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<b>Study No.:</b> ARI40007			
<b>Title:</b> A Randomised, Double-Blind, Placebo-Controlled, Parallel Group Study Investigating the Effects of Either 4 or 6 Weeks Dutasteride 0.5mg Daily on Peri-Operative Bleeding Following Transurethral Resection of the Prostate (TURP) in Subjects with Benign Prostatic Hyperplasia (BPH).			
<b>Rationale:</b> TURP is conducted for relief of urinary obstructive symptoms resulting from BPH but it is associated with peri-operative complications. It is hypothesized that treatment with a 5 alpha-reductase inhibitor (5 ARI) will reduce blood loss during surgery and reduce peri-operative complications. This study in subjects with BPH assessed the clinical and safety effects of treatment with the 5 ARI Dutasteride (Dut) daily for 2 or 4 weeks pre-TURP and 2 weeks post-TURP compared with placebo to evaluate blood loss during surgery and peri-operative complications.			
<b>Phase:</b> IIIb			
<b>Study Period:</b> 16Jun03 - 10Aug04			
<b>Study Design:</b> International, multi-centre, randomised, double-blind, placebo-controlled, parallel group study to evaluate the clinical and safety effects of Dut 0.5mg once daily relating to blood loss during surgery and peri-operative complications.			
<b>Centres:</b> 24 centres in Denmark (5), Finland (2), Netherlands (6), Norway (6), Sweden (1), UK (4)			
<b>Indication:</b> Reduction in blood loss and perioperative complications in patients undergoing TURP for relief of BPH signs and symptoms			
<b>Treatment:</b> Eligible subjects were randomised in a 1:1:1 ratio to once daily dosing in one of three groups: Group 1: Placebo (Pbo) for 4 weeks prior to TURP and 2 weeks post-TURP; Group 2: Pbo for 2 weeks and then Dut 0.5mg for 2 weeks prior to TURP and Dut 0.5mg for 2 weeks post-TURP; Group 3: Dut 0.5mg for 4 weeks prior to TURP and for 2 weeks post-TURP.			
<b>Objectives:</b> The primary objective was to assess the effect of Dut 0.5 mg compared with placebo on the reduction of blood loss during TURP surgery.			
<b>Primary Outcome/Efficacy Variable:</b> The primary efficacy outcome was total blood loss during TURP surgery (operating theatre) and was calculated as quantity of haemoglobin per gram of prostate resected.			
<b>Secondary Outcome/Efficacy Variables:</b> Secondary efficacy outcomes included incidence of peri-operative bleeding 4 weeks post-TURP and incidence of post-TURP complications including clot retention, blood transfusion, acute urinary retention (AUR), urinary tract infection (UTI), and urinary incontinence.			
<b>Statistical Methods:</b> The sample size of 50 subjects per arm was based on power to detect differences for both the primary endpoint (total blood loss during TURP) and the secondary endpoint of peri-operative bleeding. Primary efficacy analyses plan was for pairwise comparison of the mean of Group 1 with the means for Group 2 and Group 3 using a t-test from a general linear model. If the Group 1 versus Group 3 test was significant at alpha=0.05 then the comparison of Group 1 versus Group 2 would be performed. Estimates of the adjusted mean for each treatment group were presented; adjusted mean differences along with the 95% confidence interval (CI) on the difference between groups were presented. The incidence of peri-operative bleeding, clot retention, transfusion, AUR, UTI, and urinary incontinence were summarized by treatment group. Differences in treatment group proportions and 95% CI on the differences in proportion of subjects in Group 1 versus those for Group 2 and Group 3 were calculated. The population of subjects which was statistically analysed was the 'Intent-to-Treat' population which consisted of all subjects randomised to study treatment and who received at least one dose of study treatment.			
<b>Study Population:</b> Main criteria for inclusion: Subjects with BPH aged $\geq 50$ years, scheduled for TURP in a period that allowed 28 – 32 days of study medication treatment, and with a prostate volume $\geq 30$ cc measured by transrectal ultrasound (TRUS) in the preceding 6 months. Main criteria for exclusion: history or evidence of prostate cancer or serum PSA $> 10$ ng/mL; history of prostate surgery or any other invasive BPH treatments; patients with Von Willebrand's disease, haemophilia or HIV/AIDS, history of bleeding disorders other than associated with chronic BPH; predicted to be taking NSAIDs (other than aspirin) within 10 days prior to TURP and/or predicted to need these agents during the study; predicted to be taking aspirin within 10 days prior to TURP and /or predicted to need aspirin within 5 days after TURP; concomitant use of phytotherapy for BPH, anabolic steroids, antiandrogens, 5-alpha-reductase inhibitor or alpha blockers; use of 5-alpha-reductase inhibitor within 12 months; use of alpha blockers within two weeks.			
<b>Number of Subjects</b>	<b>Pbo + Pbo</b>	<b>Pbo/Dut 0.5mg + Dut 0.5mg</b>	<b>Dut 0.5mg + Dut 0.5mg</b>
Planned, N	50	50	50

Randomised, N ^1 subject withdrew prior to dosing	70	72	72 ^
Completed, n (%)	64 (91%)	66 (92%)	67 (94%)
Total Number Subjects Withdrawn, n (%)	6 (9%)	6 (8%)	4 (6%)
Withdrawn due to Adverse Events, n (%)	2 (3%)	2 (3%)	2 (3%)
Withdrawn for other reasons, n (%)	4 (6%)	4 (6%)	2 (3%)
<b>Demographics</b>			
N (ITT)	70	72	71
Males : Females	70 : 0	72 : 0	71 : 0
Mean Age, years (SD)	65.8 (7.11)	67.4 (6.74)	66.8 (8.06)
White, n (%)	70 (100%)	72 (100%)	71 (100%)
<b>Primary Efficacy Results</b>	<b>Pbo + Pbo</b>	<b>Pbo/Dut 0.5mg + Dut 0.5mg</b>	<b>Dut 0.5mg + Dut 0.5mg</b>
<b>Total blood loss during TURP</b> (grams of haemoglobin per gram of resected prostate tissue)	n = 58	n = 61	n = 64
Adjusted Mean (SE)	2.55 (0.407)	2.15 (0.400)	2.55 (0.392)
Adjusted Mean Difference from Pbo	-	-0.4	0.0
95% Confidence Interval vs Pbo	-	-1.48 , 0.70	-1.08 , 1.08
p-value	-	0.48	1.00
<b>Secondary Efficacy Results</b>			
<b>Post-TURP Peri-Operative Bleeding</b>	n = 70	n = 72	n = 71
Number of subjects with event (%)	64 (91%)	67 (93%)	67 (94%)
Diff in proportion of subjects vs Pbo	-	0.016	0.029
95% CI on Diff in proportion of subjects vs Pbo	-	-0.072 , 0.104	-0.055 , 0.114
<b>Post-TURP Clot Retention</b>	n = 70	n = 72	n = 71
Number of subjects with event (%)	4 (6%)	8 (11%)	4 (6%)
Diff in proportion of subjects vs Pbo	-	0.054	-0.001
95% CI on Diff in proportion of subjects vs Pbo	-	-0.037 , 0.145	-0.077 , 0.076
<b>Post-TURP Blood Transfusions</b>	n = 70	n = 72	n = 71
Number of subjects with event (%)	2 (3%)	2 (3%)	1 (1%)
Diff in proportion of subjects vs Pbo	-	-0.001	-0.014
95% CI on Diff in proportion of subjects vs Pbo	-	-0.055 , 0.054	-0.062 , 0.033
<b>Post-TURP Acute Urinary Retention (AUR)</b>	n = 70	n = 72	n = 71
Number of subjects with event (%)	8 (11%)	12 (17%)	9 (13%)
Diff in proportion of subjects vs Pbo	-	0.052	0.012
95% CI on Diff in proportion of subjects vs Pbo	-	-0.061 , 0.166	-0.095 , 0.120
<b>Post-TURP Urinary Tract Infection (UTI)</b>	n = 70	n = 72	n = 71
Number of subjects with event (%)	14 (20%)	19 (26%)	22 (31%)
Diff in proportion of subjects vs Pbo	-	0.064	0.110
95% CI on Diff in proportion of subjects vs Pbo	-	-0.074 , 0.202	-0.033 , 0.253
<b>Post-TURP Urinary Incontinence</b>	n = 70	n = 72	n = 71
Number of subjects with event (%)	10 (14%)	10 (14%)	11 (15%)
Diff in proportion of subjects vs Pbo	-	-0.004	0.012
95% CI on Diff in proportion of subjects vs Pbo	-	-0.118 , 0.110	-0.105 , 0.130
<b>Safety results:</b>			
	<b>Pbo + Pbo</b>	<b>Pbo/Dut 0.5mg + Dut 0.5mg</b>	<b>Dut 0.5mg + Dut 0.5mg</b>
<b>Most Frequent Adverse Events(AEs) – On-Therapy</b>	n = 70	n = 72	n = 71
<b>Subjects with any AE(s), n(%)</b>	30 (43)	31 (43)	40 (56)
Abdominal pain	7 (10)	5 (7)	4 (6)
Nausea	4 (6)	4 (6)	1 (1)
Constipation	1 (1)	3 (4)	4 (6)
Diarrhoea	3 (4)	1 (1)	2 (3)
Abdominal pain upper	0	0	3 (4)
Gastrooesophageal reflux disease	1 (1)	0	0
Nasopharyngitis	0	1 (1)	4 (6)
Herpes zoster	1 (1)	1 (1)	0
Viral infection	1 (1)	0	1 (1)
Pharyngitis	1 (1)	0	0

Pneumonia	1 (1)	0	0
Purulent discharge	1 (1)	0	0
Subcutaneous abscess	1 (1)	0	0
Urinary tract infection	1 (1)	0	0
Pollakiuria	0	2 (3)	2 (3)
Bladder pain	0	3 (4)	0
Dysuria	0	1 (1)	2 (3)
Urethral pain	1 (1)	0	1 (1)
Urinary retention	1 (1)	0	1 (1)
Calculus bladder	1 (1)	0	0
Urethral meatus stenosis	1 (1)	0	0
Bradycardia	4 (6)	1 (1)	3 (4)
Bundle branch block right	1 (1)	1 (1)	0
Cardiac arrest	1 (1)	0	0
Ventricular hypertrophy	1 (1)	0	0
Post procedural pain	0	2 (3)	1 (1)
Procedural complication	2 (3)	1 (1)	0
Bladder perforation postoperative	1 (1)	0	0
Fall	1 (1)	0	0
Femur fracture	1 (1)	0	0
Contusion	1 (1)	0	0
Headache	3 (4)	3 (4)	3 (4)
Dizziness	1 (1)	2 (3)	0
Syncope	1 (1)	1 (1)	0
Paraesthesia	1 (1)	0	0
Paraesthesia oral	1 (1)	0	0
Prostate cancer	3 (4)	2 (3)	3 (4)
Pyrexia	1 (1)	1 (1)	2 (3)
Fatigue	1 (1)	0	2 (3)
Feeling abnormal	1 (1)	0	0
Sleep disorder	1 (1)	2 (3)	2 (3)
Insomnia	1 (1)	0	0
Prostate specific antigen increased	0	0	2 (3)
Blood sodium decreased	1 (1)	0	0
Heart rate increased	1 (1)	0	0
Arthralgia	1 (1)	0	0
Local swelling	1 (1)	0	0
Erectile dysfunction	1 (1)	2 (3)	0
Dyspnoea	0	2 (3)	0
Cough	1 (1)	0	0
Eczema	1 (1)	0	0
Pruritus	1 (1)	0	0
Anaemia	1 (1)	0	2 (3)
Hot flush	1 (1)	0	0
Vertigo	1 (1)	1 (1)	0
Decreased appetite	1 (1)	0	0
<b>Serious Adverse Events - On-Therapy n (%) [n considered by the investigator to be related to study medication]</b>	<b>Pbo + Pbo n = 70</b>	<b>Pbo/Dut 0.5mg + Dut 0.5mg n = 72</b>	<b>Dut 0.5mg + Dut 0.5mg n = 71</b>
<b>Subjects with non-fatal SAEs, n (%) [related]</b>	<b>5 (7) [1]</b>	<b>4 (6) [0]</b>	<b>3 (4) [0]</b>
Cardiac arrest	1 (1) [1]	0	0
Pyrexia	1 (1) [0]	0	0
Calculus bladder	1 (1) [0]	0	0
Prostate cancer	1 (1) [0]	1 (1) [0]	1 (1) [0]
Femur fracture	1 (1) [0]	0	0
Bile duct stone	0	1 (1) [0]	0
Non-Hodgkin's lymphoma	0	1 (1) [0]	0
Lower respiratory tract infection	0	1 (1) [0]	0

Post procedural complication	0	0	1 (1) [0]
Urosepsis	0	0	1 (1) [0]
Metastases to liver	0	0	1 (1) [0]
Metastases to bone	0	0	1 (1) [0]
Urinary retention	0	0	1 (1) [0]
<b>Subjects with fatal SAEs, n (%)</b>	0	0	0
<p><b>Conclusion:</b>  Despite the presence of dutasteride pharmacological activity (effects on testosterone and DHT) and pharmacokinetic evidence of drug exposure, there was no evidence that administration of dutasteride 0.5mg od for 2 or 4 weeks reduced blood loss during or after TURP surgery. There was also no indication of an improvement in the frequency of post-operative complications following dutasteride treatment for 4 or 6 weeks compared with placebo. Adverse events were reported in 30 (43%) of the placebo group, with abdominal pain, nausea and bradycardia being the most frequently reported. In the placebo + Dut/Dut group adverse events were reported in 31 (43%) of the subjects with abdominal pain and nausea being the most frequently reported. In the Dut+Dut group 40 (56%) subjects reported adverse events, the most frequently reported being abdominal pain, constipation and nasopharyngitis. Serious adverse events were reported in 5 (7%) subjects in the placebo group, 4 (6%) of the subjects in the placebo+Dut/Dut group and 3(4%) of the subjects in the Dut/Dut group, with no event being reported by more than one subject in a treatment group. No fatal serious adverse events were reported.</p>			
<p><b>Publications:</b>  No Publication</p>			

Date Updated: 8-Sep-2005