

The study listed may include approved and non-approved uses, formulations or treatment regimens. The results reported in any single study may not reflect the overall results obtained on studies of a product. Before prescribing any product mentioned in this Register, healthcare professionals should consult prescribing information for the product approved in their country.

Study No.: ARI400NL/104274
Title: Preliminary Evaluation of the Effect of Dutasteride on PCA3 in Post-DRE Urine Sediments:A Randomized, Open-Label,Parallel-Group Pilot Study
Rationale: Prostate cancer gene 3 (PCA3) is a prostate-specific non-coding mRNA that is highly overexpressed in prostate cancer (PCa) tissue compared with benign prostate tissue. Its value as a diagnostic marker by means of the PCA3 score identifying PCa cells in urine or urinary sediments after digital rectal examination (DRE) has been shown in several large multicenter studies. The PCA3 score is calculated by dividing the number of PCA3 mRNA transcripts by the number of PSA mRNA transcripts detected in a urine sample and multiplying the result by 1,000. In vitro data has shown that, similar to the expression of PSA, the expression of PCA3 is androgen dependent. This exploratory, randomized, open-label, parallel-group pilot study is the first study to investigate the effect of dutasteride on the PCA3 score longitudinally and in a dose dependent manner, in both men with benign prostatic hyperplasia (BPH) and men with clinically localized PCa.
Phase: IV
Study Period: From April 25th 2005 to July 4th 2007
Study Design: Randomized, open-label,parallel-group pilot study
Centres: 2 centers in the Netherlands
Indication: Benign prostatic hyperplasia (BPH) and biopsy proven, clinically localized PCa.
Treatment: Both the subjects with BPH and the subjects with PCa were randomly assigned to take either 0.5 or 3.5 mg, that is, seven 0.5mg capsules, dutasteride orally once daily. The study thus comprised four groups of subjects: eight subjects with BPH and five with PCa received 0.5 mg dutasteride once daily for three months, eight with BPH and four with PCa received 3.5 mg dutasteride.
Objectives: This exploratory, randomized, open-label, parallel-group pilot study is the first study to investigate the effect of dutasteride on the PCA3 score longitudinally and in a dose dependent manner, in both men with benign prostatic hyperplasia (BPH) and men with clinically localized PCa.
Primary Outcome/Efficacy Variable: The mean relative change from baseline PCA3 score per group after 1, 2, and 3 months of dutasteride treatment.
Secondary Outcome/Efficacy Variable(s): The mean relative change from baseline of serum DHT, T, PSA and prostate volume per group after 1, 2, and 3 months of dutasteride treatment.
Statistical Methods: The results of an intention-to-treat analysis are presented. The method of handling missing values was the observed-cases approach, that is, missing values at post-baseline assessments were not imputed and were regarded as missing. Change from baseline for each man was computed as post-baseline value minus baseline value, relative change from baseline as change from baseline divided by baseline value. Data were analyzed using the Statistical Package for the Social Sciences (SPSS, Chicago, IL) version 15.0.1 for Microsoft Windows.
Study Population: <u>BPH Groups Inclusion Criteria:</u> Men aged 50 or over, with a clinical diagnosis of BPH by medical history and physical examination including DRE, were considered eligible for inclusion. Other principle inclusion criteria for the BPH groups were an international prostate symptom score ≥ 12 points at screening, a prostate volume ≥ 30 ml measured by transrectal ultrasound (TRUS), a total serum PSA of 2.5–10 ng/ml at screening (extremes included), a Qmax ≥ 5 ml/sec at screening, a post-void residual volume ≤ 250 ml (measured by suprapubic ultrasound) at screening, and the exclusion of PCa by a negative prostate biopsy as a result of local management within 6 months prior to screening.

PCaGroups Inclusion Criteria:

Men aged 50 or over, with biopsy-proven, clinically localized PCa (defined as at least 5% of one biopsy core and at least 1mm of cancer), eligible and scheduled for radical prostatectomy, were considered eligible for inclusion.

BPH and PCa Groups Exclusion Criteria:

Principle exclusion criteria for both the BPH and the PCa groups were the inability to void spontaneously (e.g., the dependence on transurethral or suprapubic catheter for micturation), a history of PCa (prior to the current diagnosis for the PCa groups), previous prostatic surgery, a history of acute urinary retention within 3 months prior to screening and the use of any investigational or marketed 5ARI, anabolic steroids or any drug with anti-androgenic properties within

12 months prior to screening.

A total of 31 subjects were assessed for eligibility, that is, 21 subjects with BPH and 10 subjects with PCa. Six of these subjects (five with BPH and one with PCa) did not meet the inclusion criteria and were therefore excluded. Thus 25 subjects (16 with BPH and nine with PCa) were enrolled and randomized to treatment. No subjects were lost to follow-up, discontinued treatment because of adverse effects or other reasons, or had to be excluded from analysis. Therefore, all 25 enrolled subjects could be analyzed.

Number of Subjects:	BPH 0.5mg dutasteride	BPH 3.5mg dutasteride	PCa 0.5mg dutasteride	PCa 3.5mg dutasteride
Planned, N	10	10	10	10
Randomised,	8	8	5	4
Completed, n	8	8	5	4
Total Number Subjects Withdrawn, N	0	0	0	0
Demographics/ Baseline clinical features				
N (ITT)	8	8	5	4
Males	8	8	5	4
PCa clinical stage				
cT1c			4 (80%)	3 (75%)
cT2			1 (20%)	1 (25%)
Prostate biopsy pathology Gleason score				
4			1 (20%)	
6			3 (60%)	4 (100%)
7			1 (20%)	
Radical prostatectomy pathology Gleason score				
5			1 (20%)	
6			1 (20%)	
7			2 (40%)	3 (75%)
8				1 (25%)
Biopsy Gleason score vs. radical prostatectomy PCa Gleason score				
Identical			2 (40%)	
Upgrading			1 (20%)	4 (100%)
Downgrading			1 (20%)	
PCa pathological stage				
pT2			5 (100%)	4 (100%)

Mean Age, years (SD)	63.4 (\pm 6.2)	62.9 (\pm 2.0)	56.1 (\pm 4.7)	58.8 (\pm 2.8)
Mean PCA3 score (SD)	24 (\pm 22)	22 (\pm 13)	77 (\pm 52)	31 (\pm 36)
Mean Total prostate volume (ml) (SD)	78.5 (\pm 25.3)	61.4 (\pm 24.7)	32.1 (\pm 16.2)	38.8 (\pm 18.8)
Mean Serum DHT value (ng/ml) (SD)	1.78 (\pm 0.85)	1.75 (\pm 0.95)	1.60 (\pm 0.58)	1.58 (\pm 0.62)
Mean Serum T value (ng/ml) (SD)	18.18 (\pm 6.87)	16.33 (\pm 4.36)	17.44 (\pm 6.03)	13.00 (\pm 2.45)
Mean Serum PSA value (ng/ml) (SD)	6.76 (\pm 2.06)	6.55 (\pm 2.93)	7.26 (\pm 2.12)	10.80 (\pm 6.38)
No statistically significant differences in Baseline clinical features between groups				

Primary Efficacy Results:						
Mean relative change from baseline PCA3 score (SD)						
Group	Dutasteride dose (mg)	After 1 month	After 2 months	After 3 months		
BPH	0.5	12 (86)	85 (186)	113 (249)		
BPH	3.5	13 (80)	-18 (77)	42 (129)		
PCa	0.5	-18 (69)	-47 (21)	-26 (14)		
PCa	3.5	76 (126)	158 (284)	13 (75)		
PCA3 scores per subject at Baseline and after 1, 2, and 3 months of dutasteride treatment (relative change from baseline)						
Subject number	Group	Dutasteride dose (mg)	Baseline	After 1 month	After 2 months	After 3 months
5	BPH	0.5	1	3 (+200%)	6 (+500%)	6 (+500%)
6			6	5 (-17%)	7 (+17%)	7 (+17%)
8			12	18 (+50%)	20 (+67%)	74 (+517%)
11			15	6 (-60%)	12 (-20%)	6 (-60%)
12			21	17 (-19%)	16 (-24%)	33 (+57%)
19			22	13 (-41%)	4 (-82%)	5 (-77%)
21			52	25 (-52%)	69 (+33%)	17 (-67%)
53			62	84 (+35%)	181 (+192%)	74 (+19%)
1	BPH	3.5	9	2 (-78%)	2 (-78%)	0 (-100%)
7			19	14 (-26%)	20 (+5%)	23 (+21%)
10			5	6 (+20%)	12 (+140%)	10 (+100%)
13			18	44 (+144%)	17 (-6%)	70 (+289%)
14			24	45 (+88%)	14 (-42%)	41 (+71%)
24			44	16 (-64%)	12 (-73%)	21 (-52%)
27			24	26 (+8%)	7 (-71%)	16 (-33%)
51			35	a	19 (-46%)	31 (-11%)
9	PCa	0.5	131	102 (-22%)	112 (-15%)	112 (-15%)
16			19	23 (+21%)	12 (-37%)	12 (-37%)
17			61	108 (+77%)	25 (-59%)	44 (-28%)
23			42	7 (-83%)	16 (-62%)	24 (-43%)
28			132	21 (-84%)	52 (-61%)	120 (-9%)
3	PCa	3.5	15	33 (+120%)	17 (+13%)	4 (-73%)
4			85	79 (-7%)	76 (-11%)	157 (+85%)
15			19	11 (-42%)	28 (+47%)	14 (-26%)
18			6	20 (+233%)	41 (+583%)	10 (+67%)
a: Value missing						
Secondary Outcome Variable(s):						
Mean relative change from baseline serum DHT (SD)						
Group	Dutasteride dose (mg)	After 1 month	After 2 months	After 3 months		
BPH	0.5	-93 (5)	-93 (5)	-94 (4)		
BPH	3.5	-90 (9)	-95 (2)	-96 (3)		
PCa	0.5	-84 (21)	-94 (4)	-89 (7)		
PCa	3.5	-94 (4)	-96 (1)	-96 (2)		
Mean relative change from baseline serum T (SD)						
Group	Dutasteride dose (mg)	After 1 month	After 2 months	After 3 months		

BPH	0.5	13 (25)	13 (15)	20 (17)
BPH	3.5	16 (21)	26 (23)	22 (23)
PCa	0.5	6 (25)	12 (17)	21 (38)
PCa	3.5	40 (36)	38 (16)	29 (15)
Mean relative change from baseline serum PSA (SD)				
Group	Dutasteride dose (mg)	After 1 month	After 2 months	After 3 months
BPH	0.5	-20 (21)	-38 (22)	-42 (24)
BPH	3.5	-28 (18)	-43 (16)	-54 (18)
PCa	0.5	-45 (12)	-59 (7)	-61 (10)
PCa	3.5	-31 (38)	-60 (13)	-45 (20)
Mean relative change from baseline prostate volume (SD)				
Group	Dutasteride dose (mg)	After 1 month	After 2 months	After 3 months
BPH	0.5			-11 (8%)
BPH	3.5			-16 (8%)
PCa	0.5			-15 (11%)
PCa	3.5			-10 (9%)
Safety Results: 15 subjects (60%) reported an adverse event, 69% in the 0.5mg group vs. 50% in the 3.5mg group. In general, adverse events were mild to moderate and resolved spontaneously. No serious adverse events were reported. Drug-related adverse events were mostly sexually related, and were reported by 7 subjects (28%), with slightly more in the high dose group (see table). None of the subjects withdrew from the study as a result of these adverse events.				
		0.5 mg	3.5 mg	
Most Frequent Adverse Events – On-Therapy		n (%)	n (%)	
Subjects with any AE(s), n(%)		9 (69%)	6 (50%)	
Subjects with drug-related AEs, n(%)		2 (15%)	5 (42%)	
Drug-related events reported:				
• Erectile dysfunction			3	
• Painful erections			1	
• Decreased ejaculate volume		1		
• Orgasmic sensation decreased		1		
• Stomach ache			2	

Conclusion: See publication.

Publication:

Preliminary evaluation of the effect of dutasteride on PCA3 in post-DRE urine sediments: A randomized, open-label, parallel-group pilot study
 Martijn P.M.Q. van Gils, Daphne Hessels, W. Pim Peelen, Henk Vergunst, Peter F.A. Mulders, Jack A. Schalken
 The Prostate, Vol. 69, 2009.
 Published Online (www.interscience.wiley.com): Jul 8 2009 12:40PM
 DOI: 10.1002/pros.21011