3. STUDY SYNOPSIS

Sponsor:	Astellas Pharma China, Inc.
Test Drug:	Tamsulosin hydrochloride sustained release tablet (0.4mg)
Study Title:	A multi-site, randomized, double-blind, double-dummy clinical trial to compare the efficacy and the safety of tamsulosin hydrochloride sustained-release tablet 0.4mg and tamsulosin hydrochloride sustained-release capsule 0.2mg to treat dysuria accompanied by benign prostatic hyperplasia.
Indication:	Lower urinary tract symptoms (LUTS) accompanied by benign prostatic hyperplasia
Coordinating Investigator:	[redacted]
Publication(s) based on data from the study:	None.
Study Duration:	Date of start: 23 Nov. 2009 (FPFV) Date of completion: 8 Oct. 2010 (LPLV)
Study Objectives:	To evaluate the efficacy and the safety of tamsulosin hydrochloride sustained release tablet (0.4mg) to treat lower urinary tract symptoms associated with benign prostatic hyperplasia among Chinese population.
Study Design and Methodology :	This study was a multi-site, randomized, double-blind, double-dummy clinical trial. The total period of administration of this trial was 10 weeks in which placebo washout period was 2 weeks and placebo was taken by patients; drug treatment period lasted 8 weeks and patients were treated with investigational drugs. After the patients signed informed consent form, they took orally one tamsulosin hydrochloride sustained-release tablet placebo and one tamsulosin hydrochloride sustained-release capsule placebo after daily breakfast during the washout period, After 2 weeks of placebo washout period, patients who met the inclusion criteria and did not meet the exclusion criteria would be randomized into tamsulosin hydrochloride sustained-release tablet group (TOCAS group) or tamsulosin hydrochloride sustained-release capsule group (Harnal group). Patients in TOCAS group took orally one tamsulosin hydrochloride sustained-release tablet and one tamsulosin hydrochloride sustained-release capsule placebo after daily breakfast. Patients in Harnal group took orally one tamsulosin hydrochloride sustained-release capsule and one tamsulosin hydrochloride sustained-release tablet placebo after daily breakfast. 4 and 8 weeks (end of trial) after administration, follow-up visit should be done respectively.
Number of Subjects (planned Vs. actual):	The target screen number for each group was 180-200. Total number was 360-400; completed number was 120 cases for each group and total 240 cases for the two groups. All target screenings were carried out in 10 study sites. A total of 252 subjects

	were randomized into the study, 235 subjects (TOCAS: 118, Harnal: 117) completed the study and 17 subjects (TOCAS: 6, Harnal: 11) discontinued from the study.
Subject Admission Criteria：	**Inclusion Criteria:** Only patients who met all of the following criteria would be enrolled in the study. Screening period (Visit 1): (1) Male patient whose age is more than 50 years old; (2) 8 points ≤International prostate symptom score (I-PSS)≤30 points; (3) QOL≥3 points; (4) 5ml/s≤The maximum flow rate≤15ml/s； urinary volume≥150ml (Urinary flow rate is recommended to be tested when bladder capacity is within 250ml~300ml); (5) Bladder residual urine volume≤100ml; (6) Prostate volume tested by B ultrasonic≥20ml; (7) Voluntarily signed the informed consent form Randomization period (Visit 2): (1) 8 points ≤International prostate symptom score (I-PSS)≤30 points；Patients with unstable I-PSS scores will be excluded. (See Protocol appendix 2) (2) The results of blood routine test, urine routine test, blood biochemical test (including PSA) and ECG determined at the first visit should be within normal value range; or although it is outside the normal range, but investigators think it has no clinical significance. **Exclusion Criteria:** Patients who met any of the following criteria would be excluded from the study Screening period (Visit 1): (1) Patient whose PSA≥10ng/ml or 10ng/ml>PSA>4ng/ml, F/T<0.16； (2) Rectal palpation indicates patient is suspected to have prostate cancer; (3) Patients with suspected neurogenic bladder; (4) Patients previously or currently have suspected bladder cancer and have been treated with pelvic radiation therapy; patients have experienced prostate surgery or bladder neck obstruction surgery; (5) Patients with confirmed urethral stricture; (6) Patients with orthostatic hypotension [a] or previously suffer from hypotension; (7) Patients who need a surgery recently; (8) Patients with chronic bacterial prostatitis or recurrent urinary tract infections [b]; (9) Patients with liver and kidney dysfunctions [c] (10) Patients who suffered from cardiovascular or cerebrovascular disease during 6 months before the first visit such as unstable angina, myocardial infarction, transient ischemic attack and obvious ventricular arrhythmia or stroke etc;

	(11)Patients with central nervous system diseases such as schizophrenia, senile dementia, multiple sclerosis and Parkinson's disease etc; (12)Patients with alcohol or drug addiction which will affect the compliance of the protocol; (13)Patients who are allergic or have an allergic history for α-receptor blocker before; (14)Patients who took some drugs which will influence urination or absorption and metabolism of drug; (a) Patients who are taking 5α-reductase inhibitors or took the drug during 3 months before the first visit; (b) Patients who are taking other drugs for BPH such as α-AR antagonist (Including tamsulosin) and plant extracts or took the drug during 1 month before the first visit; (c) Patients who are taking other drugs which may influence the pharmacokinetics of tamsulosin hydrochloride such as α-AR antagonist, concomitant α/β-AR antagonist, α-agonists and cholinergic or anti-cholinergic drugs etc; (15)Patients with other tumors within 5 years; (16)Patients who are taking other investigational drugs or have participated in drug clinical trials within 3 months before the first visit; (17)Other patients who are unsuitable for the study by attending physician's estimation (18)Employees from Astellas Pharmaceutical (China) Co., Ltd., clinical study organizations or research sties should be excluded by the study. a. Orthostatic hypotension: it refers to excessive blood pressure drop when patient is at an upright position, comparing with the blood pressure determined at supine position, it decreases by more than 20/10mmHg. b. Recurrent urinary tract infection: it refers to there are at least two urinary tract infections within the past 6 months. c. Liver and kidney dysfunctions: it refers to blood biochemical test results are two times higher than normal upper limit and investigators consider it has clinical significance.
Test Drug and Administration :	Test drug: Format: Tamsulosin hydrochloride sustained release tablet (0.4mg/tablet) Batch No. (shelf life): [redacted] (36 months) Placebo: Tamsulosin hydrochloride sustained release capsule Batch No：[redacted] Usage and Dosage: Placebo washout period was 2 weeks and patients would take orally one

	tamsulosin hydrochloride sustained release capsule placebo and one tamsulosin hydrochloride sustained release tablet placebo after daily breakfast. Drug treatment period would last 8 weeks and patients would take orally one tamsulosin hydrochloride sustained-release tablet and one tamsulosin hydrochloride capsule placebo after daily breakfast.
Control Drug and Administration :	Control drug: Format: Tamsulosin hydrochloride sustained release capsule (0.2mg/ capsule) Batch No.(shelf life): [redacted] (36 months) Placebo: Tamsulosin hydrochloride sustained release tablet Batch No：[redacted],[redacted] Usage and Dosage: Placebo washout period was 2 weeks and patients would take orally one tamsulosin hydrochloride sustained release capsule placebo and one tamsulosin hydrochloride sustained release tablet placebo after daily breakfast. Drug treatment period would last 8 weeks and patients would take orally one tamsulosin hydrochloride sustained-release tablet placebo and one tamsulosin hydrochloride capsule after daily breakfast.
Evaluation Variables:	**Efficacy variables:** Primary efficacy variable: Changes in total I-PSS score before and after administration. Secondary efficacy variables: (1) Changes and change percentages of individual I-PSS symptom score (Incomplete bladder emptying (Q1), frequent micturition (Q2), emiction interruption (Q3), urgent urination (Q4), thin urine stream (Q5), urinary hesitation (Q6), and nocturia (Q7) (2) Change percentages of total I-PSS scores before and after administration (3) Changes and change percentages of maximum urinary flow rate before and after administration (4) Changes and change percentages of average urinary flow rate before and after administration (5) The decrease percentage of total I-PSS score by at least 25% or 50％ than baseline level before and after administration (6) The increase percentage of maximum urinary flow rate by at least 30％ than baseline level before and after administration (7) Changes and change percentages of I-PSS classification score for voiding symptoms 1 [Emiction interruption（Q3）, thin urine stream (Q5) and urinary hesitation (Q6)] before and after administration. (8) Changes and change percentages of I-PSS classification score for voiding symptoms 2 [Incomplete bladder emptying (Q1), emiction interruption (Q3), thin urine stream (Q5) and urinary hesitation (Q6)] before and after

	administration (9) Changes and change percentages of I-PSS classification score for storage symptoms including frequent micturition (Q2), urgent urination (Q4) and nocturia (Q7) before and after administration (10) Changes and change percentages of*nocturia times recorded in the voiding diary (11) Changes in QOL score before and after administration (12) Changes in residual urine volume before and after administration (13) Investigators' comprehensive assessment (including progress of symptoms, no change, slight improvement, a great improvement) *Nocturia: urination during sleep (the last urination before going to sleep and the first urination after waking up should not be recorded). **Safety variables:** (1) Blood pressure, heart rate (2) Clinical laboratory tests results (3) ECG (4) Adverse event
Statistical Analysis :	Professional statistical software SAS V9.1.3 was used for statistical analysis. The primary objective of this study was to demonstrate tamsulosin hydrochloride sustained release tablet 0.4mg was superior to tamsulosin hydrochloride sustained release capsule 0.2mg. The hypothesis was as follows: H0: $\mu_t-\mu_c=0$ H1: $\mu_t-\mu_c\neq0$ μ_t and μ_c referred to the change in total I-PSS score between the baseline and the endpoint comparing Tamsulosin Hydrochloride Sustained Release Tablet 0.4mg to Tamsulosin Hydrochloride Sustained Release Capsule 0.2mg. H0 (Null hypothesis) was : No statistically significant differences of the change in total I-PSS score between the baseline and the endpoint comparing Tamsulosin Hydrochloride Sustained Release Tablet 0.4mg to Tamsulosin Hydrochloride Sustained Release Capsule 0.2mg were observed. H1 (Alternative hypothesis) was: Significant differences between groups were observed. All statistical tests were two-sided tests; P values not more than 0.05 were considered statistically significant. For continuous variables, choosing two sample t test (adjusted by satterthwaite when heterogeneity) for intergroup comparison. For categorical variables, choosing $\chi 2$ test or fisher exact test (one or more expected cell count was less than 5) for intergroup comparison. Variables analyzed were summarized using descriptive analysis by treatment group respectively. ANCOVA was performed for intergroup comparison of change in total I-PSS score/ secondary efficacy endpoints from baseline, with baseline total I-PSS score/

	secondary efficacy endpoints and prostate volume as covariates, and treatment groups, and sites as factors. The same analysis would be performed for change in total I-PSS score / secondary efficacy endpoints from baseline to the time when subjects received 4 weeks and 8 weeks of treatment. Single sample t test would be performed for within group comparison.
Results and Conclusions:	**Results of efficacy:** Efficacy analysis was conducted in both FAS and PPS. FAS was the primary analysis set for efficacy analysis. Among 252 randomized subjects, 246 were included in FAS (TOCAS: 122, Harnal: 124) and 228 were included in PPS (TOCAS: 115, Harnal: 113). The efficacy summary based on FAS analysis was as follows. The results of PPS were consistent with those in FAS analysis. **Primary efficacy variables:** ● At the endpoint of treatment, in ANCOVA model, with baseline total I-PSS score as covariate and treatment groups and sites as factors, there was no statistically significant difference in changes in total I-PSS score between TOCAS group and Harnal group (*P*=0.227). The adjusted mean (95% CI) of changes in total I-PSS score in TOCAS group was -6.2(-7.0, -5.4), and in Harnal group was -6.8 (-7.5, -6.0). The adjusted mean value of difference (95% CI) between the two groups (TOCAS - Harnal) was 0.6(-0.4, 1.5). **Second efficacy variables:** ● There was no statistically significant difference in the changes of individual I-PSS scores (Q1, Q2, Q3, Q4, Q5, Q6, and Q7) from baseline between treatment groups at the endpoint. For the change percentages in individual I-PSS score, the adjusted mean change percentage in frequent micturition (Q2) at week 4 in TOCAS group (-24.08%) was bigger than that in Harnal group (-13.14%) (*P*=0.035), and the difference (95% CI) (TOCAS - Harnal) was -10.94% (-21.10%, -0.78%); while the adjusted mean change percentage in nocturia (Q7) at week 8 and the endpoint in TOCAS group were both smaller than that in Harnal group (*P*=0.033 and P=0.049, respectively), and the difference (95% CI) (TOCAS - Harnal) at the endpoint was 8.38% (0.05%, 16.71%). ● The difference (95% CI) in the change percentages of total I-PSS score from baseline to the endpoint between treatment groups (TOCAS - Harnal) was 3.63%(-1.58%, 8.85%) without any statistical significance (*P*=0.172). ● The differences (95% CI) in the changes and change percentages of the maximum urinary flow rate from baseline to the endpoint between treatment groups (TOCAS - Harnal) were -0.75(-2.03, 0.53) ml/s and -4.60%(-18.48%, 9.27%) without any statistical significance (*P*=0.252 and *P*=0.514, respectively). ● The differences (95% CI) in the changes and change percentages of the average flow rate from baseline to the endpoint between treatment groups (TOCAS - Harnal) were -0.02(-0.76, 0.73) ml/s and 2.28%(-14.66%, 19.23%) without any statistical significance (*P*=0.966 and *P*=0.791, respectively).

	● The percentage of decrease in total I-PSS scores from baseline to the endpoint by at least 25% was 68.0% and was 68.5% in TOCAS group and in Harnal group respectively. The percentage of decrease in total I-PSS scores from the baseline to the endpoint by at least 50% was 35.2% in TOCAS group and was 41.1% in Harnal group respectively. The differences in the above variables between two groups had no statistical significance (*P*=0.931 and *P*=0.342, respectively). ● The percentage of increase in the maximum urinary flow rate compared from baseline to the endpoint by at least 30% was 35.5% in TOCAS group and was 42.7% Harnal group respectively, but the difference between two groups had no statistical significance (*P*=0.248). ● The differences (95% CI) in the changes and change percentages of I-PSS classification score for voiding symptoms 1 (Q3, Q5, Q6) between the two groups (TOCAS - Harnal) from baseline to the endpoint were 0.3(-0.3, 0.8) and 3.53%(-4.61%, 11.67%) without any statistical significance (*P*=0.342 and *P*=0.394, respectively). ● The differences (95% CI) in the changes and change percentages of I-PSS classification score for voiding symptoms 2 (Q1, Q3, Q5, Q6) between the two groups (TOCAS - Harnal) from baseline to the endpoint were 0.3(-0.4, 1.0) and 4.05%(-3.28%, 11.39%) without any statistical significance (*P*=0.414 and *P*=0.278, respectively). ● The differences (95% CI) in the changes and change percentages of I-PSS classification score for storage symptoms (Q2, Q4, Q7) between the two groups (TOCAS - Harnal) from baseline to the endpoint were 0.3(-0.2, 0.8) and 3.93%(-2.34%, 10.20%) without any statistical significance (both *P*=0.218). ● The differences (95% CI) in the changes of the number of nocturia recorded in the voiding diary from baseline to week8 and to the endpoint between the two groups (TOCAS - Harnal) were 0.28(0.08, 0.47) times and 0.22(0.03, 0.41) times with statistical significance (*P*=0.005 and *P*=0.023, respectively). The differences (95% CI) in the change percentages of the number of nocturia recorded in the voiding diary between the two groups from baseline to week8 and to the end point (TOCAS - Harnal) were 11.33% (2.61%, 20.05%) and 9.33% (0.86%, 17.80%) respectively with statistical significance (*P*=0.011 and *P*=0.031, respectively).Harnal had a little superiority over TOCAS. ● The difference (95% CI) in the changes of QOL score from baseline to the endpoint between the two groups (TOCAS - Harnal) was 0.1(-0.2, 0.3) without any statistical significance (*P*=0.611). ● The difference (95% CI) in the changes of residual urine volume from baseline to the endpoint between the two groups (TOCAS - Harnal) was 3.66(-2.98, 10.31) ml without any statistical significance (*P*=0.279). ● At the end of the study, there was no statistically significant difference in the investigator's comprehensive assessment between the two treatment groups

	(*P*=0.765). The percentage of improved (little improved + greatly improved) in TOCAS group (96.6%) was a little higher than that in Harnal group (93.4%) in numeric. **Results of safety:** Safety analysis was conducted in SS. There were 122 subjects in TOCAS group and 126 subjects in Harnal group. ● The mean treatment period was 59.2 days for TOCAS group, and 58.1 days for Harnal group. ● 6/122 (4.9%) subjects in TOCAS group and 10/126 (7.9%) subjects in Harnal group were reported with at least one adverse event (*P*=0.333). ● 2/122 (1.6%) subjects in TOCAS group and 4/126 (3.2%) subjects in Harnal group had at least one adverse drug reaction (*P*=0.684). ● No subject discontinued from the study for AE in TOCAS group, but 2/122 (1.6%) subjects in Harnal group discontinued from the study due to AEs (urinary tract infection, listless), and one AE (listless) was judged as an adverse reaction. ● Each group had one subject who experienced SAE (TOCAS: calculus bladder, Harnal: urinary tract infection), but neither of them was judged as being related to the study medications. No death was reported in this study. ● No subject had any severe AE in TOCAS group, while one subject in Harnal group had a severe AE (urinary tract infection). ● 2/122 (1.6%) subjects in TOCAS group and 5/126 (4.0%) subjects in Harnal group had clinically significant changes in laboratory examinations. ● No subject had clinically significant changes in vital signs and ECG in both groups. **Conclusions:** It was suggested in this study that 8week treatment with TOCAS 0.4 mg or Harnal 0.2 mg was effective in the treatment of dysuria accompanied by benign prostatic hyperplasia, while no statistically significant difference was detected between the treatment groups of TOCAS 0.4 mg and Harnal 0.2 mg in the primary endpoint (changes in total I-PSS score at endpoint from baseline). In all the secondary endpoints, both TOCAS 0.4 mg and Harnal 0.2 mg showed clinical efficacy after the 8week treatment, while no statistically significance was found at the endpoint between the two treatment groups except that Harnal 0.2 mg group showed statistically significant improvement on nocturia compared to TOCAS group at endpoint. In both treatment groups, safety and tolerability were suggested to be favorable.
Date of Current Report:	Jul 25 2012