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<b>Study No.:</b> ARI20005
<b>Title:</b> A Multicentre, Double-Blind, Randomised, Placebo-Controlled, Parallel-Group, Dose-Finding Study of GI198745 in Subjects with Benign Prostatic Hyperplasia
<b>Rationale:</b> This phase II study was designed to assess the efficacy and safety of GI198745 (dutasteride-DUT) over a 24-week treatment period in subjects with benign prostatic hyperplasia (BPH). The aim of this study was to determine the recommended dose of dutasteride for the treatment of Japanese BPH subjects.
<b>Phase:</b> II
<b>Study Period:</b> 17 February 2003 – 23 August 2004
<b>Study Design:</b> Multicentre, double-blind, randomised, placebo-controlled, parallel-group
<b>Centres:</b> 25 centres in Japan
<b>Indication:</b> BPH
<b>Treatment:</b> Subjects received an oral dose of dutasteride 0.05mg, 0.5mg, 2.5mg, or placebo daily for 24 weeks followed by up to 16 weeks of post-dosing assessments.
<b>Objectives:</b> The primary objectives were: To assess the efficacy and safety of dutasteride 0.05mg, 0.5mg, 2.5mg, and placebo. To assess the pharmacodynamics of dutasteride 0.05mg, 0.5mg, 2.5mg, and placebo. To determine the recommended dose of dutasteride for the treatment of Japanese BPH subjects.
<b>Primary Outcome/Efficacy Variable:</b> The primary efficacy outcome was the percent change from baseline in prostate volume (PV) as measured by transrectal ultrasound (TRUS).
<b>Secondary Outcome/Efficacy Variable(s):</b> The secondary efficacy outcomes were the change from baseline in PV as measured by TRUS, the change from baseline in symptom scores (IPSS), the change from baseline in maximum urinary flow (Qmax) and the level of change of serum dihydrotestosterone (DHT) and testosterone.
<b>Statistical Methods:</b> In order to demonstrate a 14% difference between the dutasteride groups and the placebo group (assuming 23% as the standard deviation) at the 0.05 significance level with 90% power, 57 subjects per arm were required. On the basis of this estimation, the target sample size was set at 60 subjects per arm.
With regard to the percent change from baseline in PV, comparisons between the dutasteride groups and the placebo group were made using a general linear model taking into consideration log-transformed "PV at Week 24/PV at baseline" as the objective variable and treatment, concurrent use of tamsulosin HCl at baseline, log-transformed PV at baseline, and cluster of study centres as covariates. The changes from baseline in PV, IPSS and Qmax were also assessed using a general linear model. To address issues of multiplicity, comparisons between the dutasteride groups and the placebo group were made in a step-down manner through hierarchical dose hypotheses (producing a closed testing procedure) at the 0.05 level of significance.
The population of efficacy analysis was the Full Analysis Set (FAS) which consisted of all subjects who entered into the treatment phase excluding the following subjects: subjects who received no dose (capsule) of study medication and who have no post baseline PV measurement. The population of safety analysis was the Safety Population (SP) which was defined as all subjects who received at least one dose of study medication.
<b>Study Population:</b> Male subjects $\geq$ 50 years of age, with a diagnosis of BPH. PV $\geq$ 30cc as

measured by TRUS, IPSS $\geq$ 8, Qmax $\leq$ 15mL/sec with a minimum voided volume of $\geq$ 150mL. Subjects were excluded if they had a post void residual volume $\geq$ 250mL or a serum PSA > 4.0ng/mL and PSA free/total ratio <0.150.				
<b>Number of Subjects:</b>	<b>Placebo</b>	<b>0.05mg DUT</b>	<b>0.5mg DUT</b>	<b>2.5mg DUT</b>
Planned, N	60	60	60	60
Randomised, N	72	70	72	70
Completed, n (%)	58 (81)	65 (93)	62 (86)	59 (84)
Total Number Subjects Withdrawn, N (%)	14 (19)	5 (7)	10 (14)	11 (16)
Withdrawn due to Adverse Events n (%)	9 (13)	3 (4)	3 (4)	7 (10)
Withdrawn due to Lack of Efficacy n (%)	0	2 (3)	0	0
Withdrawn for other reasons n (%)	5 (7)	0	7 (10)	4 (6)
<b>Demographics</b>	<b>Placebo</b>	<b>0.05mg DUT</b>	<b>0.5mg DUT</b>	<b>2.5mg DUT</b>
N (FAS)	70	67	70	67
Females: Males	0 : 70	0 : 67	0 : 70	0 : 67
Mean Age, years (SD)	65.8 (7.69)	65.7 (8.14)	66.1 (6.85)	65.0 (6.94)
Race, n (%)				
Asian	70 (100)	67 (100)	70 (100)	67 (100)
<b>Primary Efficacy Results:</b> FAS and Last Observation Carried Forward (LOCF)				
<b>PV (cc)</b>	<b>Placebo</b>	<b>0.05mg DUT</b>	<b>0.5mg DUT</b>	<b>2.5mg DUT</b>
Mean (SD) baseline	45.7 (20.26)	44.4 (14.22)	45.4 (15.20)	41.0 (13.61)
Week 24	n=70	n=67	n=70	n=67
Adjusted mean percent change from baseline	-8.7	-15.5	-25.3	-25.6
Adjusted mean percent difference from placebo	-	-6.8	-16.6	-16.9
95% Confidence Interval	-	-12.5, -1.0	-22.0, -11.2	-22.3, -11.4
p-value	-	0.021	<0.001	<0.001
<b>Secondary Outcome Variable(s):</b> FAS and LOCF				
<b>PV (cc)</b>	<b>Placebo</b>	<b>0.05mg DUT</b>	<b>0.5mg DUT</b>	<b>2.5mg DUT</b>
Mean (SD) baseline	45.7 (20.26)	44.4 (14.22)	45.4 (15.20)	41.0 (13.61)
Week 24	n=70	n=67	n=70	n=67
Adjusted mean change from baseline	-2.9	-6.0	-10.2	-10.4
Adjusted mean difference from placebo	-	-3.1	-7.3	-7.5
95% Confidence Interval	-	-5.3, -0.8	-9.5, -5.1	-9.7, -5.2
p-value	-	0.007	<0.001	<0.001
<b>IPSS</b>	<b>Placebo</b>	<b>0.05mg DUT</b>	<b>0.5mg DUT</b>	<b>2.5mg DUT</b>
Mean (SD) baseline	15.9 (6.33)	17.0 (6.59)	14.6 (5.65)	15.6 (5.95)
Week 24	n=70	n=67	n=70	n=67
Adjusted mean change from baseline	-4.3	-5.9	-6.5	-7.0
Adjusted mean difference from placebo	-	-1.5	-2.2	-2.6
95% Confidence Interval	-	-3.3, 0.2	-3.9, -0.5	-4.4, -0.9
p-value	-	0.082	0.012	0.003

Qmax (mL/sec)	Placebo	0.05mg DUT	0.5mg DUT	2.5mg DUT
Mean (SD) baseline	11.3 (4.54)	10.9 (4.30)	11.5 (3.65)	11.3 (4.10)
Week 24	n=70	n=65	n=69	n=67
Adjusted mean change from baseline	1.4	2.6	2.8	3.0
Adjusted mean difference from placebo	-	1.2	1.5	1.7
95% Confidence Interval	-	-0.2, 2.7	0.0, 2.9	0.2, 3.1
p-value	-	0.098	0.047	0.026
DHT (pg/mL)	Placebo	0.05mg DUT	0.5mg DUT	2.5mg DUT
Mean (SD) baseline	469.0 (232.04)	468.1 (187.09)	517.4 (240.34)	528.3 (237.81)
Week 24	n=70	n=67	n=70	n=67
Adjusted mean percent change from baseline	1.4	-69.2	-89.7	-89.7
Adjusted mean percent difference from placebo	-	-70.6	-91.1	-91.1
95% Confidence Interval	-	-83.1, -58.2	-103.1, -79.1	-103.1, -79.1
p-value	-	<0.001	<0.001	<0.001
Testosterone (pg/mL)	Placebo	0.05mg DUT	0.5mg DUT	2.5mg DUT
Mean (SD) baseline	4887.3 (2102.00)	4833.6 (1767.83)	5189.0 (1913.23)	5225.8 (1696.46)
Week 24	n=70	n=67	n=70	n=67
Adjusted mean percent change from baseline	3.1	11.6	18.8	21.1
Adjusted mean percent difference from placebo	-	8.5	15.7	18.0
95% Confidence Interval	-	-1.0, 18.0	6.1, 25.4	8.1, 28.0
p-value	-	0.077	0.001	<0.001
<b>Safety Results:</b>				
An on therapy Adverse Event (AE) was defined as an AE with onset on or after the start date of study medication				
Most Frequent Adverse Events – On-Therapy	Placebo	0.05mg DUT	0.5mg DUT	2.5mg DUT
N (Safety Analysis Set)	72	70	71	69
Subjects with any AE(s), n(%)	56 (78)	55 (79)	46 (65)	53 (77)
Nasopharyngitis	13 (18)	19 (27)	18 (25)	16 (23)
Diarrhoea	7 (10)	11 (16)	6 (8)	10 (14)
Upper respiratory tract inflammation	3 (4)	6 (9)	6 (8)	5 (7)
Headache	4 (6)	6 (9)	2 (3)	3 (4)
Dizziness	6 (8)	4 (6)	4 (6)	5 (7)
Abdominal pain upper	0	2 (3)	6 (8)	0
Constipation	2(3)	1(1)	5(7)	3(4)
Erectile dysfunction	1(1)	2(3)	4(6)	4(6)
Malaise	3(4)	4(6)	2(3)	2(3)
Back pain	4(6)	2(3)	3(4)	1(1)
Dyspepsia	1(1)	4(6)	0	2(3)
Stomach discomfort	0	4(6)	2(3)	0

<b>Serious Adverse Events - On-Therapy</b>				
<b>n (%) [n considered by the investigator to be related to study medication]</b>				
An on therapy Serious Adverse Event (SAE) was defined as an SAE with onset on or after the start date of study medication				
	<b>Placebo</b>	<b>0.05mg DUT</b>	<b>0.5mg DUT</b>	<b>2.5mg DUT</b>
Subjects with non-fatal SAEs, n(%)	4 (6) [0]	2 (3) [0]	0	2 (3) [0]
Enterocolitis	1 (1) [0]	0	0	0
Intestinal obstruction	1 (1) [0]	0	0	0
Colonic polyp	1 (1) [0]	0	0	0
Gastric cancer	1 (1) [0]	0	0	0
Metastases to liver	1 (1) [0]	0	0	0
Joint ligament rupture	1 (1) [0]	0	0	0
Inguinal hernia	0	1 (1) [0]	0	0
Diabetes mellitus	0	1 (1) [0]	0	0
Oesophageal carcinoma recurrent	0	0	0	1 (1) [0]
Metastases to lymph nodes	0	0	0	1 (1) [0]
Large intestine carcinoma	0	0	0	1 (1) [0]
Subjects with fatal SAEs, n (%)	0	0	0	0
<b>Conclusion:</b>				
At Week 24, all three doses of dutasteride significantly reduced prostate volume compared with placebo with the most significant decreases being observed with dutasteride doses $\geq 0.5\text{mg}$ ( $p < 0.001$ ).				
On-therapy adverse events were reported in 78% of subjects in the placebo group, 79% of subjects in the dutasteride 0.05 mg group, 65% of subjects in the dutasteride 0.5mg group and 77% of subjects in the dutasteride 2.5 mg group. The most frequently reported adverse event in all treatment groups being nasopharyngitis.				
Serious Adverse Events (SAE) were reported by 6% of subjects receiving placebo; 3% of subjects receiving dutasteride 0.05mg and by 3% of subjects receiving dutasteride 2.5mg. No SAE was reported by more than one study subject and no SAE was considered by the investigator to be related to study medication.				
As a result of this study the dutasteride 0.5mg dose was selected for further evaluation in phase III studies in Japanese subjects.				
<b>Publications:</b> No publication				

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