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<b>Study No:</b> ARI109882			
<b>Title :</b> An Open-Label, Randomized, Single Dose Three-Period Partial Crossover Study to Determine the Bioequivalence and Food Effect of a Combination Capsule Formulation of Dutasteride and Tamsulosin Hydrochloride (0.5mg/0.4mg) Compared to Concomitant Dosing of ADOVART 0.5mg and Flomax 0.4mg Commercial Capsules in Healthy Male Subjects			
<b>Rationale:</b> A combination formulation of dutasteride 0.5 mg and tamsulosin hydrochloride (HCl) 0.4 mg is being developed for the treatment of males with symptomatic benign prostatic hyperplasia (BPH). This study established bioequivalence of the Dutasteride and Tamsulosin HCl Combination Capsule in a fed state to concomitant dosing with separate capsules of dutasteride and tamsulosin HCl commercial formulations (AVODART and Flomax, respectively). This study also evaluated the effect of food on the absorption of dutasteride and tamsulosin HCl when given as the Dutasteride and Tamsulosin HCl Combination Capsule.			
<b>Phase:</b> I			
<b>Study Period:</b> 18 October 2007 – 22 February 2008			
<b>Study Design:</b> This was a multi-center, open-label, single dose, randomized, 3-way partial crossover study in healthy adult males. Subjects were randomized to one of the following treatment sequences: ABC, ACB, BAC, BCA, CAB, CBA, ABD, ADB, BAD, BDA, DAB or DBA. Each subject participated in 3 sessions and received 3 of the 4 treatment regimens. Dosing in each session was separated by an approximate 28-day washout period.			
<b>Centres:</b> Conducted at 2 sites in the US.			
<b>Indication:</b> Benign prostatic hyperplasia			
<b>Treatment:</b> In each of the 3 sessions, subjects received Regimen A, B, C or D as per the randomization schedule. Subjects in the fed groups (Regimen A and Regimen B) were dosed approximately 30 minutes after the start of the meal. Each subject received the dose at approximately the same time in each session. Study medication was swallowed, without chewing, with 240 mL of water at room temperature.			
<b>Drug</b>	<b>Dose/Form/Route</b>	<b>Frequency /Duration</b>	<b>Lot or Batch Number</b>
Flomax	0.4 mg tamsulosin/ sustained release capsule / oral	Single dose	Lot # G0700308
AVODART (G1198745)	0.5 mg dutasteride/ capsule / oral	Single dose	Batch # E09094
Dutasteride and Tamsulosin Hydrochloride Combination Capsule	0.5 mg dutasteride, 0.4 mg tamsulosin HCl / capsules / oral	Single dose	Batch # 705002-91294
Dutasteride and Tamsulosin HCl Combination Capsules were supplied by GlaxoSmithKline. AVODART was supplied by GlaxoSmithKline as oblong, dull yellow, soft gelatin capsules containing 0.5 mg dutasteride (G1198745). These capsules were identical in formulation to the commercially available AVODART except they were plain. They were not branded with the red ink commercial print. Flomax was supplied by GlaxoSmithKline as the commercially available product.			
<b>Objectives:</b>			
<ul style="list-style-type: none"> <li>• To investigate the bioequivalence of a Combination Capsule formulation of dutasteride 0.5 mg/ tamsulosin hydrochloride 0.4 mg relative to concomitant dosing of AVODART® 0.5 mg and the US-sourced Flomax 0.4 mg in the fed state.</li> <li>• To investigate the bioequivalence of a Combination Capsule formulation of dutasteride 0.5 mg/ tamsulosin hydrochloride 0.4 mg relative to concomitant dosing of AVODART 0.5 mg and the US-sourced Flomax 0.4 mg in the fasted state.</li> <li>• To assess the effect of a high fat meal on the pharmacokinetics of a Combination Capsule formulation of dutasteride 0.5 mg / tamsulosin hydrochloride 0.4 mg.</li> </ul>			
<b>Statistical Methods:</b> Based on PK data from previous studies, it was determined that 78			

evaluable subjects were needed to have 90% power to conclude bioequivalence (with both C<sub>max</sub> and AUC for dutasteride and tamsulosin) under fed state per FDA guidance and had at least 90% power to conclude bioequivalence (with AUC of dutasteride and tamsulosin) under fasted state per related Health Canada guidance.

An interim analysis was not planned or conducted.

**Pharmacokinetics:** To assess bioequivalence of the test and reference treatments of dutasteride and tamsulosin, log<sub>e</sub>-transformed values of PK parameters AUC(0-72), AUC(0-t), and C<sub>max</sub> for dutasteride, and AUC(0-∞), AUC(0-t), C<sub>max</sub> and t<sub>1/2</sub> were analyzed by analysis of variance (ANOVA) using mixed effects model, fitting the fixed effects for treatment sequence, session, and treatment and subject within sequence as a random effect. For each endpoint, results from these analyses were exponentiated back to obtain point and 90% confidence interval (CI) estimates of the test-to-reference ratios of geometric least-squares (GLS) means (B:A in fed state and D:C in fasted state). For dutasteride, AUC(0-72) could not be consistently determined due to the fact that for over 25% of the PK concentration from the last sample was not quantifiable (NQ) or the actual sampling time of 72 hour sample was earlier than 72 hour. Therefore, AUC(0-t) was used as the primary PK parameter for dutasteride instead of AUC(0-72).

To assess the effect of food on the combination capsule formulation, a similar analysis was performed to obtain the point estimate (PE) and CI for the comparison of B (fed) : D (fasted). T<sub>max</sub> was analyzed non-parametrically using the Wilcoxon Matched Pairs Method (B-A in fed state, B (fed)-D (fasted)) and Mann-Whitney Method (D-C in fasted state) to compute the PE and 90% CI 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.

**Number of Subjects:**

	<b>N (%)</b>
Number of subjects planned, n:	98
Number of subjects randomized, n:	101
Number of subjects completed as planned, n (%):	81 (80)
Number of subjects withdrawn (any reason), n (%):	20 (20)
Withdrew consent	7 (7)
Protocol deviation	7 (7)
Adverse event	4 (4)
Investigator discretion (missed 72 hour post-dose visit in Periods 1 and 2)	1 (1)
Lost to follow-up	1 (1)
Number of subjects included in safety population, n (%):	101 (100)
Number of subjects included in PK population, n (%):	101 (100)

**Demographics:**

Subjects were all male, the majority White (77%), with a median age of 29.5 years.

<b>Age in Years, Mean (Range)</b>	29.5 (19-45)
<b>Sex, n (%)</b>	
Female:	0
Male:	101 (100)
<b>BMI (kg/m<sup>2</sup>), Mean (Range)</b>	25.6 (19-30)
<b>Height (cm), Mean (Range)</b>	176.2 (164-191)
<b>Weight (kg), Mean (Range)</b>	79.4 (59.0-106.4)
<b>Ethnicity, n (%)</b>	
Hispanic or Latino:	10 (10)
Not Hispanic or Latino:	91 (90)
<b>Race, n (%)</b>	
African American/African Heritage	22 (22)
White – White/Caucasian/European Heritage	78 (77)
White - Mixed Race	1 (1)

**Pharmacokinetics (PK) Results:**

Statistical assessment of dutasteride serum PK parameters showed there were no significant differences observed for dutasteride C<sub>max</sub> or AUC values between the fasted or fed state, whether administered alone or in combination with 0.4 mg tamsulosin HCl. Dutasteride C<sub>max</sub> and AUC(0-t) PEs were within 9% of unity, and the 90% CIs for each regimen comparison were entirely contained within the equivalence interval of 0.8-1.25. Dutasteride t<sub>max</sub> values were found to be equivalent between regimens, except for Regimens B-D and A-C, where the mean t<sub>max</sub> was observed 1 hour later in the fed compared to fasted state.

<b>Dutasteride PK Parameters</b>				
<b>Parameter</b>	<b>Comparison of</b>	<b>Point Estimate</b>	<b>90% CI</b>	<b>CVw%<sup>3</sup></b>
AUC(0-t) <sup>1</sup>	B : A	0.97	(0.92,1.03)	24.1
	A : C	1.09	(1.01,1.18)	
	D : C	1.01	(0.91,1.12)	
	B : D	1.05	(0.97,1.13)	
C <sub>max</sub> <sup>1</sup>	B : A	1.00	(0.94,1.05)	23.4
	A : C	1.01	(0.93,1.09)	
	D : C	0.99	(0.89,1.09)	
	B : D	1.01	(0.94,1.09)	
t <sub>max</sub> <sup>2</sup>	B – A	0.00	(-0.02,0.50)	NA
	A - C	1.02	(0.50,1.53)	
	D - C	0.00	(0.00,0.00)	
	B - D	1.00	(0.50,1.50)	

1. Point estimate is the ratio of adjusted geometric means between regimens
2. Point estimate is the estimated median difference between regimens
3. CVw% represents a pooled estimate of within-subject variability across regimens  
Regimen A = Flomax 0.4 mg and AVODART 0.5 mg in a fed state (Reference)  
Regimen B = Dutasteride and Tamsulosin Hydrochloride Combination Capsules, 0.5 mg dutasteride, 0.4 mg tamsulosin hydrochloride in a fed state (Test)  
Regimen C = Flomax 0.4 mg and AVODART 0.5 mg in a fasted state (Reference)  
Regimen D = Dutasteride and Tamsulosin Hydrochloride Combination Capsules, 0.5 mg dutasteride, 0.4 mg tamsulosin hydrochloride in a fasted state (Test)

For tamsulosin, C<sub>max</sub> values for Regimen A and Regimen B were found to be 30% less than Regimen C and Regimen D, respectively, indicating the magnitude of the food effect was similar in both the test and reference dosage forms. The 90% CIs associated with tamsulosin C<sub>max</sub> were entirely contained within the 0.8-1.25 interval for all regimen comparisons, except treatments A:C and B:D, where the 90% CIs were found to be entirely outside the interval. The 90% CIs associated with tamsulosin AUC and t<sub>1/2</sub>

values for all regimen comparisons were entirely contained within the 0.8-1.25 equivalence interval. The 90% CIs for tamsulosin tmax values included 0, indicating no significant differences between regimens, except for Regimen A-C comparisons, where a 1.50 hour increase in tmax was observed for Regimen A compared to Regimen C.

Tamsulosin PK Parameters				
Parameter	Comparison of	Point Estimate	90% CI	CVw% <sup>3</sup>
AUC(0-∞) <sup>1</sup>	B : A	1.04	(0.98,1.10)	21.6
	A : C	0.93	(0.86,0.99)	
	D : C	1.01	(0.92,1.10)	
	B : D	0.96	(0.89,1.03)	
AUC(0-t) <sup>1</sup>	B : A	1.03	(0.97,1.09)	22.0
	A : C	0.91	(0.85,0.98)	
	D : C	1.00	(0.91,1.10)	
	B : D	0.94	(0.87,1.01)	
Cmax <sup>1</sup>	B : A	1.08	(1.00,1.15)	28.4
	A : C	0.70	(0.64,0.77)	
	D : C	1.07	(0.95,1.21)	
	B : D	0.70	(0.64,0.77)	
t1/2 <sup>1</sup>	B : A	1.01	(0.97,1.06)	16.7
	A : C	1.06	(1.00,1.11)	
	D : C	0.99	(0.92,1.06)	
	B : D	1.09	(1.03,1.15)	
tmax <sup>2</sup>	B - A	-0.50	(-1.50,0.00)	N/A
	A - C	1.50	(0.96,2.50)	
	D - C	0.00	(-0.07,0.00)	
	B - D	1.00	(0.00,1.50)	

1. Point estimate is the ratio of adjusted geometric means between regimens
  2. Point estimate is the estimated median difference between regimens
  3. CVw% represents a pooled estimate of within-subject variability across regimens
- Regimen A = Flomax 0.4 mg and AVODART 0.5 mg in a fed state (Reference)  
 Regimen B = Dutasteride and Tamsulosin Hydrochloride Combination Capsules, 0.5 mg dutasteride, 0.4 mg tamsulosin hydrochloride in a fed state (Test)  
 Regimen C = Flomax 0.4 mg and AVODART 0.5 mg in a fasted state (Reference)  
 Regimen D = Dutasteride and Tamsulosin Hydrochloride Combination Capsules, 0.5 mg dutasteride, 0.4 mg tamsulosin hydrochloride in a fasted state (Test)

#### Safety Results:

There were no deaths, SAEs or partner pregnancies reported during the study. Four (4) subjects were withdrawn due to AEs. Subject 106 (randomized to treatment sequence DAB) was withdrawn prior to dosing in Session 2 and Subject 203 (randomized to treatment sequence CAB) was withdrawn prior to dosing in Session 3, both due to clinical laboratory related AEs (moderate increased liver enzymes and increased creatine kinase in Subject 106 and moderate elevated ALT, AST and GGT in Subject 203). AEs for Subject 106 and 203 were not considered related to treatment with study medication. Subject 150 (randomized to treatment sequence DBA) was withdrawn after dosing in Session 2 due to mild dizziness which was considered related to treatment with study medication. Subject 218 (randomized to treatment sequence BDA) was withdrawn approximately 4 hours after dosing in Session 2 due to a mild AE of orthostatic hypotension which was considered related to treatment with study medication.

The most commonly reported AEs (>20%) were dizziness and headache. These AEs are consistent with the expected side effects of tamsulosin. A slightly lower proportion of AEs were reported following administration of dutasteride and tamsulosin under fed conditions (Regimen A and Regimen B) as compared to administration of dutasteride and tamsulosin under fasted conditions (Regimen C and Regimen D). A similar proportion of AEs was reported following administration of dutasteride and tamsulosin as separate capsules with food (Regimen A) or fasted (Regimen C) as compared to administration of the Combination Capsule with food (Regimen B) or fasted (Regimen D).

All of the AEs reported in the study were considered by the Investigator to be either mild or moderate in nature. All but one AE resolved by the end of the study (Subject 2035 elevated GGT was ongoing at study end).

**Adverse Events:**

	Number of Subjects with AE (%)				
	Regimen A (n=91)	Regimen B (n=93)	Regimen C (n=46)	Regimen D (n=46)	Total (n=101)
Subjects with any AE	21 (23)	24 (26)	14 (30)	15 (33)	50 (50)
Preferred Term					
Dizziness	7 (8)	8 (9)	6 (13)	6 (13)	22 (22)
Headache	6 (7)	9 (10)	3 (7)	4 (9)	21 (21)
Vertigo	0	2 (2)	3 (7)	4 (9)	9 (9)
Nausea	2 (2)	4 (4)	2 (4)	2 (4)	8 (8)
Hot flush	1 (1)	2 (2)	1 (2)	0	4 (4)
Abdominal pain	2 (2)	1 (1)	0	0	3 (3)
Diarrhea	2 (2)	1 (1)	0	0	3 (3)
Flushing	1 (1)	0	0	2 (4)	3 (3)
Hyperhidrosis	0	2 (2)	0	1 (2)	3 (3)
Dyspnea	2 (2)	1 (1)	0	0	2 (2)
Fatigue	0	2 (2)	0	0	2 (2)
Orthostatic hypotension	0	0	0	2 (4)	2 (2)
Rhinorrea	0	2 (2)	0	0	2 (2)
Upper respiratory tract infection	2 (2)	0	0	0	2 (2)

AEs reported in only 1 subject in any treatment regimen: acne, ALT increased, anxiety, AST increased, alopecia, blood creatinine phosphokinase increased, cold sweat, dry mouth, GGT increased, feeling hot, hepatic enzymes increased, hypotension, migraine, nasal congestion, oral pain, otitis media, neck pain, pallor, palpitations, pharyngolaryngeal pain, pneumonia, presyncope, pyrexia, rhinitis, sinus congestion, sinusitis, vision blurred, vomiting

Regimen A = Flomax 0.4 mg and AVODART 0.5 mg in a fed state (Reference)

Regimen B = Dutasteride and Tamsulosin Hydrochloride Combination Capsules, 0.5 mg dutasteride, 0.4 mg tamsulosin hydrochloride in a fed state (Test)

Regimen C = Flomax 0.4 mg and AVODART 0.5 mg in a fasted state (Reference)

Regimen D = Dutasteride and Tamsulosin Hydrochloride Combination Capsules, 0.5 mg dutasteride, 0.4 mg tamsulosin hydrochloride in a fasted state (Test)

<b>Serious Adverse Events, n (%) [n considered by the investigator to be related, possibly related, or probably related to study medication]:</b> None
<b>Publications:</b> None

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