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Study No.: ARI 40013 (Prostowell).
Title: GI 198745 in the Treatment of Symptomatic Benign Prostatic Hyperplasia (BPH): An Open, Multicentre, Phase IIIb Study.
Rationale: To evaluate the efficacy and safety of dutasteride (GI 198745) under everyday routine conditions in the clinical practice in a large cohort of subjects suffering from symptomatic BPH.
Phase: IIIb
Study Period: 07 Mar 2003 - 02 Mar 2004.
Study Design: Single-country, open-label, multicentre study over a treatment period of at least 36 weeks (maximum duration of 72 weeks) with 2 treatment regimens based on the baseline disease severity as measured by the Quality of Life (QoL) question of the International Prostate Symptom Score (IPSS).
Centres: 477 centres in Germany.
Indication: Symptomatic BPH.
Treatment: Subjects with an IPSS-QoL score of <4 score points at baseline: dutasteride (DUT) 0.5mg once daily (od); Subjects with an IPSS-QoL score of ≥4 score points at baseline: DUT 0.5mg od plus tamsulosin (TAM) 0.4mg od for the first 24 weeks of treatment, followed by DUT 0.5mg od as monotherapy from Week 24 onwards. Treatment duration was 36-72 weeks dependent on the time point of inclusion.
Objectives: To obtain further information about the efficacy and safety of DUT under everyday routine conditions in the clinical practice in a large cohort of subjects suffering from symptomatic BPH.
Primary Efficacy Variables: The primary efficacy variables (no sample size estimation) were the IPSS and the BPH Impact Index (BII).
Secondary Efficacy Variables: The secondary efficacy variables were IPSS-QoL, prostate volume (PV), post-void residual urine volume (PVR), and the incidences of acute urinary retention (AUR), and prostate surgery.
Statistical Methods: No statistical sample size estimation was performed, since there were no statistical hypotheses generated and no confirmatory tests to be performed. The planned sample size of 3,000 subjects was based on considerations to obtain comprehensive information about the safety of DUT in a broad subject population, in particular about possible rare side effects. It was expected that the sample size of approx. 3,000 subjects should allow the identification of rare (ie, occurring with an incidence of 0.1%) adverse events with a probability of 90%. Demographic data were analysed by providing common sample statistics (ie, n, mean, standard deviation, median, ranges, and 25%/75%-quartiles). The course of the mean IPSS and BII total scores was descriptively analysed with sample statistics using both "last observation carried forward" (LOCF) values until Week 36 and actually observed cases (ie, without LOCF). The explorative statistical analyses were restricted to pre-post comparisons within groups by giving the 95% confidence intervals (CIs) for the respective changes from baseline. The primary analysis was done in the Intent To Treat (ITT) population, which included subjects who were exposed to study medication at least once and did not show critical protocol violations. Between-group comparisons were not performed. The secondary efficacy variables (IPSS-QoL, PV, and PVR) were analysed in the same way the primary efficacy variables were analysed, but last assessment values were used for the pre-post analyses. An additional correlation analysis (Spearman) was performed in order to evaluate the associations between IPSS, BII, PVR, and PV. A further post hoc analysis was done by study periods in order to evaluate the number of subjects with a specifically defined improvement/deterioration based on the IPSS changes during the respective study period (worsening in IPSS: increase by >2 score points; composite deterioration: worsening of IPSS and/or introduction of a new urological drug and/or AUR and/or prostate surgery and/or adverse events related to BPH). Particular attention was drawn on subjects of the DUT/TAM group who had ceased treatment with TAM from Week 24 onwards according to protocol (Full Analysis Set [FAS]-4 population: ITT-subjects with DUT monotherapy from Week 24 onwards). The safety analysis was performed in the safety population (ie, subjects exposed at least once to study medication). Adverse events (AEs) were coded by Medical Dictionary for Regulatory Activities (MedDRA). The AE tables summarised the incidence and percentage of AEs/serious AEs (SAEs) by body system and preferred term. Additionally, an ad hoc classification of AEs of special interest was performed generating the following classes: erectile dysfunction, decrease in libido, ejaculation disorders, breast disorders, pain and other disorders of the reproductive system (excluding infections), BPH, ischuria (urinary retention), resections of prostate, and cancer of prostate, pancreas, or breast.
Study Population: Men with symptomatic BPH were to be included. Essential criteria for inclusion were: Aged >50 years, confirmed diagnosis of BPH, IPSS of >7 score points at baseline, prostatic enlargement of ≥30mL, prostate-

specific antigen within a range of >1.5ng/mL and <10.0ng/mL, and PVR of <200 mL. Among others, subjects with past or present prostatic carcinoma, irritable bladder, contraction of the bladder neck, urethral constriction, urinary tract infections, bladder carcinoma, acute/chronic prostatitis, neurogenic voiding dysfunction, or previous treatment with 5-alpha-reductase inhibitors were excluded.

Number of Subjects:	DUT	DUT / TAM
Planned, N	1,000	2,000
Entered, N	811	1,574
Completed, n (%)	713 (87.9)	1,291 (82.0)
Total Number Subjects Withdrawn, n (%)	98 (12.1)	283 (18.0)
Withdrawn due to Adverse Events n (%)	59 (7.3)	173 (11.0)
Withdrawn due to Lack of Efficacy n (%)	13 (1.6)	58 (3.7)
Withdrawn for other reasons n (%)	26 (3.2)	52 (3.3)
Demographics	DUT	DUT / TAM
N (ITT)	810	1,573
N (FAS-4)	725	1,340
Mean Age, years, ITT population (±SD)	67.1 ± 7.2	67.0 ± 7.3
Mean Weight, kg, ITT population (±SD)	82.0 ± 10.6	83.0 ± 11.7
Inherently, all study participants were men. The race was not analysed.		
Primary Efficacy Results (ITT population)		
Total IPSS score (score points) (LOCF)	DUT	DUT / TAM
Mean baseline value (SD)	14.3 (5.1)	18.7 (5.7)
Mean value at Week 36 (SD)	9.2 (5.1)	11.6 (6.8)
Mean change from baseline (SD)	-5.1 (5.3)	-7.1 (7.2)
95% CI for the mean change from baseline	[-5.4; -4.7]	[-7.4; -6.7]
BPH Impact Index (score points) (LOCF)	DUT	DUT / TAM
Mean baseline value (SD)	5.5 (2.6)	7.7 (2.7)
Mean value at Week 36 (SD)	3.2 (2.6)	4.2 (3.1)
Mean change from baseline (SD)	-2.3 (2.8)	-3.5 (3.3)
95% CI for the mean change from baseline	[-2.5; -2.1]	[-3.6; -3.3]
Secondary Efficacy Results (ITT population)		
IPSS-QoL question (score points)	DUT	DUT / TAM
Mean baseline value (SD)	2.8 (0.8)	4.3 (0.8)
Mean value at last visit assessment (SD)	1.8 (1.0)	2.1 (1.2)
Mean change from baseline (SD)	-0.9 (1.2)	-2.2 (1.4)
PV (mL)	DUT	DUT / TAM
Mean baseline value (SD)	57.4 (21.1)	60.3 (25.8)
Mean value at last visit assessment (SD)	42.5 (18.4)	45.3 (26.2)
Mean % change from baseline (SD)	-25.4 (20.7)	-25.5 (21.3)
Mean absolute change from baseline (SD)	-15.1 (13.9)	-15.8 (16.6)
95% CI for the mean absolute change	[-16.2; -14.1]	[-16.7; -14.9]
PVR (mL)	DUT	DUT / TAM
Mean baseline value (SD)	48.5 (42.1)	58.2 (47.7)
Mean value at last visit assessment (SD)	26.9 (41.7)	35.6 (51.8)
Mean change from baseline (SD)	-21.3 (47.9)	-21.7 (54.8)
95% CI for the mean change	[-24.9; -17.8]	[-24.7; -18.8]
Subjects with AUR / prostate surgery during study (ITT)		
Subjects with AUR during the treatment phase, n/N (%)	DUT	DUT / TAM
Subjects with AUR during the treatment phase, n/N (%)	4/811 (0.5)	26/1574 (1.7)
Subjects with prostate surgery during the treatment phase, n/N (%)	DUT	DUT / TAM
Subjects with prostate surgery during the treatment phase, n/N (%)	1/811 (0.1)	1/1574 (0.1)
Frequency of deterioration from Week 24 to last visit assessment after discontinuation of TAM at Week 24 (FAS-4) (with LOCF up to Week 36)		
	DUT	DUT / TAM
Subj. with worsening of IPSS value compared to Week 24, n (%)	108 (14.9)	365 (27.2)
Subj. with composite deterioration compared to Week 24, n (%)	113 (15.6)	406 (30.3)
Safety Results: Safety was analysed in the safety population by primarily focussing on events which occurred on-therapy during the study treatment period (ie, treatment-emergent adverse events; TEAEs).		

	DUT N=811	DUT / TAM N=1,574
Most Frequent Adverse Events – On-Therapy	n (%)	n (%)
Subjects with any AEs, n (%)	303 (37.4)	613 (39.0)
Erectile dysfunction	38 (4.7)	68 (4.3)
Urinary tract infection	19 (2.3)	37 (2.4)
Dysuria	6 (0.7)	40 (2.5)
Vertigo	8 (1.0)	37 (2.4)
Headache	11 (1.4)	25 (1.6)
Urinary retention	5 (0.6)	29 (1.8)
Hypertension	10 (1.2)	22 (1.4)
Prostatitis	7 (0.9)	24 (1.5)
Retrograde ejaculation	4 (0.5)	27 (1.7)
Influenza	10 (1.2)	18 (1.1)
Loss of libido	8 (1.0)	20 (1.3)
Fatigue	10 (1.2)	15 (1.0)
Diarrhoea	8 (1.0)	13 (0.8)
Gastritis	8 (1.0)	7 (0.4)
Serious Adverse Events, n (%) [n considered by the investigator to be related to study medication]		
Subjects with any non-fatal SAEs, n (%) [related]	48 (5.9) [3]	93 (5.9) [5] ^a
Subjects with non-fatal SAEs - On-Therapy, n (%) [related]	40 (4.9) [2]	78 (5.0) [4] ^b
Anal abscess	0	1 (0.1) [0]
Acute coronary syndrome	1 (0.1) [0]	0
Acute myocardial infarction	0	2 (0.1) [1]
Alcohol poisoning	0	1 (0.1) [0]
Angina pectoris	1 (0.1) [0]	5 (0.3) [0]
Angiopathy	0	1 (0.1) [0]
Aortic valve incompetence	0	1 (0.1) [0]
Appendicitis	0	1 (0.1) [0]
Arrhythmia	1 (0.1) [0]	1 (0.1) [0]
Arthropathy	0	1 (0.1) [0]
Atrial fibrillation	4 (0.5) [0]	2 (0.1) [1] ^b
Benign gastric neoplasm	0	1 (0.1) [0]
Biliary neoplasm	1 (0.1) [0]	0
Bladder cancer	1 (0.1) [0]	1 (0.1) [0]
Bladder neoplasm	1 (0.1) [0]	0
Blood pressure increased	1 (0.1) [1]	0
Bone pain	1 (0.1) [0]	0
Bradycardia	1 (0.1) [0]	0
Brain stem infarction	0	1 (0.1) [0]
Bronchial carcinoma	1 (0.1) [0]	0
Bronchitis chronic	0	1 (0.1) [0]
Calculus bladder	0	1 (0.1) [0]
Calculus ureteric	0	4 (0.3) [0]
Cardiac disorder	1 (0.1) [0]	0
Cardiac failure	1 (0.1) [0]	2 (0.1) [0]
Carotid artery stenosis	1 (0.1) [0]	0
Cerebral haemorrhage	1 (0.1) [0]	0
Cerebrovascular accident	1 (0.1) [0]	0
Cholecystitis	0	1 (0.1) [0]
Cholecystitis acute	0	1 (0.1) [0]
Cholelithiasis	0	1 (0.1) [0]
Chondrocalcinosis pyrophosphate	0	1 (0.1) [0]
Circulatory collapse	0	1 (0.1) [0]

Colon cancer	1 (0.1) [0]	0
Colonic polyp	0	1 (0.1) [0]
Coronary artery atherosclerosis	0	1 (0.1) [0]
Coronary artery disease	2 (0.3) [0]	2 (0.1) [0]
Cough	1 (0.1) [0]	0
Cystitis	0	1 (0.1) [0]
Deep vein thrombosis	0	1 (0.1) [0]
Diabetes mellitus	1 (0.1) [0]	1 (0.1) [0]
Diabetic gangrene	0	1 (0.1) [0]
Diverticulitis	1 (0.1) [0]	0
Duodenal ulcer	0	1 (0.1) [0]
Epididymitis	0	1 (0.1) [0]
Eye haemorrhage	1 (0.1) [0]	0
Femoral artery occlusion	0	1 (0.1) [0]
Fibula fracture	0	1 (0.1) [0]
Foot fracture	1 (0.1) [0]	1 (0.1) [0]
Gastric cancer	1 (0.1) [0]	0
Gastric haemorrhage	0	1 (0.1) [0]
Gastroduodenal ulcer	1 (0.1) [0]	0
Haemarthrosis	1 (0.1) [0]	0
Haematoma	1 (0.1) [0]	0
Hand fracture	0	1 (0.1) [0]
Humerus fracture	0	2 (0.1) [0]
Hyperbilirubinaemia	0	1 (0.1) [1]
Hypertension	0	2 (0.1) [0]
Hypertensive crisis	1 (0.1) [0]	3 (0.2) [0]
Ileus	0	1 (0.1) [0]
Inguinal hernia	1 (0.1) [0]	2 (0.1) [0]
Intervertebral disc disorder	0	1 (0.1) [0]
Intervertebral disc protrusion	0	1 (0.1) [0]
Intestinal obstruction	0	1 (0.1) [0]
Intracardiac thrombus	0	1 (0.1) [0]
Irritable bowel syndrome	1 (0.1) [0]	0
Jaw fracture	0	1 (0.1) [0]
Leg amputation	0	1 (0.1) [0]
Ligament injury	0	1 (0.1) [0]
Lipoma	1 (0.1) [0]	0
Liver abscess	0	1 (0.1) [0]
Lower limb fracture	0	1 (0.1) [0]
Mouth ulceration	1 (0.1) [0]	0
Myocardial infarction	0	4 (0.3) [0]
Naevus cell naevus	1 (0.1) [0]	0
Nausea	0	1 (0.1) [0]
Neoplasm skin	0	1 (0.1) [0]
Nocturia	0	1 (0.1) [0]
Oedema peripheral	0	1 (0.1) [0]
Pancreatitis	0	2 (0.1) [0]
Paraproteinaemia	0	1 (0.1) [0]
Peritoneal haemorrhage	1 (0.1) [0]	0
Peritoneal neoplasm	1 (0.1) [1]	0
Pernicious anaemia	1 (0.1) [0]	0
Pneumonia	1 (0.1) [0]	1 (0.1) [0]
Pollakiuria	0	1 (0.1) [0]
Prostate cancer	0	5 (0.3) [0]
Pulmonary embolism	0	3 (0.2) [0]

Pulmonary infarction	0	1 (0.1) [0]
Rectal cancer	1 (0.1) [0]	1 (0.1) [0]
Retinal detachment	0	1 (0.1) [0]
Retinal vein occlusion	1 (0.1) [0]	0
Reversible ischaemic neurological deficit	0	1 (0.1) [0]
Road traffic accident	0	1 (0.1) [0]
Rotator cuff syndrome	1 (0.1) [0]	0
Sick sinus syndrome	1 (0.1) [0]	0
Sinus bradycardia	0	1 (0.1) [0]
Speech disorder	0	1 (0.1) [0]
Stasis dermatitis	0	1 (0.1) [0]
Syncope	1 (0.1) [0]	3 (0.2) [1]
Tachyarrhythmia	0	1 (0.1) [0]
Tendon rupture	0	1 (0.1) [0]
Thrombosis	0	1 (0.1) [0]
Transient ischaemic attack	1 (0.1) [0]	0
Upper limb fracture	0	1 (0.1) [0]
Urethral stricture	1 (0.1) [0]	0
Urinary retention	0	1 (0.1) [0]
Urinary tract infection	1 (0.1) [0]	0
Venous insufficiency	0	1 (0.1) [0]
Ventricular failure	0	1 (0.1) [0]
Vertigo	1 (0.1) [0]	1 (0.1) [0]
Vestibular neuronitis	1 (0.1) [0]	0
Subjects with non-fatal SAEs - Post Therapy, n (%) [related]	12 (1.5) [1]	23 (1.5) [1]
Acute myocardial infarction	0	1 (0.1) [0]
Aortic valve incompetence	0	1 (0.1) [0]
Atrial fibrillation	0	2 (0.1) [0]
Bladder neoplasm	0	1 (0.1) [0]
Bladder tumour resection	0	1 (0.1) [0]
Brain neoplasm	1 (0.1) [0]	0
Cardiac assistance device user	1 (0.1) [0]	0
Cardiac failure	0	2 (0.1) [0]
Cerebral ischaemia	0	1 (0.1) [0]
Cerebrovascular accident	1 (0.1) [0]	0
Chest pain	1 (0.1) [0]	0
Colon cancer	1 (0.1) [0]	0
Contusion	0	1 (0.1) [0]
Coronary artery atherosclerosis	0	1 (0.1) [0]
Coronary artery disease	2 (0.3) [0]	2 (0.1) [0]
Coronary artery surgery	1 (0.1) [0]	1 (0.1) [0]
Deep vein thrombosis	2 (0.3) [0]	0
Dyspnoea	0	1 (0.1) [0]
Endocarditis	0	1 (0.1) [0]
Epididymitis	1 (0.1) [0]	0
Excoriation	0	1 (0.1) [0]
Gastroenteritis salmonella	0	1 (0.1) [0]
Gynaecomastia	1 (0.1) [1]	0
Hypertension	0	1 (0.1) [0]
Hypertensive crisis	0	1 (0.1) [0]
Jaundice	1 (0.1) [0]	0
Myocardial infarction	0	1 (0.1) [0]
Palpitations	0	1 (0.1) [1] ^b
Pancreatic carcinoma	1 (0.1) [0]	1 (0.1) [0]
Pancreatitis chronic	0	1 (0.1) [0]

Post procedural haemorrhage	0	1 (0.1) [0]
Prostate cancer	1 (0.1) [0]	4 (0.3) [0]
Prostate induration	0	1 (0.1) [0]
Prostatitis	0	1 (0.1) [0]
Pulmonary embolism	2 (0.3) [0]	0
Rectal polyp	0	1 (0.1) [0]
Urethral stricture	0	1 (0.1) [0]
Ventricular tachycardia	1 (0.1) [0]	0
Vertigo	1 (0.1) [0]	0
Subjects with any fatal SAEs, n (%) [related]	1 (0.1) [0]	12 (0.8) [0]
Subjects with fatal SAEs - On-Therapy, n (%) [related]	1 (0.1) [0]	9 (0.6) [0]
Bronchial carcinoma	1 (0.1) [0]	0
Cardiac death	0	1 (0.1) [0]
Cerebral haemorrhage	0	2 (0.1) [0]
Cerebrovascular accident	0	1 (0.1) [0]
Death	0	1 (0.1) [0]
Metastases to lung	1 (0.1) [0]	0
Metastases to liver	0	1 (0.1) [0]
Myocardial infarction	0	1 (0.1) [0]
Lung neoplasm malignant	1 (0.1) [0]	0
Pancreatitis	0	1 (0.1) [0] ^c
Pancreatitis acute	0	1 (0.1) [0]
Thyrotoxic crisis	0	1 (0.1) [0]
Subjects with fatal SAEs - Post Therapy, n (%) [related]	0	4 (0.3) [0]
Bronchopneumonia	0	1 (0.1) [0]
Carcinoma	0	1 (0.1) [0]
Cerebrovascular accident	0	1 (0.1) [0]
Metastases to liver	0	1 (0.1) [0]
Multi-organ failure	0	1 (0.1) [0]
^a	In 2 subjects the SAE was considered by the investigator to be related to TAM only.	
^b	In 1 subject the SAE was considered by the investigator to be related to TAM only.	
^c	This subject additionally experienced a multi-organ failure post therapy.	
Conclusion:	Improvements in the efficacy variables IPSS, BII, prostate volume, and post-void residual volume were observed during the treatment period in both treatment groups. Subjects with BPH and a worse IPSS-QoL score at baseline, which received combination therapy of dutasteride and tamsulosin followed by dutasteride monotherapy reached approximately the same IPSS-QoL score compared to subjects with BPH and a better IPSS-QoL score at baseline, treated with dutasteride alone. On-therapy adverse events were reported in 303 (37.4%) subjects in the DUT group, and 613 (39.0%) subjects in the DUT/TAM group. The most frequently reported on-therapy adverse events were erectile dysfunction, and urinary tract infection in the DUT group, and erectile dysfunction, and dysuria in the DUT/TAM group. On therapy non-fatal serious adverse events were reported in 40 (4.9%) subjects in the DUT group, and 78 (5%) subjects in the DUT/TAM group. The most frequently reported on-therapy serious adverse events were atrial fibrillation in the DUT group, and angina pectoris, prostate cancer, myocardial infarction, and calculus ureteric in the DUT/TAM group. On therapy fatal serious adverse events were reported in 1 (0.1%) subject in the DUT group, and 9 (0.6%) subjects in the DUT/TAM group.	
Publications:	No Publication	

Date Updated: 06-Jan-2006