standardized breakfast (750 kcal in total), which decreased the AE rate to some extent.

Therefore, the study findings provide important information for clinical combination therapy with finasteride and tamsulosin hydrochloride and for further drug development of a fixed-dose combination formulation of finasteride and tamsulosin hydrochloride.

## CONCLUSIONS

Both finasteride and tamsulosin hydrochloride were safe and well tolerated in healthy Chinese subjects after oral coadministration of single and multiple doses of 5 mg finasteride and 0.2 mg tamsulosin hydrochloride or administration alone. Coadministration of

finasteride and tamsulosin hydrochloride did not lead to clinically significant PK drug-drug interaction between the 2 agents, both after a single dose and at steady state when comparing with the predefined no drug-drug interaction effect boundaries of 0.5–2.0. Therefore, coadministration of 5 mg finasteride and 0.2 mg tamsulosin hydrochloride can be used to assess the efficacy and safety of the 2 agents in patients with BPH. A fixed-dose combination formulation of finasteride and tamsulosin hydrochloride may be further developed as an agent for the treatment of BPH without the need to adjust the dose of either drug.

### ACKNOWLEDGMENTS

The authors thank the sponsor (Merck Sharp & Dohme Corp) for designing the study and reviewing the manuscript. The authors also thank all the study subjects and medical staff for their contribution and efforts.

Nannan Chu wrote the manuscript and ran the study with Hongrong Xu, Weili Chen, Fei Yuan, Mengjie Yang and Xuening Li. Xuening Li also reviewed and gave valuable comments on the manuscript. Guoqin Wang helped revise the manuscript. Jiangdian Wang performed data statistical analysis. The authors thank WuXi AppTec Co., Ltd. for assistance with the blood samples analysis. The authors have indicated that they have no conflicts of interest with the sponsor.

### CONFLICTS OF INTEREST

The authors have indicated that they have no other conflicts of interest regarding the content of this article.

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