

The study listed may include approved and non-approved uses, formulations or treatment regimens. The results reported in any single study may not reflect the overall results obtained on studies of a product. Before prescribing any product mentioned in this Register, healthcare professionals should consult prescribing information for the product approved in their country.

Study No.: ARI40014		
Title: Effects of Dutasteride on Intraprostatic Dihydrotestosterone (DHT) Levels		
Rationale: ARI40014 was conducted to provide intraprostatic DHT data for the currently approved 0.5mg dose of dutasteride.		
Phase: IV		
Study Period: 07-Oct-03 to 12-Jul-05		
Study Design: This was a multicenter, double-blind, randomized, placebo-controlled trial designed to assess intraprostatic DHT, testosterone (T), and dutasteride concentrations after daily dosing of 0.5 mg dutasteride or placebo for 3 months.		
Centers: Six centers in the United States.		
Indication: Subjects with benign prostatic hyperplasia (BPH) and scheduled to undergo transurethral resection of the prostate (TURP)		
Treatment: 0.5 mg dutasteride or placebo for 3 months		
Objectives: The primary study objective was to assess the effect of repeat oral once daily dosing of 0.5 mg dutasteride compared to placebo on prostatic tissue content of DHT in subjects treated for 3 months prior to TURP.		
Primary Outcome/Efficacy Variable: The primary endpoint was intraprostatic DHT measured at Visit 5 (TURP) in subjects receiving dutasteride or placebo for 3 months prior to TURP.		
Secondary Outcome/Efficacy Variables: Intraprostatic T at Visit 5, change in serum DHT and T from screening to Visit 5, intraprostatic and serum dutasteride concentrations at Visit 5, and number of subjects who had prostatic surgical interventions.		
Statistical Methods: Enrollment of approximately 25 subjects per treatment group (20 evaluable subjects per treatment group) was originally planned in order to provide 99% power to declare superiority of the 0.5 mg dutasteride treatment vs. placebo for intraprostatic DHT. The power estimate was computed using the following assumptions: mean intraprostatic DHT for placebo=6000 pg/g, standard deviation=2000, and a 90% relative treatment effect. This treatment effect corresponds to a reduction in mean intraprostatic DHT to 600 pg/g for dutasteride. The population of subjects used for statistical analysis was the "Intent to Treat" (ITT) population which consists of all subjects randomized to study treatment who received at least one dose of study treatment. The primary endpoint was intraprostatic DHT measured in subjects receiving dutasteride or placebo for 3 months prior to TURP. The primary analysis of intraprostatic DHT was based on t-tests from the general linear model. Analyses of intraprostatic DHT were planned in terms of logarithmically transformed data. Treatment groups were compared using the general linear model: $\text{Log(Intraprostatic DHT)} = \text{Treatment}$.		
Study Population: Eligible subjects were males ≥ 50 years of age with a diagnosis of BPH, and scheduled to undergo a TURP (and able to wait 3 months for the procedure). Subjects could not have a history or current evidence of prostate cancer, serum prostate specific antigen (PSA) < 1.5 ng/mL or ≥ 15 ng/mL [if ≥ 4 ng/mL the subject must have had a negative ultrasound or biopsy within 12 months], abnormal liver function test results (greater than two times the upper limit of normal for alanine aminotransferase [ALT], aspartate aminotransferase [AST], or alkaline phosphatase [ALP]); or bilirubin > 1.5 times the upper limit of normal, or serum creatinine > 1.5 times the upper limit of normal.		
Study Population	Placebo	Dutasteride
Number of Subjects:		
Planned, N	25	25
Randomised, N	21	22
Completed, n (%)	18 (86)	20 (91)
Total Number Subjects Withdrawn, N (%)	3 (14)	2 (9)
Withdrawn Due to Adverse Events n (%)	0	2 (9)
Withdrawn Due to Consent Withdrawn n (%)	1 (4.8)	0
Withdrawn Due to Lost To Follow-Up n (%)	1 (4.8)	0
Withdrawn For Other reasons n (%)	1 (4.8)	0

Demographics	Placebo	Dutasteride
N (ITT)	21	22
Males	21	22
Median Age, Years (Minimum-Maximum)	67.0 (50-83)	68.0 (57-80)
White, n (%)	11 (52)	12 (55)
Median Duration of BPH symptoms (years)	4.0	6.3
Median Time Since BPH diagnosis (years)	3.0	6.5
Primary Efficacy Results (ITT Population):		
Intraprostatic DHT (pg/g)	Placebo (N=21)	Dutasteride (N=22)
n	17	21
Adjusted Mean	3230.9	208.9
Ratio of Adjusted Means Vs. Placebo	0.06	
95% CI For The Ratio Vs. Placebo	0.05, 0.09	
P-Value Vs. Placebo	<0.001	
Secondary Outcome Variables (ITT Population):		
Intraprostatic Testosterone (pg/g)	Placebo (N=21)	Dutasteride (N=22)
n	17	21
Adjusted Mean	91.9	2536.0
Serum DHT % Change From Screening to Visit 5	Placebo (N=21)	Dutasteride (N=22)
n	11	12
Adjusted Mean	-15.2	-92.7
Serum T % Change From Screening to Visit 5	Placebo (N=21)	Dutasteride (N=22)
n	14	18
Adjusted Mean	9.9	7.8
Intraprostatic Dutasteride Concentrations (ng/g) at Visit 5	Placebo (N=21)	Dutasteride (N=22)
n	0	20
Median	0	26.4
Serum Trough Dutasteride Concentrations (ng/mL) at Visit 5	Placebo (N=21)	Dutasteride (N=22)
n	1	19
Median	22.4	28.1
Other (not TURP) Prostatic Surgical Interventions	Placebo (N=21)	Dutasteride (N=22)
Number of subjects	0	0
Safety Results: Adverse event (AE) and serious adverse event (SAE) reporting began as soon as a subject took the first dose of study medication (randomization visit), and continued until the follow-up telephone call (4 months post-TURP) was completed.		
	Placebo (N=21)	Dutasteride (N=22)
Most Frequent Adverse Events	n (%)	n (%)
Subjects With Any AE(s), n(%)	13 (62)	9 (41)
Urinary Tract Infection	3 (14)	1 (5)
Prostate Cancer	1 (5)	2 (9)
Subjects with any SAEs, n (%)		
	Placebo (N=21)	Dutasteride (N=22)
Subjects with non-fatal SAEs, n (%)	n (%) [related]	n (%) [related]
Any non-fatal SAE	3 (14) [0]	3 (14) [0]
Prostate Cancer	1 (5) [0]	2 (9) [0]
Bladder Neoplasm	0	1 (5) [0]
Diarrhea	1 (5) [0]	0
Hematochezia	1 (5) [0]	0
Syncope	1 (5) [0]	0
Hypotension	1 (5) [0]	0
	Placebo (N=21)	Dutasteride (N=22)
Subjects with Fatal SAEs	n (%) [related]	n (%) [related]
Subjects with Fatal SAEs, n (%)	0	0

Conclusions:

Intraprostatic DHT levels were significantly lower in subjects receiving dutasteride 0.5 mg compared with those receiving placebo (94% versus placebo; $p < 0.001$). Reductions in serum DHT were significantly greater in dutasteride-treated subjects (93%) compared to the placebo group (15%). Intraprostatic testosterone levels were significantly higher in subjects receiving dutasteride 0.5 mg compared with those receiving placebo. No significant differences in percent change from baseline in serum T levels were noted between the dutasteride (7.8%) and placebo (9.9%) groups. Steady state concentrations of dutasteride in the serum were reached in 52.4% of subjects. Significant intraprostatic DHT suppression was achieved at varying levels of intraprostatic dutasteride concentrations.

Adverse events were reported in 13 (62%) subjects in the placebo group, and 9 (41%) subjects in the dutasteride group. Urinary tract infection was the most frequently reported adverse event in the placebo group, and prostate cancer was the most frequently reported adverse event in the dutasteride group. Non-fatal serious adverse events were reported in 3 subjects in the placebo group, and 3 subjects in the dutasteride group. No fatal serious adverse events were reported.

Publications: None