

Study No: ARI40001 - Year 1
Title: A Multicentre, Randomised, Double-Blind, Double-Dummy, Parallel-Group Study to Compare the Efficacy of Dutasteride/GI198745 0.5mg od Versus Finasteride 5mg od for 12 Months in the Treatment of Subjects with Benign Prostatic Hyperplasia (BPH), Followed by an Optional 24 Months Open Label Phase.
Rationale: This study aimed directly compare the clinical effects of Fin, the type 2 5- $\alpha$ reductase, versus Dut, the dual type 1 and 2 5- $\alpha$ reductase.
Phase: IIIb
Study Period: 10 Nov 1998 - 23 Oct 2000
Study Design: Randomised double-blind, double-dummy, parallel group
Centres: 134 centres in 27 countries: Argentina, Austria, Australia, Belgium, Brazil, Canada, Czech Republic, Finland, Germany, Greece, Hungary, Ireland, Israel, Italy, Mexico, Netherlands, New Zealand, Norway, Portugal, Russia, Singapore, Slovakia, South Africa, Sweden, Taiwan, UK and Ukraine.
Indication: BPH
Treatment: Subjects had a 4-week placebo run-in prior to randomisation to either Dut 0.5mg capsules or Fin 5 mg tablets (1:1 ratio) once daily. Each randomised subject self-administered double-blind study medication orally once daily for 12, 4-week months.
Objectives: To assess the efficacy (prostate volume reduction) of repeat oral once daily dosing of Dut 0.5 mg compared with Fin 5 mg.
Primary Outcome Variable: The primary efficacy measurement of this study was percent change from baseline in prostate volume. Prostate volume was to be measured pre-randomisation and post-randomisation at Months 3 and 12 using transrectal ultrasound.
Secondary Outcome Variable: The secondary efficacy measures were improvement in symptom scores, as assessed by American Urological Association-Symptom Index (AUA-SI) and improvement in maximum urine flow (Q <sub>max</sub> ).
Statistical Methods: At the 0.05 significance level and 90% power, 445 subjects per treatment group were needed to detect a 5% difference in the percent change in prostate volume between dutasteride 0.5mg and finasteride 5mg at 12 months (using a 23% estimate for the standard deviation). Assuming 30% of the subjects will prematurely discontinue, 1272 subjects were required to be randomly allocated to treatment. The reported p-values corresponded to the pairwise comparisons between finasteride and dutasteride. All statistical analyses were performed using two-sided tests of significance. To address multiplicity in terms of statistical testing at multiple time points and separately for multiple prostate volume subgroups, 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 primary population of subjects which was analysed was the 'Intent-to-Treat' Population which consisted of all subjects randomised to double-blind study medication (after the 4 week placebo run-in) who received at least one dose of study treatment.
Study Population: Subjects were male, $\geq 50$ years of age, with a diagnosis of BPH (according to medical history and physical examination including a digital rectal exam), AUA-SI $\geq 12$ , a urinary flow rate $\leq 15$ mL/sec with a minimum voided volume $\geq 125$ mL, prostate volume $\geq 30$ cm <sup>3</sup> as determined by transrectal ultrasound. Subjects were excluded if they had a post void residual volume $> 250$ mL or a serum prostate specific antigen (PSA) $< 1.5$ ng/mL or $> 10$

ng/mL.		
Number of Subjects:	Dut	Fin
Planned N	636	636
Randomised N	813	817
Completed n (%)	719 (88.4)	735 (90.0)
Withdrawn n (%)	94 (11.6)	82 (10.0)
Withdrawn due to Adverse Events n (%)	40 (5%)	36 (4%)
Withdrawn due to Lack of Efficacy n (%)	12 (1%)	8 (<1%)
Withdrawn for other reasons n (%)	42 (5%)	38 (5%)
Demographics	Dut	Fin
N (ITT)	813	817
Females: Males	0:813	0:817
Mean Age in Years (SD)	66.8 (7.18)	66.9 (7.37)
Mean Weight in kg (SD)	80.2 (12.75)	79.4 (12.40)
White n (%)	729 (89.7)	719 (88.0)
Primary Efficacy Results: Intention to treat (ITT) population with last observation carried forward (LOCF)		
Prostate Volume Percent Change from Baseline	Dut	Fin
Mean Baseline Prostate Volume cm <sup>3</sup> (SD)	54.2 (21.90)	52.4 (19.37)
Month 3	n=779	n=781
Adjusted mean	-18.3	-18.5
Adjusted mean difference from Fin	0.3	
95% Confidence Interval	-1.5, 2.1	
p-value	0.76	
Month 12	n=787	n=788
Adjusted mean :	-26.3	-26.7
Adjusted mean difference from Fin	0.4	
95% Confidence Interval	-1.6, 2.3	
p-value	0.65	
Secondary Efficacy Results: ITT with LOCF		
Change From Baseline AUA-SI	Dut	Fin
Mean Baseline AUA-SI (SD)	16.7 (5.75)	16.5 (5.49)
Month 3	n=793	n=791
Adjusted mean	-3.6	-3.8
Adjusted mean difference from Fin	0.2	
95% Confidence Interval	-0.3, 0.7	
Month 6	n=795	n=795

Adjusted mean	-4.9	-4.9
Adjusted mean difference from Fin	0.0	
95% Confidence Interval	-0.6, 0.5	
Month 12	n=795	n=795
Adjusted mean	-5.8	-5.5
Adjusted mean difference from Fin	-0.3	
95% Confidence Interval	-0.8, 0.3	
Change From Baseline Qmax	Dut	Fin
Mean Baseline Qmax mL/sec (SD)	10.1 (3.46)	10.0 (3.38)
Month 3	n=768	n=763
Adjusted mean	1.6	1.5
Adjusted mean difference from Fin	0.2	
95% Confidence Interval	-0.2, 0.5	
Month 6	n=781	n=782
Adjusted mean	2.0	1.6
Adjusted mean difference from Fin	0.3	
95% Confidence Interval	-0.0, 0.7	
Month 12	n=784	n=789
Adjusted mean	2.0	1.7
Adjusted mean difference from Fin	0.3	
95% Confidence Interval	-0.1, 0.7	
Safety results: Adverse events were coded and grouped by body system.		
Most Frequent Adverse Events (AEs) – On Therapy	Dut N=813	Fin N=817
Subjects with any AEs, n (%)	396 (49)	409 (50)
Impotence	63 (8)	74 (9)
Altered (decreased) libido	41 (5)	50 (6)
Viral respiratory infections	34 (4)	40 (5)
Headaches	26 (3)	28 (3)
Malaise and fatigue	25 (3)	22 (3)
Musculoskeletal pain	29 (4)	24 (3)
Viral ear nose and throat infections	19 (2)	22 (3)
Hypertension	19 (2)	16 (2)
Diarrhea	19 (2)	13 (2)
Dizziness	18 (2)	20 (2)
Abdominal discomfort and pain	16 (2)	14 (2)
Ejaculation disorders	14 (2)	14 (2)

Bronchitis	7 (<1)	14 (2)
Serious Adverse Events- On Therapy		
	Dut	Fin
Subjects with SAEs, n (%) [considered by the investigator to be related, possibly related, or probably related to study medication]:	55 (7) [1]	43 (5) [0]
Angina pectoris	5 (<1) [0]	4 (<1) [0]
Myocardial infarction	3 (<1) [0]	3 (<1) [0]
Cerebrovascular accidents	3 (<1) [0]	2 (<1) [0]
Tachyarrhythmias	3 (<1) [0]	2 (<1) [0]
Atrioventricular block	3 (<1) [0]	1 (<1) [0]
Coronary artery disorder	2 (<1) [0]	1 (<1) [0]
Syncope	2 (<1) [0]	0
Ischemic heart disease	1 (<1) [0]	1 (<1) [0]
Hypertension	1 (<1) [0]	0
Embolisms	0	1 (<1) [0]
Cerebrovascular disorders	0	1 (<1) [0]
Disturbances of intracranial blood flow	1 (<1) [0]	0
Varicosities	1 (<1) [0]	0
Cardiac failure	0	1 (<1) [0]
Biventricular heart failure	1 (<1) [0]	0
Myocardial ischemia	0	1 (<1) [0]
Aortic valve disorders	1 (<1) [0]	0
Primary malignant gastrointestinal neoplasia	4 (<1) [0]	3 (<1) [0]
Gastrointestinal herniae	0	3 (<1) [0]
Gastric ulcers	1 (<1) [0]	1 (<1) [0]
Gastrointestinal polyps	0	2 (<1) [0]
Gastroenteritis	1 (<1) [0]	0
Abdominal discomfort & pain	1 (<1) [0]	0
Peptic ulcers	0	1 (<1) [0]
Gastroduodenal ulcers	0	1 (<1) [0]
Diverticulosis	1 (<1) [0]	0
Hemorrhoids	0	1 (<1) [0]
Pneumonia	1 (<1) [0]	2 (<1) [0]
Primary malignant lower respiratory neoplasia	1 (<1) [0]	1 (<1) [0]
Viral respiratory infections	0	1 (<1) [0]
Chronic obstructive airways disease	0	1 (<1) [0]
Lower respiratory failure	0	1 (<1) [0]
Pleura disorders	1 (<1) [1]	0

Fractures	3 (<1) [0]	3 (<1) [0]
Injuries	1 (<1) [0]	1 (<1) [0]
Craniocerebral injuries	0	1 (<1) [0]
Accidents	0	1 (<1) [0]
Death	1 (<1) [0]	0
Multisystem disorders	1 (<1) [0]	0
Chest symptoms	1 (<1) [0]	0
Cysts lumps & masses	1 (<1) [0]	0
Primary malignant neoplasia	1 (<1) [0]	0
Neoplasia of uncertain behavior	1 (<1) [0]	0
Urinary neoplasia of uncertain behavior	2 (<1) [0]	0
Urinary infections	0	1 (<1) [0]
Renal failure	0	1 (<1) [0]
Urinary calculi	1 (<1) [0]	0
Primary malignant urinary neoplasia	0	1 (<1) [0]
Vertigo	2 (<1) [0]	0
Primary malignant neurological neoplasia	0	1 (<1) [0]
Neurological neoplasia of uncertain behavior	1 (<1) [0]	0
Ear nose & throat hemorrhage	2 (<1) [0]	1 (<1) [0]
Deafness	0	1 (<1) [0]
Cholelithiasis	0	2 (<1) [0]
Pancreatitis	0	1 (<1) [0]
Hepatobiliary & pancreatic neoplasia of uncertain behavior	1 (<1) [0]	0
Anemia	1 (<1) [0]	0
Increased white cells	1 (<1) [1]	0
Primary malignant blood & lymphatic neoplasia	1 (<1) [0]	0
Fluid disturbances	1 (<1) [0]	0
Benign endocrine neoplasia	0	1 (<1) [0]
Cataracts	1 (<1) [0]	0
Primary malignant eye neoplasia	1 (<1) [0]	0
Arthritis	0	1 (<1) [0]
Bone & skeletal pain	1 (<1) [0]	0
Primary malignant male reproductive neoplasia	1 (<1) [0]	1 (<1) [0]
Situational disorders	1 (<1) [0]	0

Subjects with fatal SAEs, n (%) [considered by the investigator to be related, possibly related, or probably related to study medication]:	4 (0.5) [0]	8 (1.0) [0]
Metastatic lung cancer	1 (0.1) [0]	0
Tumour cerebelli	1 (0.1) [0]	0
Sudden death	1 (0.1) [0]	0
Cerebrovascular accident	1 (0.1) [0]	0
Pneumonia right side	0	1 (0.1) [0]
Cerebrovascular disorder	0	1 (0.1) [0]
Complete heart block	0	1 (0.1) [0]
Car accident	0	1 (0.1) [0]
Anaplastic mixed glioma	0	1 (0.1) [0]
Cerebral stroke	0	1 (0.1) [0]
Acute renal failure	0	1 (0.1) [0]
Exacerbation of COPD	0	1 (0.1) [0]
<p>Conclusions:  These data suggest that dutasteride 0.5mg reduces prostate volume and improves peak urine flow and lower urinary tract symptoms (LUTS), as assessed by improvement in AUA-SI score. Dutasteride exhibited a similar efficacy and safety profile to finasteride 5mg, which is a licensed treatment for BPH. Therefore these data suggest that dutasteride 0.5mg will be a useful additional treatment for individuals with LUTS secondary to BPH.</p>		

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Publications:

Andriole GL and Kirby R. Safety and Tolerability of the Dual 5 alpha Reductase Inhibitor Dutasteride in the Treatment of Benign Prostatic Hyperplasia. *European Urology* 44 (July 2003) 82-88

Abstract: Efficacy of dutasteride and finasteride for the treatment of benign prostate hyperplasia: results of the 1-year enlarged prostate international comparator study (epics). GILLING, P. J., JACOBI, G., TAMMELA, T. L., and VAN ERPS, P. Annual Scientific Meeting of the Urological Society of Australasia 2/13/2005 Melbourne; Australia