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Study No.: ARI105326
Title: Clinical Evaluation of dutasteride in Benign Prostatic Hyperplasia: A Randomized, Double-Blind, Placebo-Controlled, Parallel Group Comparative Study of GI198745 (dutasteride) in Subjects with Benign Prostatic Hyperplasia.
Rationale: This study was designed to assess the efficacy and safety of dutasteride 0.5 mg administered once daily over 52 weeks in Japanese subjects with benign prostatic hyperplasia (BPH).
Phase: III
Study Period: 17 February 2006 to 6 December 2007
Study Design: This study was a multicentre, stratified randomized, double-blind, placebo-controlled, parallel group study to assess the efficacy and safety of dutasteride 0.5 mg administered once daily for 52 weeks. The study consisted of a screening phase (up to 4 weeks), a treatment phase (52 weeks), and a follow-up phase (16 weeks). The overall study duration was 68 to 72 weeks.
Centres: 26 centres in Japan.
Indication: BPH
Treatment: After the screening phase (up to 4 weeks), subject orally received dutasteride (0.5 mg capsule) or placebo once daily for 52 weeks followed by up to 16 weeks of post-dosing assessments.
Objectives: The primary objective was to assess the efficacy, as determined by International Prostate Symptom Score (IPSS), of dutasteride 0.5 mg administered once daily for 52 weeks to BPH subjects compared with placebo.
Primary Outcome/Efficacy Variable: The primary efficacy outcome was change from baseline in IPSS.
Secondary Outcome/Efficacy Variable(s): The secondary efficacy outcomes were percent change from baseline in prostate volume as measured by transrectal ultrasound (TRUS), proportion of subjects with IPSS improvement from baseline of ≥ 2 -points, ≥ 3 -points, ≥ 4 -points, ≥ 5 -points, ≥ 6 -points, $\geq 20\%$, $\geq 25\%$, $\geq 30\%$, $\geq 40\%$, $\geq 50\%$ and $\geq 75\%$, change from baseline in maximum flow rate (Qmax), proportion of subjects with Qmax improvement from baseline of ≥ 1 mL/sec, ≥ 2 mL/sec, ≥ 2.5 mL/sec, ≥ 3 mL/sec, ≥ 4 mL/sec, ≥ 5 mL/sec, ≥ 10 mL/sec and $\geq 30\%$.
Statistical Methods: In order to demonstrate a 2.0 points difference for the mean change from baseline in IPSS at Week 52 between the dutasteride group and the placebo group (assuming 6.0 points as the standard deviation) at the 0.05 significance level with 90% and 80% power, 190 subjects and 142 subjects per arm were required, respectively. Assuming 2.2 points difference between the dutasteride group and the placebo group (6.0 points as the standard deviation), the sample sizes to demonstrate the superiority of dutasteride over placebo at the 0.05 significance level with the power of 90% and 80% were estimated at 157 subjects and 117 subjects per arm, respectively. Based on these estimates, the target sample size was set at 150 subjects per arm, 300 subjects in total, as the Full Analysis Set (FAS).
The primary efficacy analysis was performed on the FAS which consisted of all randomized subjects excluding those who received no dose of the investigational product and who had no baseline or post baseline IPSS data. The population of safety analysis was all subjects who received at least one dose of the investigational product.
For the change from baseline in IPSS and Qmax at each scheduled post-baseline assessment, comparisons between the dutasteride group and the placebo group were performed using a general linear model with effects for treatment, baseline value, baseline tamsulosin HCl use (No/Yes), and cluster at the 0.05 level of significance. Adjusted mean estimates and adjusted

mean differences and 95% confidence intervals were presented. The percent change from baseline in prostate volume was similarly analysed except that treatment groups were compared using log-transformed analysis. For the proportion of subjects with IPSS and Qmax improvement were compared at each scheduled visit between the treatment groups using the Mantel-Haenszel test controlling for cluster and tamsulosin HCl use(No/Yes) at alpha=0.05.

Study Population: Male aged ≥ 50 years with a diagnosis of BPH, prostate volume ≥ 30 cc as measured by transrectal ultrasound, an IPSS ≥ 8 points, and a Qmax ≤ 15 mL/sec with a minimum voided volume of ≥ 150 mL at screening were included. Subjects who were receiving tamsulosin HCl continuously for at least 4 weeks just before the study were required to remain on their tamsulosin dose during study treatment without any change to regimen. In addition, subjects who were not receiving tamsulosin HCL and not likely to require tamsulosin during the study were also eligible. Subjects with a history of prostate cancer or with a screening prostate specific antigen >10 ng/mL were excluded.

	Placebo	Dutasteride
Number of Subjects:		
Planned, N	150	150
Randomised, N	185	193
Completed, n (%)	160(86)	163(84)
Total Number Subjects Withdrawn, N (%)	25(14)	30(16)
Withdrawn due to Adverse Events n (%)	9(5)	16(8)
Withdrawn due to Lack of Efficacy n (%)	5(3)	3(2)
Withdrawn for other reasons n (%)	11(6)	11(6)
Demographics	Placebo	Dutasteride
N (FAS)	N=181	N=184
Females: Males	0:181	0:184
Mean Age, years (SD)	66.9 (6.76)	68.0 (6.07)
Race-Asian - Japanese, n (%)	181 (100)	184 (100)
Primary Efficacy Results:		
	Placebo	Dutasteride
IPSS (point) change from baseline	N=181	N=184
Mean (SD) Baseline	16.0 (6.01)	16.6 (6.56)
Week 52 FAS-LOCF	N=181	N=184
Adjusted mean change from baseline	-3.7	-5.3
Adjusted mean difference from placebo	-	-1.6
95% Confidence Interval	-	-2.7, -0.5
p-value	-	0.003
Secondary Outcome Variable(s):		
Prostate volume (cc) percent change from baseline	Placebo	Dutasteride
FAS	N=181	N=184
Mean (SD) Baseline	49.4(17.16)	50.2(19.79)
Week 52 FAS-LOCF	N=180	N=183
Adjusted mean percent change from baseline	-10.8	-33.8
Adjusted mean difference from placebo	-	-22.9
95% Confidence Interval	-	-26.9, -18.9
Proportion of subjects with IPSS improvement from baseline	Placebo	Dutasteride
Week 52 FAS-LOCF	N=181	N=184
Improvement category	n (%)	n (%)
≥ 2 -points	113 (62)	139 (76)
≥ 3 -points	102 (56)	128 (70)
≥ 4 -points	82 (45)	115 (63)
≥ 5 -points	75 (41)	94 (51)

≥6-points	62 (34)	82 (45)
≥20%	99 (55)	122 (66)
≥25%	84 (46)	114 (62)
≥30%	71 (39)	106 (58)
≥40%	54 (30)	86 (47)
≥50%	39 (22)	67 (36)
≥75%	7 (4)	17 (9)
Qmax (mL/sec) change from baseline	Placebo	Dutasteride
FAS	N=181	N=184
Mean (SD) Baseline	11.2(4.41)	11.2(4.13)
Week 52 FAS-LOCF	N=179	N=183
Adjusted mean change from baseline	0.7	2.2
Adjusted mean difference from placebo	-	1.6
95% Confidence Interval	-	0.7, 2.5
Proportion of subjects with Qmax improvement from baseline	Placebo	Dutasteride
Week 52 FAS-LOCF	N=179	N=183
Improvement category	n (%)	n (%)
≥1 mL/sec	79 (44)	103 (56)
≥2 mL/sec	56 (31)	86 (47)
≥2.5 mL/sec	45 (25)	73 (40)
≥3 mL/sec	44 (25)	70 (38)
≥4 mL/sec	29 (16)	53 (29)
≥5 mL/sec	22 (12)	44 (24)
≥10 mL/sec	4 (2)	11 (6)
≥30%	41 (23)	63 (34)
SafetyResults:		
Most Frequent Adverse Events – On-Therapy , n (%)	Placebo N=184	Dutasteride N=193
Subjects with any AE (%)	166(90)	170(88)
Nasopharyngitis	78(42)	80(41)
Diarrhoea	16(9)	19(10)
Upper respiratory tract inflammation	14(8)	19(10)
Eczema	8(4)	14(7)
Constipation	12(7)	13(7)
Back pain	14(8)	12(6)
Arthralgia	6(3)	10(5)
Gastritis	4(2)	10(5)
Abdominal pain upper	3(2)	8(4)
Dental caries	7 (4)	8(4)
Dizziness	5(3)	8(4)
Headache	11(6)	8(4)
Stomach discomfort	6(3)	8(4)
Abdominal pain	8(4)	6(3)
Pharyngitis	7(4)	6(3)
Dyspepsia	8(4)	3(2)
Rhinitis	7(4)	3(2)
Prostatitis	7(4)	2(1)
Serious Adverse Events - On-Therapyn (%) [n considered by the investigator to be related to study medication]		

	Placebo N=184	Dutasteride N=193
	n (%) [related]	n (%) [related]
Subjects with any AE(s), n (%)	8 (4)[0]	20 (10)[0]
Colonic polyp	0	3(2)[0]
Cerebral infarction	2(1)[0]	1(<1)[0]
Inguinal hernia	2(1)[0]	0
Gastric cancer	1(<1)[0]	1(<1)[0]
Enterocolitis	0	1(<1)[0]
Haemorrhoids	1(<1)[0]	0
Intestinal obstruction	0	1(<1)[0]
Bladder cancer	1(<1)[0]	0
Lymph node cancer metastatic	0	1(<1)[0]
Meningioma	0	1(<1)[0]
Pancreatic carcinoma	0	1(<1)[0]
Dementia Alzheimer's type	0	1(<1)[0]
Thrombotic stroke	0	1(<1)[0]
Intervertebral disc protrusion	0	1(<1)[0]
Lumbar spinal stenosis	1(<1)[0]	0
Synovitis	0	1(<1)[0]
Acute myocardial infarction	0	1(<1)[0]
Coronary artery stenosis	1(<1)[0]	0
Pneumonia	0	1(<1)[0]
Urinary tract infection	0	1(<1)[0]
Aortic dissection	0	1(<1)[0]
Microscopic polyangiitis	1(<1)[0]	0
Macular degeneration	0	1(<1)[0]
Cholangitis	0	1(<1)[0]
Subjects with fatal SAEs, n (%)	n (%) [related]	n (%) [related]
Pancreatic carcinoma	0	1(<1)[0]

Conclusion:

At Week 52, dutasteride statistically reduced IPSS compared with placebo ($p=0.003$). In addition, dutasteride statistically improved prostate volume and Qmax at Week 52 compared with placebo. On-therapy adverse events were reported in 90% of subjects in the placebo group and 88% of subjects in the dutasteride group. Serious AEs were reported in 4% of subjects in the placebo group and 10% of subjects in the dutasteride group; with the exception of colonic polyp (3 subjects), no serious AE was reported in more than one subject in the dutasteride group. No serious AE was considered by the investigator to be related to study medication.

Publications: No publication

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