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Study No.: ARI30016				
Title: A Long-term Extension Study of G198745 in Subjects with Benign Prostatic Hyperplasia				
Rationale: The aim of this study was to assess the safety of G198745 (dutasteride-DUT) in subjects with benign prostatic hyperplasia (BPH) over a 52-week treatment period.				
Phase: II				
Study Period: 12 August 2003 – 18 February 2005				
Study Design: Extension study [a 28-week extension treatment in the subjects entered into the 24-week dose finding study (ARI20005: multicentre, double-blind, randomised, placebo-controlled, parallel-group)]				
Centres: 22 centres in Japan				
Indication: BPH				
Treatment: Upon completion of 24 weeks of dutasteride 0.05 mg, 0.5 mg, 2.5 mg, or placebo therapy in study ARI20005, subjects were enrolled into an extension phase and were continued on the same therapy once daily for up to further 28 weeks, followed by up to 16 weeks of post-dosing assessments.				
Objectives: The primary objective was to assess the safety of dutasteride 0.05mg, 0.5mg, 2.5mg, and placebo once daily for 52 weeks.				
Primary Outcome/Efficacy Variable: The primary outcome was safety: adverse events, laboratory test values (hematology, serum chemistry, electrolyte, and urinalysis), prostate specific antigen (PSA), vital signs (blood pressure, pulse rate), and post-void residual volume.				
Secondary Outcome/Efficacy Variable(s): The percent change and the change from baseline in prostate volume (PV) as measured by transrectal ultrasound (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.				
Statistical Methods: The target sample size for ARI20005 was 60 subjects per arm. Assuming that 50% of the subjects in ARI20005 would continue and complete this study, the sample size was expected to be 30 subjects per arm.				
For safety variables, summary tables and listings were generated. Efficacy assessments and the change from baseline (Screening or Week 0 of ARI20005) at each visit were summarized. No statistical comparison was performed.				
The population for safety analysis was the Safety Population (SP) which was defined as all subjects who received at least one dose of study medication in this study. 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 had no assessment for efficacy variables (PV, IPSS, and Qmax).				
Study Population: Received the study treatment for at least 20 weeks in the study ARI20005, investigator/subinvestigator had confirmed the tolerability and had judged as appropriate to participate continuously in further 28 weeks treatment, given a written informed consent				
Number of Subjects:	Placebo	0.05mg DUT	0.5mg DUT	2.5mg DUT
Planned, N	30	30	30	30
Started extension study, N	31	38	49	43
Completed, n (%)	30 (97)	37 (97)	47 (96)	38 (88)
Total Number Subjects Withdrawn, N (%)	1 (3)	1 (3)	2 (4)	5 (12)
Withdrawn due to Adverse Events n (%)	1 (3)	0	0	3 (7)
Withdrawn due to Lack of Efficacy n (%)	0	0	0	0
Withdrawn for other reasons n (%)	0	1 (3)	2 (4)	2 (5)
Demographics	Placebo	0.05mg DUT	0.5mg DUT	2.5mg DUT
N (SP)	31	38	49	43
Females: Males	0 : 31	0 : 38	0 : 49	0 : 43
Mean Age, years (SD)	65.9 (7.17)	65.3 (8.52)	66.3 (6.93)	66.3 (6.60)
Asian, n (%)	31 (100)	38 (100)	49 (100)	43 (100)

Primary Efficacy Results: The primary outcome for this study was safety. See Adverse Events reported below.				
Secondary Outcome Variable(s):				
FAS				
PV (cc)	Placebo	0.05mg DUT	0.5mg DUT	2.5mg DUT
Mean (SD) baseline	43.9 (13.42)	42.9 (13.83)	47.4 (16.96)	39.4 (9.02)
Week 24	n=31	n=38	n=49	n=43
Adjusted mean percent change from baseline	-16.7	-21.5	-27.9	-28.2
Adjusted mean change from baseline	-6.9	-9.2	-11.5	-11.8
Week 52	n=31	n=37	n=48	n=38
Adjusted mean percent change from baseline	-20.0	-24.8	-34.6	-36.0
Adjusted mean change from baseline	-8.2	-10.5	-14.0	-14.9
IPSS	Placebo	0.05mg DUT	0.5mg DUT	2.5mg DUT
Mean (SD) baseline	15.9 (6.28)	16.7 (6.49)	14.8 (5.84)	15.0 (6.13)
Week 24	n=31	n=38	n=49	n=43
Adjusted mean change from baseline	-6.2	-6.6	-6.7	-7.6
Week 52	n=31	n=37	n=48	n=38
Adjusted mean change from baseline	-5.6	-7.0	-6.9	-8.6
Qmax (mL/sec)	Placebo	0.05mg DUT	0.5mg DUT	2.5mg DUT
Mean (SD) baseline	11.8 (5.10)	11.4 (4.49)	11.3 (3.43)	11.7 (4.03)
Week 24	n=30	n=37	n=49	n=40
Adjusted mean change from baseline	2.3	2.7	3.0	3.2
Week 52	n=30	n=37	n=48	n=35
Adjusted mean change from baseline	2.4	2.2	2.2	3.1
DHT (pg/mL)	Placebo	0.05mg DUT	0.5mg DUT	2.5mg DUT
Mean (SD) baseline	408.1 (199.92)	487.9 (191.21)	521.5 (233.68)	523.1 (234.74)
Week 24	n=30	n=38	n=49	n=43
Adjusted mean percent change from baseline	-12.9	-70.8	-90.3	-90.7
Week 52	n=31	n=37	n=48	n=38
Adjusted mean percent change from baseline	-12.5	-69.2	-89.6	-90.5
Testosterone (pg/mL)	Placebo	0.05mg DUT	0.5mg DUT	2.5mg DUT
Mean (SD) baseline	4408.1 (1249.47)	4800.8 (1750.38)	5246.9 (1947.47)	5014.0 (1588.99)
Week 24	n=30	N=38	n=49	n=43
Adjusted mean percent change from baseline	1.1	16.2	17.8	22.4
Week 52	n=31	n=37	n=48	n=38
Adjusted mean percent change from baseline	-5.2	9.6	18.1	14.7
Safety Results:				
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 (SP)	31	38	49	43
Subjects with any AE(s), n(%)	25 (81)	34 (89)	44 (90)	37 (86)
Nasopharyngitis	10 (32)	13 (34)	25 (51)	21 (49)
Diarrhoea	5 (16)	7 (18)	5 (10)	3 (7)
Upper respiratory tract inflammation	1 (3)	5 (13)	8 (16)	6 (14)
Eczema	2 (6)	5 (13)	3 (6)	4 (9)
Arthralgia	4 (13)	2 (5)	2 (4)	1 (2)
Back pain	3 (10)	4 (11)	5 (10)	3 (7)
Headache	2 (6)	4 (11)	3 (6)	3 (7)
Dizziness	3 (10)	1 (3)	5 (10)	3 (7)
Pyrexia	3 (10)	2 (5)	0	3 (7)
Erectile dysfunction	0	1 (3)	2 (4)	4 (9)
Constipation	1 (3)	0	3 (6)	3 (7)
Thirst	1 (3)	1 (3)	0	3 (7)

Serious Adverse Events - On-Therapy				
n (%) [n considered by the investigator to be related to study medication]				
An on therapy Serious Adverse Event (SAE) was defined as an SAE with onset on or after the start date of study medication				
	Placebo	0.05mg DUT	0.5mg DUT	2.5mg DUT
Subjects with non-fatal SAEs, n(%)	4 (13) [0]	0	2 (4) [0]	1 (2) [0]
Gastric cancer	0	0	1 (2) [0]	1 (2) [0]
Metastases to liver	0	0	1 (2) [0]	0
Nasal polyps	0	0	1 (2) [0]	0
Inguinal hernia	1 (3) [0]	0	0	0
Gastric ulcer haemorrhage	1 (3) [0]	0	0	0
Prostatitis	1 (3) [0]	0	0	0
Joint ligament rupture	1 (3) [0]	0	0	0
Subjects with fatal SAEs, n (%)	0	0	0	0

Conclusion:

The primary outcome of this study was an assessment of safety. Summary tables and listings were generated, however, no statistical comparisons were undertaken.

In the placebo group 25 subjects reported at least one adverse event with nasopharyngitis being the most frequently reported event. In the 0.05 mg, 0.5 mg and 2.5 mg dutasteride groups, 34, 44 and 37 subjects, respectively, reported at least one adverse event with nasopharyngitis being the most frequently reported event in all these groups.

Four non-fatal serious adverse events were reported in the placebo group, these were an inguinal hernia, haemorrhage of a gastric ulcer, prostatitis and a joint ligament rupture. Two subjects reported three non-fatal serious adverse events in the 0.5 mg dutasteride group, these were gastric cancer with associated liver cancer (metastatic) and nasal polyps. One subject in the 2.5 mg dutasteride group had a non-fatal serious adverse event of gastric cancer. There were no fatalities reported in any treatment group.

Publications:

No publication

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