

<b>Study No:</b> ARI111402									
<b>Title :</b> An open-label, randomized, repeat dose, 3 period crossover study to determine the bioequivalence of 3 different formulations of tamsulosin at steady state in healthy male volunteers.									
<b>Rationale:</b> Depending on the results this study and completed studies as well as the results of ongoing formulation development work, the decision will be made to move forward with either the 10% or the 15% enteric coated formulation of tamsulosin in the combination capsule. This current study will establish bioequivalence of the 10% enteric coated tamsulosin in the combination product and the 15% enteric coated tamsulosin in the modified combination product relative to concomitant dosing with separate capsules of dutasteride and tamsulosin commercial formulations at steady state, with respect to tamsulosin.									
<b>Phase:</b> I									
<b>Study Period:</b> 26 February 2008 – 23 April 2008									
<b>Study Design:</b> This was an open-label, randomized, repeat dose, 3 period crossover study healthy adult males.									
<b>Centres:</b> One site in the U.S.									
<b>Indication:</b> Benign prostatic hyperplasia									
<b>Treatment:</b> In each of the 3 sessions, subjects received Regimen A, B, or C as per the randomization schedule. Subjects were randomized to one of 6 treatment sequences ABC, ACB, BAC, BCA, CAB, or CBA. Subjects were fasted for 10 hours prior to dosing on Days 1 and 7, with the exception of water, which will be allowed freely except for 1 hour before and 1 hour after dosing. On other study days, subjects were dosed approximately 30 minutes after the start of breakfast. Following dosing, subjects were not allowed food for 4 hours. Study medication was swallowed, without chewing, with 240 mL of water at room temperature.									
<table border="1"> <thead> <tr> <th>Regimen</th> <th>Description</th> </tr> </thead> <tbody> <tr> <td>A</td> <td>Dutasteride and Tamsulosin Hydrochloride Combination Capsule, 0.5 mg dutasteride, 10% enteric coated 0.4 mg tamsulosin hydrochloride (test)</td> </tr> <tr> <td>B</td> <td>Dutasteride and Tamsulosin Hydrochloride Combination Capsule, 0.5 mg dutasteride, 15% enteric coated 0.4 mg tamsulosin hydrochloride (test)</td> </tr> <tr> <td>C</td> <td>Flomax® 0.4 mg (sustained release capsule commercially available in United States) and AVODART® 0.5 mg (reference)</td> </tr> </tbody> </table>		Regimen	Description	A	Dutasteride and Tamsulosin Hydrochloride Combination Capsule, 0.5 mg dutasteride, 10% enteric coated 0.4 mg tamsulosin hydrochloride (test)	B	Dutasteride and Tamsulosin Hydrochloride Combination Capsule, 0.5 mg dutasteride, 15% enteric coated 0.4 mg tamsulosin hydrochloride (test)	C	Flomax® 0.4 mg (sustained release capsule commercially available in United States) and AVODART® 0.5 mg (reference)
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<b>Objectives:</b>									
<ol style="list-style-type: none"> <li>To investigate the bioequivalence of tamsulosin at steady state of a Combination Capsule formulation of dutasteride 0.5 mg/ 10% enteric coated tamsulosin HCl 0.4 mg relative to concomitant dosing of AVODART® 0.5 mg and the U.S.-sourced Flomax® 0.4 mg under fasting conditions.</li> <li>To investigate the bioequivalence of tamsulosin at steady state of a Combination Capsule formulation of dutasteride 0.5 mg/ 15% enteric coated tamsulosin HCl 0.4 mg relative to concomitant dosing of AVODART® 0.5 mg and the U.S.-sourced Flomax® 0.4 mg under fasting conditions.</li> </ol>									
<b>Statistical Methods:</b> There were no interim analyses planned or conducted in this study. The final PK analyses were performed as follows:									
<ol style="list-style-type: none"> <li>A linear regression analysis was performed for the loge-transformed C<sub>s</sub> in Days 4, 5 and 6 (i.e. pre-dose concentration data in Days 5, 6 and 7) versus day, to check the achievement of the steady state for each regimen.</li> <li>To assess the bioequivalence of the test and reference treatments of tamsulosin, loge-transformed values of PK parameter AUC(0-24)-ss, C<sub>max</sub>-ss, C<sub>min</sub>-ss, C<sub>s</sub>, t<sub>1/2</sub> and fluctuation were analyzed by analysis of variance (ANOVA) using mixed effects model, fitting the fixed effects for treatment sequence, period and regimen, and fitting subject within sequence as a random effect. Point estimates and 90% confidence intervals for the test-to-reference ratios A:C and B:C were constructed.</li> </ol>									

3. Tmax-ss was analyzed nonparametrically using the Wilcoxon Matched Pairs Method to compute the point estimate and 90% confidence interval for the median difference for each comparison of interest.

**Study Population:** Healthy male subjects aged 18 - 45 years (inclusive), with a body weight between 55 – 95 kg (inclusive) and body mass index between 19 – 30 kg/m<sup>2</sup> (inclusive) were eligible for the study

<b>Number of Subjects:</b>	<b>N (%)</b>
Planned	24
Dosed	24
Completed	23 (96)
Total Number Subjects Withdrawn for Any Reason	1 (4)
Withdrawn due to Serious Adverse Events	1 (4)
<b>Demographics</b>	
N	24
Females: Males	0:24
Mean Age in Years (range)	24 (19-45)
Mean Weight in Kg (range)	81.4 (65.3-95)
White n (%)	10 (42)
African American/African Heritage n (%)	11 (46)
Asian – South East Asian Heritage n (%)	2 (8)
Mixed - Other n (%)	1 (4)

**Pharmacokinetics (PK) Results:**

Statistical assessment of tamsulosin serum PK parameters showed that at the steady state tamsulosin C<sub>max</sub> and AUC(0-24), point estimates were within 9% of unity, and the 90% CIs for each regimen comparison were entirely contained within the equivalence interval of 0.80-1.25. Similarly, 90% CIs for C<sub>min</sub>, C<sub>T</sub>, t<sub>1/2</sub> and Fluctuation at steady state were entirely contained within the equivalence interval of 0.80-1.23. Tamsulosin t<sub>max</sub> values were found to be no difference between regimens.

Parameter	Comparison	Least Square Geometric Mean		Point Estimate of Ratio	90% CI	CVw <sup>3</sup> (%)	CVb <sup>4</sup> (%)
		Test	Reference				
AUC(0-24)-ss <sup>1</sup> (ng*hr/ML)	A : C	182.52	179.89	1.01	(0.93,1.11)	17.8	33.0
	B : C	167.60	179.89	0.93	(0.85,1.02)		
C <sub>max</sub> -ss <sup>1</sup> (ng/ML)	A : C	16.74	17.01	0.98	(0.91,1.06)	14.8	27.0
	B : C	15.55	17.01	0.91	(0.85,0.98)		
C <sub>min</sub> -ss <sup>1</sup> (ng/ML)	A : C	2.83	2.74	1.03	(0.90,1.19)	27.7	55.5
	B : C	2.86	2.74	1.04	(0.91,1.20)		
C <sup>1</sup> (ng/ML)	A : C	3.16	2.93	1.08	(0.95,1.23)	26.8	56.2
	B : C	3.05	2.93	1.04	(0.91,1.18)		
t <sub>1/2</sub> <sup>1</sup> (hr)	A : C	13.69	13.85	0.99	(0.94,1.04)	11.2	20.7
	B : C	14.13	13.85	1.02	(0.97,1.08)		
Fluctuation <sup>1</sup> (%)	A : C	179.11	188.32	0.95	(0.90,1.01)	12.3	26.4
	B : C	177.96	188.32	0.94	(0.89,1.00)		
t <sub>max</sub> <sup>2</sup> (hr)	A - C	5.00	5.00	0.00	(-0.50,0.50)		
	B - C	5.00	5.00	0.01	(0.00,0.50)		

Source data: Pharmacokinetic Tables 10.7 and 10.9

1. Point estimate is the ratio of adjusted geometric means between regimens
2. Point estimate represents the estimated median difference between regimens
3. CVw% represents a pooled estimate of within-subject variability across regimens
4. CVb% represents a pooled estimate of between-subject variability across regimens

Regimens:

A 0.5 mg dutasteride, 10% enteric coated 0.4 mg tamsulosin hydrochloride

B 0.5 mg dutasteride, 15% enteric coated 0.4 mg tamsulosin hydrochloride

C Flomax® 0.4 mg and AVODART® 0.5 mg

**Safety results:**

There were no deaths or partner pregnancies reported during this study.

There was one SAE which lead to withdrawal from the study. Subject 122 (randomized to treatment sequence BAC) was withdrawn from the study after dosing in Session 1 due to an SAE of hospitalization for epididymitis which was not considered to be related to study drug.

The most commonly reported AEs in any regimen (>10%) were headache, dizziness and nasal congestion. A slightly higher proportion of AEs were seen with Regimen A (Dutasteride and Tamsulosin Hydrochloride (10%) Combination Capsule) than with either Regimens B or C. All adverse events were considered by the investigator to be mild or moderate in intensity. All adverse events were considered to be resolved at the end of the study, except for Subject 120 who experienced mild right thigh pain, considered unrelated to study medication. The investigator was unable to reach the subject after the end of the study for follow-up.

	Number of Subjects with AE (%)			
	Regimen A (n=23)	Regimen B (n=24)	Regimen C (n=23)	Total (n=24)
<b>Subjects with any AE</b>	15 (65)	10 (42)	9 (39)	20 (83)
<b>System Organ Class Preferred Term</b>				
Headache	4 (17)	5 (21)	4 (17)	8 (33)
Dizziness	1 (4)	2 (8)	3 (13)	5 (21)
Dizziness postural	2 (9)	1 (4)	0	3 (13)
Nasal congestion	1 (4)	3 (13)	0	4 (17)
Cough	0	2 (8)	1 (4)	3 (13)
Pharyngolaryngeal Pain	0	0	1 (4)	1 (4)
Respiratory Tract Congestion	1 (4)	0	0	1 (4)
Pain in extremity	2 (9)	0	0	2 (8)
Musculoskeletal Pain	1 (4)	1 (4)	0	1 (4)
Back Pain	0	0	1 (4)	1 (4)
Musculoskeletal Discomfort	0	1 (4)	0	1 (4)
Myalgia	0	0	1 (4)	1 (4)
Abnormal dreams	0	1 (4)	2 (9)	3 (13)
Abdominal Pain Upper	1 (4)	0	0	1 (4)
Diarrhoea	1 (4)	0	0	1 (4)
Flatulence	0	1 (4)	0	1 (4)
Toothache	0	0	1 (4)	1 (4)
Hyperthermia	1 (4)	0	0	1 (4)
Pyrexia	0	1 (4)	0	1 (4)
Ocular Hyperaemia	1 (4)	0	0	1 (4)
Post Procedural Complication	1 (4)	0	0	1 (4)
Anorexia	0	1 (4)	0	1 (4)
Epididymitis	0	1 (4)	0	1 (4)

Source Data: Safety Table 11.02

Regimen A: 0.5 mg dutasteride, 10% enteric coated 0.4 mg tamsulosin hydrochloride

Regimen B: 0.5 mg dutasteride, 15% enteric coated 0.4 mg tamsulosin hydrochloride

Regimen C: Flomax® 0.4 mg and AVODART® 0.5 mg

**Serious Adverse Events, 1 (4%) [not considered to be related to study medication]:** There was one SAE which lead to withdrawal from the study. Subject 122 (randomized to treatment sequence BAC) was withdrawn from the study after dosing in Session 1 due to an SAE of hospitalization for epididymitis which was not considered to be related to study drug.

**Publications:** None at the time of this report.