

Study No.: ARI40002
Title: A Pilot, Multi-centre, Double-Blind, Parallel Group, Randomised Study, to Investigate the Effect on Symptoms of Discontinuing Tamsulosin, Following 24 Weeks Combination Treatment with 0.5mg G1198745 (Dutasteride) and 0.4mg Tamsulosin Daily in Subjects with Symptomatic Benign Prostatic Hyperplasia (BPH) (Amendment 1 with follow-up, cumulative data).
Rationale: For those symptomatic BPH patients who have been identified as likely to benefit from long term treatment with dutasteride (Dut) (e.g. prostate volume ≥ 30 cc, PSA ≥ 1.5 ng/mL), a logical management regimen would appear to be a combination of an $\alpha 1$ -adrenoreceptor antagonist and Dut until the time when Dut alone is able to maintain and/or improve symptom relief, and thereafter the patient would receive Dut monotherapy.
Phase: IIIb
Study Period: 15 Feb 2000 to 25 Sep 2001.
Study Design: Randomised, blinded, parallel group, multi-centre pilot study.
Centres: 32 centres in 6 countries: Canada, Germany, The Netherlands, Portugal, Russia and the UK.
Indication: BPH
Treatment: Four weeks of placebo (Pbo) daily, in a run in phase, was followed by 24 weeks of Dut 0.5mg plus tamsulosin (Tam) 0.4mg orally, combination treatment once daily for all subjects, and then followed by 12 weeks of dutasteride 0.5mg plus Tam 0.4mg combination treatment (Tam 36 + Dut 36) or dutasteride 0.5mg (Tam 24 + Dut 36) only treatment daily in a double-blind phase. A final one-week of Pbo was administered following the 36 weeks of active treatment. A final safety assessment was conducted 16 weeks post active treatment.
Objectives: To assess any difference at 30 weeks post-baseline, in the proportion of subjects experiencing an improvement, or no change, in their urinary symptoms (as perceived by the subjects themselves) following discontinuation or continuation of Tam for the two treatment groups.
Primary Outcome Variable: The primary efficacy measure was the proportion of subjects in each treatment group experiencing an improvement or no change in their urinary symptoms, at 30 weeks post-baseline, as shown in response to the following question: "Over the past 2 weeks, on average have you felt better, worse, or the same, with respect to your urinary symptoms, than at your last visit?"
Secondary Outcome Variables: The above question was also asked at Week 36 post-baseline as a secondary efficacy measure. Changes in International Prostate Symptom Score (IPSS) from baseline were also assessed as a secondary efficacy measure. The IPSS questionnaire is a subjective measure that assesses the severity of BPH symptoms. It consists of seven questions dealing with the nature and frequency of problems associated with urination encompassing incomplete emptying, frequency, intermittency, urgency, weak stream, straining and nocturia. Scores were determined on a six-point scale (where 0= none and 5= almost always) with a higher score reflecting more severe symptoms. In addition there was a quality of life question which asked the subject how they would feel if they had to spend the rest of their life with their urinary condition the way it was and scores were determined on a seven point scale (0-6) with the higher score reflecting the lowest quality of life. Subjects were to self-complete the IPSS questionnaire at Screening, baseline, Week 4, 12, 24, 30 and 36 post-baseline. In addition, at Weeks 24 and 30, subjects were asked: "Did you prefer the medication you were taking up to your last visit, more than the medication you are now taking?"
Statistical Methods: This pilot study was designed to indicate whether symptom relief could be maintained on dutasteride-only treatment, following short-term combination treatment for 24 weeks. These pilot data would be used to aid accurate estimation of subject numbers in later studies. A sample size of 200 evaluable subjects was considered sufficient to show, following combination treatment for 24 weeks, whether dutasteride-only treatment was as good clinically as combination treatment within 20 percentage points in terms of the primary endpoint. This was based on a 95% confidence interval (CI) and 80% power. The responder rate to the primary endpoint question was unknown, but for the purposes of the sample size calculation was taken to be 50% responding the same or better, as this required the largest sample size. To allow for a 20% dropout rate, a target sample size of 250 subjects was chosen to provide at least 200 evaluable subjects. The primary analysis was performed on both the intent-to-treat (ITT) population and the per-protocol population, although the ITT population was considered to be primary efficacy and safety population and included all subjects randomised to study treatment and who received at least one dose of study medication. The proportion of subjects in each treatment group reporting an improvement or no change in their urinary symptoms at Week 30 was calculated and subjected to analysis using a Mantel-Haenszel test controlling for investigator country. A 95% CI was calculated and used to conclude if monotherapy treatment was non-inferior to combination treatment. The change in urinary symptoms from Weeks 24 to 30 and 36 were analysed in the same way. To assist blinding, the primary efficacy question was asked at every visit. The total IPSS was the sum of the seven questions and was summarised by treatment group. Change from Week 24 IPSS was evaluated at Weeks 30 and 36 using ANCOVA allowing for effects due to treatment, investigator country and

the Week 24 IPSS. At Weeks 30 and 36 the Quality of Life question within the IPSS was tested using ANCOVA in the same manner as the IPSS.

Subjects were asked at Weeks 24 and 30 if they had a preference for the treatment received up until the last visit compared to that taken in the most recent period. The question was asked at Week 24 for blinding purposes. At Week 30 treatment groups were compared in terms of proportion of subjects with a preference using a Mantel Haenszel test controlling for investigator country.

The 'Intent-to-Treat' (ITT) Population was considered the primary efficacy and safety population and consisted of all subjects randomised to treatment (after the 4 week placebo run-in) who received at least one dose of study treatment. Analyses were performed using both last observation carried forward (LOCF) and At Visit (missing values are not replaced) approaches as appropriate. For the primary endpoint at Week 30 the At Visit approach was used since the subjects were split by randomized treatment group at Week 24 and hence it would not be appropriate to carry forward their Week 24 assessments.

Study Population: Subjects were male, ≥ 45 years of age, with a diagnosis of BPH according to medical history and physical examination including a digital rectal examination (DRE), IPSS ≥ 12 , enlarged prostate volume ($>30\text{cm}^3$) as determined by DRE. Subjects were excluded if they had a total serum prostate specific antigen (PSA) $<1.5\text{ng/mL}$ or $>10.0\text{ng/mL}$ male.

Number of Subjects:	Tam 24 + Dut 36	Tam 36 + Dut 36
Planned N	125	125
Randomised N	163	164
Completed at Week 37, n (%)	149 (91.4)	149 (90.9)
Withdrawn before Week 37, n (%)	14 (8.6)	15 (9.1)
Completed final safety assessments at Week 52, n (%)	148 (90.8)	144 (87.8)
Withdrew before Week 52, n (%)	15 (9.2)	20 (12.2)
Withdrawn due to Adverse Events n (%)	7 (4%)	7 (4%)
Withdrawn due to Lack of Efficacy n (%)	na	na
Withdrawn for other reasons n (%)	8 (5%)	13 (8%)
Demographics	Tam 24 + Dut 36	Tam 36 + Dut 36
N (ITT)	163	164
Females: Males	0:163	0:164
Mean Age in Years (SD)	66.9 (7.5)	67.6 (7.1)
Mean Weight in kg (SD)	82.1 (12.3)	81.1 (11.7)
White n (%)	160 (98.2)	162 (98.8)

Primary Efficacy Results: Intent to treat (ITT) population, At Visit		
	Tam 24 + Dut 36 N=151	Tam 36 + Dut 36 N=154
No. subjects (%) experiencing improvement or no change in urinary symptoms at Week 30	115 (76.2%)	139 (90.3%)
Difference in proportion	-0.11	
95% Confidence Interval	-0.18, -0.04	
p value	0.001	
Secondary Efficacy Results: ITT population, last observation carried forward (LOCF)		
IPSS mean values	Tam 24 + Dut 36	Tam 36 + Dut 36
Screening	18.1 (n=163)	18.7 (n=164)
Baseline	16.5 (n=163)	16.4 (n=164)
Week 4 (LOCF)	12.0 (n=159)	12.6 (n=164)
Week 12 (LOCF)	11.1 (n=160)	11.4 (n=164)
Week 24 (LOCF)	11.2 (n=160)	11.2 (n=164)
Week 30 (at visit)	12.2 (n=149)	10.8 (n=152)
Week 36 (at visit)	11.1 (n=149)	10.3 (n=150)
Mean change from Baseline IPSS at Weeks 30 and 36 (ITT, LOCF)		
	Tam 24 + Dut 36	Tam 36 + Dut 36
Mean change from Baseline at Week 30	-4.1 (n=160)	-5.6 (n=164)
Mean change from Baseline at Week 36	-5.1 (n=161)	-6.0 (n=164)
Change in IPSS from Week 24 through Week 36 (ITT, At Visit)		
Adjusted mean change from Week 24 to Week 30	1.2	-0.5
Adjusted mean difference	1.6	
95% Confidence Interval	0.8, 2.5	
Adjusted mean change from Week 24 to Week 36	0.0	-0.9
Adjusted mean difference	0.9	
95% Confidence Interval	0.0, 1.9	
IPSS Quality of Life Question (ITT, At Visit)		
	Tam 24 + Dut 36	Tam 36 + Dut 36
Mean change from Week 24 to Week 30	0.1	-0.1
Adjusted mean change from Week 24 to Week 36	0.2	
95% Confidence Interval	0.0, 0.4	
Mean change from Week 24 to Week 36	-0.1	-0.1
Adjusted mean change from Week 24 to Week 36	0	
95% Confidence Interval	-0.2, 0.2	
Primary Endpoint Question at Week 36:		
	Tam 24 + Dut 36	Tam 36 + Dut 36
% subjects who felt same/better with respect to urinary symptoms at Week 30 and continued to feel same/better at Week 36	93%	96%
Difference in proportion	-0.03	
95% Confidence interval	-0.09, 0.02	
Treatment Preference:		
	Tam 24 + Dut 36	Tam 36 + Dut 36
% subjects who did not prefer the medication they had taken up to Week 12 to their current medication (Week 24)	79%	79%
% subjects who did not prefer the medication they had taken up to Week 24 to their current medication (Week 30)	71%	81%
Summary of Prostate Volume at Week 36 (ITT; At Visit)		
At Screening, 194/276; 70% subjects had an estimated prostate volume of 40cc or more		

	Tam 24 + Dut 36 (n=133)	Tam 36 + Dut 36 (n=131)
<30 cc	29 (22%)	25 (19%)
30-39 cc	50 (38%)	53 (40%)
40-49 cc	29 (22%)	33 (25%)
≥50 cc	25 (19%)	20 (15%)
Safety Results: AEs were coded and grouped by body system.		
Most Frequent Adverse Events – On Therapy	Tam 24 + Dut 36 (N=163)	Tam 36 + Dut 36 (N=164)
Subjects with any AEs Weeks 0-24, n (%)	71 (44)	79 (48)
Ejaculation disorders	12 (7)	12 (7)
Altered (decreased) libido	10 (6)	7 (4)
Musculoskeletal pain	6 (4)	7 (4)
Arthralgia and articular rheumatism	6 (4)	1 (<1)
Headaches	5 (3)	2 (1)
Impotence	4 (2)	8 (5)
Hyposalivation	3 (2)	2 (1)
Abdominal discomfort and pain	3 (2)	1 (<1)
Constipation	3 (2)	1 (<1)
Malaise and fatigue	3 (2)	10 (6)
Dizziness	3 (2)	6 (4)
Ear nose and throat infections	3 (2)	3 (2)
Dysuria	3 (2)	1 (<1)
Urinary incontinence	3 (2)	0
Disorders of uric acid metabolism	3 (2)	0
Pruritus	3 (2)	0
Dyspeptic symptoms	0	4 (2)
Diarrhoea	2 (1)	3 (2)
Lower respiratory infections	0	3 (2)
Disorders of lipid metabolism	0	3 (2)
Anxiety	0	3 (2)
Subjects with any AEs Weeks 24-36, n (%)	42 (26)	32 (20)
Dysuria	4 (2)	3 (2)
Urinary infections	4 (2)	0
Musculoskeletal pain	4 (2)	4 (2)
Urinary frequency	3 (2)	2 (1)
Ejaculation disorders	3 (2)	2 (1)
Viral respiratory infections	3 (2)	4 (2)
Micturition disorders	2 (1)	1 (<1)
Nocturia	2 (1)	1 (<1)
Impotence	2 (1)	2 (1)
Abdominal discomfort and pain	2 (1)	1 (<1)
Hyperacidity	2 (1)	0
Ear nose and throat infections	2 (1)	1 (<1)
Skin rashes	2 (1)	0
Angina pectoris	2 (1)	0
Anxiety	2 (1)	1 (<1)
Altered (decreased) libido	1 (<1)	2 (1)
Urinary incontinence	0	1 (<1)
Male reproductive tract pain	1 (<1)	1 (<1)
Testis disorders	0	1 (<1)
Oesophagitis	1 (<1)	1 (<1)
Gastrointestinal herniae	1 (<1)	1 (<1)
Constipation	0	1 (<1)
Gastrointestinal obstructions	0	1 (<1)

Gastrointestinal signs and symptoms	0	1 (<1)
Viral ear nose and throat infections	1 (<1)	1 (<1)
Ear nose and throat haemorrhage	0	1 (<1)
Upper respiratory inflammation	0	1 (<1)
Bronchitis	0	1 (<1)
Allergic skin reactions	0	1 (<1)
Pruritus	0	1 (<1)
Viral skin infections	0	1 (<1)
Changes in blood pressure	0	1 (<1)
Burning sensations	0	1 (<1)
Chest symptoms	0	1 (<1)
Oedema and swelling	0	1 (<1)
Glycosuria and ketonuria	0	1 (<1)
Compressed nerve syndromes	0	1 (<1)
Qualitative red cell or haemoglobin defects	0	1 (<1)
Quantitative red cell or haemoglobin defects	0	1 (<1)
Subjects with any AEs Week 36-37, n (%)	9 (6)	11 (7)
Urinary urgency	2 (1)	0
Dysuria	1 (<1)	3 (2)
Urinary frequency	1 (<1)	1 (<1)
Muscle pain	1 (<1)	0
Malaise and fatigue	1 (<1)	0
Micturition disorders	0	4 (2)
Urinary frequency	1 (<1)	1 (<1)
Regurgitation and reflux	1 (<1)	0
Syncope	1 (<1)	0
Injuries	1 (<1)	0
Abnormal liver function tests	1 (<1)	0
Nocturia	0	1 (<1)
Urinary incontinence	0	1 (<1)
Ear nose and throat infections	0	1 (<1)
Laryngitis	0	1 (<1)
Throat and tonsil discomfort and pain	0	1 (<1)
Viral ear nose and throat infection	0	1 (<1)
Diarrhoea	0	1 (<1)
Gastrointestinal discomfort and pain	0	1 (<1)
Viral respiratory infections	0	1 (<1)
Subjects with any AEs Week 37-52, n (%)	12 (7)	13 (8)
Hypertension	2 (1)	0
Musculoskeletal pain	2 (1)	1 (<1)
Disorders of lipid metabolism	2 (1)	0
Nocturia	2 (1)	1 (<1)
Urinary frequency	2 (1)	0
Pulmonary oedema	1 (<1)	0
Viral respiratory infections	1 (<1)	0
Cardiac arrest	1 (<1)	0
Coronary artery disorders	1 (<1)	0
Gastrointestinal infections	1 (<1)	0
Synovium tendon fascia and bursa disorders	1 (<1)	0
Diabetes mellitus	1 (<1)	0
Disorders of uric acid metabolism	1 (<1)	0
Anxiety	1 (<1)	0
Lower respiratory infections	0	3 (2)
Arthralgia and articular rheumatism	0	2 (1)
Breathing disorders	0	1 (<1)

Primary malignant gastrointestinal neoplasia	0	1 (<1)
Primary malignant lower respiratory neoplasia	0	1 (<1)
Embolisms	0	1 (<1)
Abdominal discomfort and pain	0	1 (<1)
Gastrointestinal haemorrhage	0	1 (<1)
Gastrointestinal herniae	0	1 (<1)
Micturition disorders	0	1 (<1)
External otitis	0	1 (<1)
Viral ear nose and throat infections	0	1 (<1)
Hepatobiliary and pancreatic cysts lumps and masses	0	1 (<1)
Dizziness	0	1 (<1)
Chest symptoms	0	1 (<1)
Serious Adverse Events – On Therapy		
(%) [considered by the investigator to be related to study medication]		
	Tam 24 + Dut 36	Tam 36 + Dut 36
Subjects with non-fatal SAEs, n (%) Weeks 0-37	3 (2) [0]	7 (4) [1]
Angina pectoris	0	1 (<1) [0]
Arterial stenosis and arteriospasm	0	1 (<1) [0]
Embolisms	0	1 (<1) [1]
Myocardial infarction	1 (<1) [0]	0
Thrombosis	0	1 (<1) [0]
Gastrointestinal herniae	0	1 (<1) [0]
Gastrointestinal obstructions	0	1 (<1) [0]
Primary malignant gastrointestinal neoplasia	1 (<1) [0]	0
Mastoiditis and salpingitis	0	1 (<1) [0]
Chronic obstructive airways disease	0	1 (<1) [0]
Musculoskeletal pain	0	1 (<1) [0]
Renal signs and symptoms	1 (<1) [0]	0
Subjects with non-fatal SAEs, n (%) Weeks 37-52	1 (<1) [0]	3 (2) [0]
Coronary artery disorders	1 (<1) [0]	0
Embolisms	0	1 (<1) [0]
Primary malignant lower respiratory neoplasia	0	1 (<1) [0]
Primary malignant gastrointestinal neoplasia	0	1 (<1) [0]
Hepatobiliary and pancreatic cysts lumps and masses	0	1 (<1) [0]
Subjects with fatal SAEs, n (%) Weeks 0-36	0	0
Subjects with fatal SAEs, n (%) Weeks 37-52	1 (<1) [0]	0
Pulmonary oedema/Cardiac arrest	1 (<1) [0]	0

Conclusions:

See publications below.

Publications

Barkin J, Guimarães M, Jacobi G, et al. Alpha-blocker therapy can be withdrawn in the majority of men following initial combination therapy with the dual 5 alpha-reductase inhibitor dutasteride. Eur Urol 2003; 44: 461–6.

Barkin J, Guimarães M, Jacobi G, Pushkar D, Taylor S, van Vierssen Trip O. The 5α-reductase inhibitor (5ARI) dutasteride provides sustained symptom relief following short term combination treatment. AUA 2002.