

Study No.: ARIA3001 (Year 1)		
Title: A Randomized, Double-Blind, Placebo-Controlled, Two Year Parallel Group Study of the Efficacy and Safety of Dutasteride GI198745 0.5mg in the Treatment and Prevention of Progression of Benign Prostatic Hyperplasia, Followed by a Two-Year Open-Label Treatment Phase (Report on Year 1 Data)		
Rationale: ARIA3001 is one of three large (approximately 1500 subject) Phase III studies (also ARIA3002 and ARIB3003) of a similar type and duration assessing the efficacy and safety of dutasteride (Dut) in subjects with benign prostatic hyperplasia (BPH) over a 4-year treatment period. ARIA3001 was designed to examine the effect of Dut on the treatment of BPH using both subjective (American Urological Association Symptom Index [AUA-SI]), and objective (prostate volume, urine flow) assessments. The longer-term effect of Dut on disease management (as measured by the incidence of acute urinary retention [AUR] and surgical intervention), and the effects of treatment on health status, was to be examined over a 2-year treatment period.		
Phase: III		
Study Period: 8 Sep 1997 – 24 Nov 1999		
Study Design: Randomized, double-blind, placebo (Pbo)-controlled, 2-year parallel group study		
Centres: 106 in the United States		
Indication: BPH		
Treatment: Four weeks of Pbo, in a run-in phase, followed by two years of Dut 0.5mg or Pbo once daily.		
Objectives: This report presents results from Year 1 of the double-blind treatment phase. The primary objective for Year 1 of this study was to assess the efficacy (AUA-SI) of repeat oral once daily dosing of Dut 0.5mg compared with Pbo.		
Primary Outcome/Efficacy Variable: The primary efficacy outcome for the Year 1 report was the improvement from baseline in symptom scores (AUA-SI).		
Secondary Outcome/Efficacy Variable: The secondary efficacy measures were the percentage change in prostate volume and change from baseline in maximum urine flow (Qmax).		
Statistical Methods: Five hundred (500) subjects per treatment group would provide > 90% power at the 0.05 significance level to detect a 1.5 unit difference in AUA-SI between Pbo and Dut (assuming 7.0 units as the standard deviation) at Month 12.		
<p>The reported p-values corresponded to the pairwise comparisons between Pbo and Dut. All statistical analyses were performed using two-sided tests of significance. To address multiplicity in terms of statistical testing at multiple time points, a closed test principle was employed. All treatment comparisons were reported; however, interpretation was restricted. The two treatment groups were compared beginning at Month 12 at the 0.05 significance level. If significant, then statistical comparisons at earlier post baseline assessments continued in a step down manner at the 0.05 level of significance. The impact of this method of addressing multiple time points is that failure to reach statistical significance in the above defined hierarchy implied restriction of interpretation for the next lower hierarchical point.</p> <p>The population of subjects which was statistically analyzed was the Intent-to-Treat population which consisted of all subjects randomized to double-blind study treatment (after the 4-week placebo run-in) who received at least one dose of study treatment.</p>		
Study Population: Male subjects, ≥50 years of age, with a diagnosis of BPH (according to medical history and physical exam, including a digital rectal exam [DRE]), AUA-SI ≥12, a urinary flow rate of ≤15mL/sec with a minimum voided volume of ≥125mL, and a prostate volume of ≥30cc as determined by transrectal ultrasound. Subjects were excluded if they had a post void residual volume >250mL or a serum prostate specific antigen (PSA) <1.5ng/mL or >10.0 ng/mL.		
Number of Subjects:	Dut	Pbo
Planned N	500	500
Randomised N	720	720
Completed n (%)	603 (83.8)	587 (81.5)
Withdrawn n (%)	117 (16.3)	133 (18.5)
Withdrawn due to Adverse Events n (%)	36 (5%)	33 (5%)
Withdrawn due to Lack of Efficacy n (%)	30 (4%)	35 (5%)
Withdrawn for other reasons n (%)	51 (7%)	65 (9%)
Demographics	Dut	Pbo
N (ITT)	720	720
Females: Males	0:720	0:720
Mean Age in Years (SD)	66.4 (7.82)	65.9 (7.47)
Mean Weight in Kg (SD)	86.2 (13.95)	86.7 (13.71)
White n (%)	634 (88.1)	640 (88.9)

Primary Efficacy Results: Intention-to-treat and last observation carried forward (LOCF)		
AUA-SI Change from Baseline	Dut	Pbo
Mean (SD) baseline AUA-SI	17.2 (6.00)	17.2 (5.98)
Month 1	n=703	n=706
Adjusted mean	-1.3	-1.4
Adjusted mean difference from Pbo	0.1	
95% Confidence Interval	-0.4, 0.5	
p-value	0.81	
Month 3	n=705	n=709
Adjusted mean	-2.3	-2.1
Adjusted mean difference from Pbo	-0.2	
95% Confidence Interval	-0.8, 0.3	
p-value	0.39	
Month 6	n=705	n=709
Adjusted mean	-2.9	-2.4
Adjusted mean difference from Pbo	-0.5	
95% Confidence Interval	-1.0, 0.1	
p-value	0.12	
Month 12	n=705	n=709
Adjusted mean	-3.0	-2.0
Adjusted mean difference from Pbo	-1.1	
95% Confidence Interval	-1.7, -0.5	
p-value	<0.001	
Secondary Efficacy Results: ITT and LOCF		
Prostate Volume Percent Change from Baseline	Dut	Pbo
Mean (SD) baseline prostate volume	53.9 (23.60)	54.7 (23.39)
Month 1	n=702	n=704
Adjusted mean	-8.5	-2.9
Adjusted mean difference from Pbo	-5.6	
95% Confidence Interval	-7.5, -3.6	
Month 6	n=705	n=706
Adjusted mean	-20.1	-3.5
Adjusted mean difference from Pbo	-16.6	
95% Confidence Interval	-18.7, -14.5	
Month 12	n=705	n=706
Adjusted mean	-23.2	-2.0
Adjusted mean difference from Pbo	-21.2	
95% Confidence Interval	-23.4, -18.9	
Maximum Urine Flow (Qmax) Change from Baseline (ml/sec)	Dut	Pbo
Mean (SD) baseline Qmax	10.2 (3.81)	10.8 (3.93)
Month 1	n=686	n=676
Adjusted mean	0.7	0.5
Adjusted mean difference from Pbo	0.2	
95% Confidence Interval	-0.2, 0.5	
Month 3	n=703	n=702
Adjusted mean	1.1	0.6
Adjusted mean difference from Pbo	0.5	
95% Confidence Interval	0.1, 0.8	
Month 6	n=706	n=703
Adjusted mean	1.1	0.7
Adjusted mean difference from Pbo	0.4	
95% Confidence Interval	0.0, 0.7	
Month 12	n=706	n=703
Adjusted mean	1.3	0.7
Adjusted mean difference from Pbo	0.7	

95% Confidence Interval	0.3, 1.1	
Safety Results: Adverse events were coded and grouped by body system.		
Most Frequent Adverse Events – On Therapy	Dut	Pbo
N (ITT)	720	720
Subjects with AEs n (%)	446 (62)	484 (67)
Ear nose and throat infections	55 (8)	53 (7)
Impotence	47 (7)	22 (3)
Musculoskeletal pain	38 (5)	49 (7)
Altered (decreased) libido	30 (4)	14 (2)
Viral ear nose and throat infections	29 (4)	36 (5)
Viral respiratory infections	28 (4)	26 (4)
Cough	20 (3)	22 (3)
Diarrhea	18 (3)	23 (3)
Hypertension	18 (3)	20 (3)
Ejaculation disorders	17 (2)	6 (<1)
Arthralgia and articular rheumatism	15 (2)	22 (3)
Urinary infections	13 (2)	29 (4)
Bronchitis	11 (2)	20 (3)
Disorders of lipid metabolism	11 (2)	20 (3)
Sleep disorders	8 (1)	20 (3)
Serious Adverse Events – On Therapy	Dut	Pbo
Subjects with SAEs n (%) [considered by the investigator to be related, possibly related or probably related to study medication]	62 (9) [0]	65 (9) [1]
Primary malignant skin neoplasia	9 (1) [0]	7 (<1) [0]
Coronary artery disorders	8 (1) [0]	8 (1) [0]
Bone and cartilage disorders	5 (<1) [0]	0
Degenerative arthritis	3 (<1) [0]	1 (<1) [0]
Chest symptoms	3 (<1) [0]	1 (<1) [0]
Primary malignant male reproductive neoplasia	3 (<1) [0]	3 (<1) [0]
Angina pectoris	2 (<1) [0]	3 (<1) [0]
Aneurysms	2 (<1) [0]	2 (<1) [0]
Arterial stenosis and arteriospasm	2 (<1) [0]	2 (<1) [0]
Musculoskeletal pain	2 (<1) [0]	0
Ligament tendon or cartilage injuries	2 (<1) [0]	2 (<1) [0]
Fractures	2 (<1) [0]	1 (<1) [0]
Cranio-cerebral injuries	2 (<1) [0]	0
Chronic obstructive airways disease	2 (<1) [0]	0
Hepatobiliary and pancreatic cysts lumps and masses	2 (<1) [0]	0
Myocardial infarction	1 (<1) [0]	5 (<1) [0]
Biventricular heart failure	1 (<1) [0]	2 (<1) [0]
Disturbances of intracranial blood flow	1 (<1) [0]	1 (<1) [0]
Cardiac arrest	1 (<1) [0]	1 (<1) [0]
Atrioventricular block	1 (<1) [0]	0
Primary musculoskeletal malignant neoplasia	1 (<1) [0]	0
Gastroenteritis	1 (<1) [0]	2 (<1) [0]
Duodenal ulcers	1 (<1) [0]	1 (<1) [0]
Abdominal discomfort and pain	1 (<1) [0]	0
Diverticulosis	1 (<1) [0]	0
Decreased gastrointestinal mobility and ileus	1 (<1) [0]	0
Infections due to medical device or graft	1 (<1) [0]	0
Contusions and hematomas	1 (<1) [0]	0
Dislocations	1 (<1) [0]	0
Fungal respiratory infections	1 (<1) [0]	0
Diaphragm disorders	1 (<1) [0]	0
Viral infections	1 (<1) [0]	0

Inflammation of epididymis	1 (<1) [0]	0
Primary malignant blood and lymphatic neoplasia	1 (<1) [0]	2 (<1) [0]
Coagulation delay	1 (<1) [0]	0
Hemorrhage	1 (<1) [0]	0
Decreased white cells	1 (<1) [0]	0
Myelopathies	1 (<1) [0]	0
Dementia	1 (<1) [0]	0
Primary malignant urinary neoplasia	1 (<1) [0]	1 (<1) [0]
Urinary calculi	1 (<1) [0]	0
Urinary neoplasia of uncertain behaviour	1 (<1) [0]	0
Cholecystitis	1 (<1) [0]	0
Cholelithiasis	1 (<1) [0]	0
Primary malignant eye neoplasia	1 (<1) [0]	0
Cerebrovascular accidents	0	3 (<1) [1]
Primary malignant gastrointestinal neoplasia	0	3 (<1) [0]
Arrhythmias	0	2 (<1) [0]
Tachyarrhythmias	0	2 (<1) [0]
Arthralgia and articular rheumatism	0	2 (<1) [0]
Gastrointestinal hemorrhage	0	2 (<1) [0]
Gastrointestinal herniae	0	2 (<1) [0]
Pneumonia	0	2 (<1) [0]
Changes in blood pressure	0	1 (<1) [0]
Hypertension	0	1 (<1) [0]
Vascular occlusion	0	1 (<1) [0]
Intracranial hemorrhage	0	1 (<1) [0]
Bradycardia	0	1 (<1) [0]
Extrasystoles	0	1 (<1) [0]
Congenital heart disease	0	1 (<1) [0]
Nevi	0	1 (<1) [0]
Arthritis	0	1 (<1) [0]
Joint disorders	0	1 (<1) [0]
Gastrointestinal disorders	0	1 (<1) [0]
Postoperative complications	0	1 (<1) [0]
Injuries	0	1 (<1) [0]
Wounds and lacerations	0	1 (<1) [0]
Lower respiratory infections	0	1 (<1) [0]
Bronchitis	0	1 (<1) [0]
Primary malignant lower respiratory neoplasia	0	1 (<1) [0]
Non-specific conditions	0	1 (<1) [0]
Temperature regulation disturbances	0	1 (<1) [0]
Malaise and fatigue	0	1 (<1) [0]
Coagulation disorders	0	1 (<1) [0]
Myeloproliferative disorders	0	1 (<1) [0]
Neurological infections	0	1 (<1) [0]
Confusion	0	1 (<1) [0]
Memory effects	0	1 (<1) [0]
Primary malignant endocrine neoplasia	0	1 (<1) [0]
Depressive disorders	0	1 (<1) [0]
Pleura disorder	0	1 (<1) [0]
Subjects with Fatal SAEs n (%) [considered by the investigator to be related, possibly related or probably related to study medication]	5 (0.7) [0]	2 (0.3) [0]
Cardiac arrest	1 (0.1) [0]	1 (0.1) [0]
Myocardial infarction	1 (0.1) [0]	0
Bladder cancer	1 (0.1) [0]	0

Worsening of COPD	1 (0.1) [0]	0
Angiosarcoma + liver metastasis	1 (0.1) [0]	0
Disseminated intravascular coagulation	0	1 (0.1) [0]

Date Updated: 31-Jan-2005

Publications:

Roehrborn CG, Boyle P, Nickel JC, et al. Efficacy and safety of a dual inhibitor of 5 alpha-reductase types 1 and 2 (dutasteride) in men with benign prostatic hyperplasia. *Urology* 2002; 60: 434-441.

O'Leary MP, Roehrborn CG, Andriole G, et al. Improvements in benign prostatic hyperplasia-specific quality of life with dutasteride, the novel dual 5alpha-reductase inhibitor. *BJU International* 2003; 92: 262-6.

Andriole G, Roehrborn CG, Nickel CJ, et al. Effect of the dual 5alpha-reductase inhibitor dutasteride on serum total PSA, free PSA and the ratio of F/T PSA. *AUA* 2002

Andriole G, Roehrborn CG, Schulman C, et al. Effect of dutasteride on the incidence of prostate cancer (PCa) in men with benign prostatic hyperplasia. *AUA* 2004

Boyle P. Early use of dutasteride arrests prostate growth, improves clinical parameters and prevents complications in men with benign prostatic hyperplasia. *AUA* 2003

Boyle P. Predictive model for acute urinary retention in man with benign prostatic hyperplasia. *AUA* 2003

Boyle P, Andriole G, Nickel CJ, et al. Effect of the dual 5alpha-reductase inhibitor dutasteride on total and transitional zone prostate volume. *SIU* 2002

Boyle P, Robertson C, Wilson T, et al. Risk factors for acute urinary retention in men with benign prostatic hyperplasia. *EAU* 2003

Boyle P, Roehrborn C, Andriole G, et al. The impact of dutasteride, a novel 5alpha-reductase inhibitor, on the hallmarks of BPH progression and outcomes. *EAU* 2002

Boyle P, Roehrborn C, Marks L, et al. The novel dual 5alpha-reductase inhibitor dutasteride is effective for the treatment and prevention of complications in men with a PV ≥ 30 - < 40 cc and ≥ 40 cc. *EAU* 2003

Boyle P, Siami P, Wachs B, et al. Effect of Dutasteride on the risk of acute urinary retention and the need for surgical treatment. *AUA* 2002

Carson C. Effect of maximal DHT suppression with Dutasteride on sexual function and gynecomastia. *AUA* 2003

Costa F, Walls R. The dual 5alpha-reductase inhibitor dutasteride is safe and effective in men with benign prostatic hyperplasia receiving a PDE-5 inhibitor. *AUA* 2004

Marks L, Roehrborn CG, Rittmaster R. Duration of dihydrotestosterone suppression following discontinuation of dutasteride: implications for missed doses. *AUA* 2004

McNicholas T, Tamella T, Te A, et al. The novel dual 5alpha-reductase inhibitor Dutasteride is well tolerated with the concomitant use of commonly prescribed cardiovascular medications and PDE-5 inhibitors. *EAU* 2003

O'Leary M, Roehrborn C, Andriole G et al. Baseline bother and symptom scores determine which BPH subjects will be bothered following treatment. *EAU* 2003

O'Leary M, Roehrborn C, Andriole G, et al. Baseline bother and symptom scores predict men likely to benefit from treatment with the novel dual 5alpha-reductase inhibitor Dutasteride. *AUA* 2003

Roehrborn C. Dutasteride provides sustained and continued improvement in BPH-related symptoms over 4 years. AUA 2003

Roehrborn C. PSA is a significant predictor of objective parameters in men at risk for BPH progression. AUA 2003

Roehrborn CG, Andriole G, Nickel CJ, et al. Effect of the dual 5alpha-reductase inhibitor Dutasteride on endocrine parameters. AUA 2002

Roehrborn CG, Andriole G, Nickel CJ, et al. Long-term effect of Dutasteride on symptoms, BPH-Specific Health Status and Urinary flow rate. SIU 2002

Roehrborn CG, Andriole G, Nickel CJ, et al. The impact of the dual 5alpha-reductase inhibitor Dutasteride on outcome of benign prostatic hyperplasia (BPH). SIU 2002

Roehrborn CG, Andriole G, Nickel CJ, et al. Effect of Dutasteride, a novel dual 5alpha-reductase inhibitor, on BPH related signs and symptoms. AUA 2002

Roehrborn CG, Andriole G, Schalken J, et al. Dutasteride, a novel 5alpha-reductase inhibitor, reduces serum DHT to a greater extent versus finasteride and achieves finasteride maximal reduction in a larger proportion of patients. EAU 2003

Roehrborn CG, Boyle P, Gabriel H, et al. Relationships between serum PSA, total and transition zone volume assessed by TRUS in men with clinical BPH. *Journal of Urology* 1999; 161: 1405

Roehrborn CG, Ramsdell J, Siami P, et al. Prostate volume at baseline predicts the margin of therapeutic response with the 5alpha-reductase inhibitor, dutasteride. AUA 2002

Roehrborn CG, Ray P, Gittelman M, et al. The novel dual 5alpha-reductase inhibitor, Dutasteride, is effective and well-tolerated for benign prostatic hyperplasia in black men. EAU 2003

Roehrborn C, Andriole G, Nickel C, et al. Long-term effect of dutasteride on symptoms, BPH-specific health status and urinary flow rate [abstract P-1.2.19]. *Br J Urol Int* 2002;90 (Suppl 2):17

Roehrborn CG, Clark R, Hobbs S, et al. Total and free PSA correlate with total prostate and transition zone volume in men aged >50 with BPH; G1198745 clinical trials. AUA 2001

Roehrborn CG, de la Rosette J, Andriole G. The utility of serial PSA measurements for the diagnosis of prostate cancer is preserved in men treated with the dual 5alpha-reductase inhibitor dutasteride. AUA 2004

Roehrborn CG, Wilson T, Rittmaster R. Does Hypogonadism (T < 300 ng/dl) affect prostate function or response to dutasteride?: Analysis of data from dutasteride Phase III BPH studies. AUA 2004

Roehrborn CG, Logie JW, Blackman N, Lamerato LE, Brown RR, Hoke GP. Racial differences in the risk of BPH progression and prostate cancer. AUA 2004

Te A, Kaplan S. Dutasteride provides improvement in urodynamic parameters over 2 years: analysis of data from the Phase III dutasteride studies. AUA 2004

Long-term sustained improvement in symptoms of benign prostatic hyperplasia with the dual 5alpha-reductase inhibitor dutasteride: results of 4-year studies. Roehrborn, C. G., Lukkarinen, O., Mark, S., Siami, P., Ramsdell, J., and Zinner, N. *BJU Int* 2005; 96 (4):572-7.

Efficacy and safety of dutasteride in the four-year treatment of men with benign prostatic hyperplasia. Roehrborn, C. G., Marks, L. S., Fenter, T., Freedman, S., Tuttle, J., Gittleman, M., Morrill, B., and Wolford, E. T. *Urology* 2004; 63 (4):709-15.

Abstract: The transition zone hypothesis in benign prostatic hyperplasia. Roehrborn, C. 1, Marks, L. 2, Wolford, E. 3, and Wilson, T. 4 20th Congress of the European Association of Urology 3/16/2005 Istanbul; Turkey

Abstract: Earlier initiation of treatment with the dual 5 alpha reductase inhibitor dutasteride reduces the risk of acute urinary retention and surgical intervention in men with benign prostatic hyperplasia. Emberton, M. 2 1 19th Congress of the European Association of Urology 3/24/2004 Vienna; Austria