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<b>Study No.:</b> ARI108898
<b>Title:</b> A randomized, double-blind, placebo-controlled parallel clinical study evaluating the efficacy and safety of 6 months of once-daily oral dutasteride 0.5mg, followed by 12 months open treatment of dutasteride in benign prostatic hyperplasia patients.
<b>Rationale:</b> The aim of this study is to evaluate the efficacy and safety of once-daily oral dutasteride 0.5mg for the treatment of benign prostatic hyperplasia with a double-blind, placebo-controlled, randomized trial.
<b>Phase:</b> III
<b>Study Period:</b> Start date: Oct, 31, 2007 End Date: March 23, 2009 (double blind phase)
<b>Study Design:</b> In this study, the efficacy and safety of dutasteride for the treatment of benign prostatic hyperplasia in China was evaluated compared with placebo in a multi-center, randomized, double-blind, placebo-controlled phase III clinical study. Eligible subjects were randomized to either dutasteride or placebo in a ratio of 1:1. Following 4 weeks of a screening period subjects received once-daily 0.5mg dutasteride or placebo for 6 months. The efficacy and safety were assessed at Month 1, 3 and 6 during the treatment period, and the eligible subjects who completed 6 months of the double-blind treatment period could enter a voluntary 12-month period of open treatment phase. The subjects, who were not willing to enter the open treatment phase or not qualified to enter the open phase, judged by the investigator, were to have a safety follow up visit one month after the end of the trial. All subjects who entered the open phase received 0.5mg oral dutasteride once daily. Efficacy and safety data were collected during the open phase.
<b>Centres:</b> 253 subjects enrolled from 12 sites in China.
<b>Indication:</b> benign prostatic hyperplasia
<b>Treatment:</b> All subjects were assigned to either daily oral dutasteride 0.5mg or placebo for 6 months. Subjects who completed 6 months of double-blind treatment period could enter a voluntary 12-month period of open treatment phase with daily oral dutasteride 0.5mg.
<b>Objectives:</b> To evaluate the efficacy and safety of once-daily oral dutasteride 0.5mg for the treatment of benign prostatic hyperplasia with a double-blind, placebo-controlled, randomized trial.
<b>Primary Outcome/Efficacy Variable:</b> Percentage change from baseline prostate volume after 6 months of dutasteride treatment compared with placebo.
<b>Secondary Outcome/Efficacy Variable(s):</b> <ul style="list-style-type: none"> <li>- Change of prostate volume at Month 3, 6</li> <li>- Change of serum DHT (number and percentage) at Month 3, 6</li> <li>- Change of AUA SI (number and percentage) at Month 3, 6</li> <li>- Change of Qmax (number and percentage) at Month 3, 6</li> </ul>
<b>Statistical Methods:</b> ITT population was used for all primary and secondary efficacy endpoints and for all safety analysis, and Per Protocol population was used for additional analysis of primary efficacy endpoints.

Null hypothesis of this study was: there is no difference between dutasteride and placebo group on prostate volume reduction percentages compared with baseline after 6 months of treatment; the alternative assumption was that there is difference between the two groups. The level of statistical significance was set at 0.05. The missing data were replaced according to LOCF for the analysis of ITT population. Software used for analysis was SAS V9.1.3.

Due to an imbalance of baseline PV between the treatment groups, an ad-hoc analysis using general linear model was performed for primary endpoint:  $\text{LOG}(\text{PV post treatment}/\text{PV baseline}) = \text{LOG}(\text{PV baseline}) + \text{group}$ .

#### Study Population:

Eligible patients were Male, age  $\geq 50$  years old; clinically diagnosed benign prostatic hyperplasia according to medical history and physical examination (including digital rectal examination); AUA symptom index score (AUA-SI)  $\geq 12$  points at screening; the maximum urinary flow rates  $> 5\text{ml/s}$  and  $\leq 15\text{ml/s}$  with a minimal voided volume  $\geq 125\text{ml}$  at two tests at screening; prostate volume  $\geq 30\text{ cm}^3$  measured by transrectal ultrasonography (TRUS); willing and able to sign informed consent before screening and agreed to be compliance with study procedures; be able to read, understand and record the AUA-SI questionnaire.

Subjects were excluded with a post void residual volume  $> 250\text{ml}$  after emptying by suprapubic ultrasonography at screening; medical history or evidences of prostate cancer; total serum prostate-specific antigen (PSA)  $< 1.5\text{ng/ml}$  or  $> 10.0\text{ng/ml}$ ; previous histories of prostate surgery or other traumatic or micro-injury operation in treating benign prostate hyperplasia; acute urinary retention within 3 months before screening; flexible or rigid cystoscopy or other instrumentation of the urethra 7 days before screening. However, routine catheterization ( $< 10\text{F}$ ) was acceptable with no frequency limits; other than benign prostatic hyperplasia, any other disease led to urinary tract symptoms or flow rate changes judged by the investigator; history of liver damage or abnormal liver function tests at screening, use of any 5-reductase inhibitors, any drugs containing androgen antagonist or other drugs specified with side effects of male breasts developing or an impact on the prostate by previous TRUS or within 6 months before screening and throughout the trial; use of  $\alpha$ -blockers 2 weeks before screening and during the trial; any use of Chinese herbs or herbal treatment 2 weeks before screening or expected using during the trial; current use of anabolic steroids; any use of adrenal  $\alpha$ -agonists or anticholinergic medication, or choline medication within 48 hours prior to urodynamic examination; history of renal dysfunction or serum creatinine  $> 1.5$  times ULN at screening.

	Dutasteride Group	Placebo group
Number of Subjects:		
Planned, N	120	120
Randomised, N	126	127
Completed, n (%)	113 (89.7%)	116 (91.3%)
Total Number Subjects Withdrawn, N (%)	13 (10.3%)	11 (8.7%)
Withdrawn due to Adverse Events n (%)	3 (2.4%)	0
Withdrawn due to Lack of Efficacy n (%)	NA	NA
Withdrawn for other reasons n (%)	10 (7.9%)	11 (8.7%)
<b>Demographics</b>	<b>A</b>	<b>B</b>
N (ITT)	126	127
Males	100%	100%
Mean Age, years (SD)	65.8 (7.7)	66.9 (8.2)
Race, n (%)		
Chinese	126 (100%)	127 (100%)
Prostate Volume (mean, $\text{cm}^3$ )	48.19	42.29 (p=0.0410)

<b>Primary Efficacy Results:</b>		
Changes of the prostate volume in percentage after 6 months of treatment.		
<b>Changes of the prostate volume in percentage after 6 months of treatment.</b>	<b>Dutasteride Group</b>	<b>Placebo group</b>
Mean (SD)	-17.00 (21.41)	-2.77 (24.96)
Difference between treatments	-14.23	
95% Confidence Interval	(-20.23,-8.22)	
p-value	0.0001	
<b>Changes of the prostate volume in percentage after 6 months of treatment. (adjusted by general linear model)</b>		
Mean	-19.3	-5.7
Difference between treatments	-13.6	
p-value	P 0.0001	

<b>Secondary Outcome Variable(s):</b>		
<b>Changes of the prostate volume in percentage after 3 months of treatment.</b>	<b>Dutasteride Group</b>	<b>Placebo group</b>
Mean (SD)	-12.02 (23.22)	-1.02 (25.79)
Difference between treatments	-11.00	
95% CI (if appropriate)	(-17.39,-4.61)	
p-value	0.0001	
<b>Safety Results:</b>		
	<b>Dutasteride Group</b>	<b>Placebo group</b>
Subjects with any AE(s), n(%)	27 (21.4%)	26 (20.5%)
<b>Most Frequent Adverse Events – On-Therapy</b>	<b>n (%)</b>	<b>n (%)</b>
Diarrhea	0 (0.0%)	2 (1.6%)
Stomach discomfort	3 (2.4%)	3 (2.4%)
Blood glucose increased	2 (1.6%)	0 (0.0%)
Back pain	2 (1.6%)	2 (1.6%)
Libido decreased	3 (2.4%)	0 (0.0%)
Nasopharyngitis	2 (1.6%)	3 (2.4%)
Pharyngodynia	2 (1.6%)	0 (0.0%)
Upper respiratory tract infection	3 (2.4%)	5 (3.9%)
<b>Serious Adverse Events - On-Therapy n (%) [n considered by the investigator to be related to study medication</b>		
	<b>Dutasteride Group</b>	<b>Placebo group</b>
Subjects with non-fatal SAEs, n (%)	0	1 (0.8%)
	<b>n (%) [related]</b>	<b>n (%) [related]</b>
glaucoma	0	1 (0.8%) [0]

Subjects with fatal SAEs, n (%)	0	0
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**Conclusion:**

This study demonstrated significant DHT suppression and reduction in prostate volume was achieved by dutasteride treatment which was significant at 3 month, the earliest point measured, and after 6-months of treatment, suggesting that dutasteride was a potent inhibitor of DHT production and can effectively reduce prostate volume. For the secondary endpoints AUA-SI and Qmax, no statistical significances were observed in dutasteride group compared to placebo which may be due to the small sample size. However, differences between these two groups constantly favored dutasteride treatment. Safety analysis showed that 0.5mg dutasteride once-daily administration for 6 months was well tolerated, with a low incidence of adverse events, which were mainly mild to moderate in degree. In conclusion, the study results demonstrated that dutasteride was safe and efficacious in Chinese BPH patients after 6 months of treatment.