Name of Sponsor/Company: Astellas Pharma Inc.		
Name of Finished Product: Not applicable		
Name of Active Ingredient: ASP4901		

SYNOPSIS

Title of Study: A Phase 2, Randomized, Double-blind, Placebo-controlled, Active-referenced, Parallel-group Comparative Study of ASP4901 in Patients with Benign Prostatic Hyperplasia: Proof-of-concept Study

Investigators: [redacted]

Study Centers: 33 sites in Japan

Publication Based on the Study: No publications based on the results of this study were available at the time this report was approved.

Study Period:

Study Initiation Date (Date of First Informed Consent): 22 Jul 2013

Study Completion Date (Date of Last Evaluation): 04 Apr 2014

Phase of Development: Phase 2

Objectives:

Primary Objective:

- To compare the efficacy of ASP4901 400 mg with placebo in patients with benign prostatic hyperplasia (BPH).

Secondary Objectives:

- To compare the safety and tolerability of ASP4901 400 mg with placebo in patients with BPH.
- To investigate the pharmacokinetics of ASP4901 400 mg in patients with BPH.

Methodology:

This was a multicenter, randomized, parallel-group, placebo-controlled, active-referenced, double-blind study, consisting of a 4-week single-blind placebo run-in period, a 4-week double-blind treatment period and a 1-week safety follow-up period.

After obtaining written consent, patients who met the eligibility criteria at the preliminary enrollment (visit 1) were preliminarily enrolled and received the placebo orally once daily after breakfast for 4 weeks in a single-blind manner (single-blind placebo run-in period). Then, patients who met the eligibility criteria at the main enrollment (visit 2) were randomized to 1 of the 3 treatment groups (ASP4901 400 mg group, placebo group or tamsulosin 0.2 mg group) in a 1:1:1 ratio and received the assigned drug orally once daily after breakfast for 4 weeks in a double-blind manner (double-blind treatment period). Patients were followed up for a further week to confirm the safety of the study drugs after the treatment period (safety follow-up period). No study drugs were administered during the safety follow-up period. Patients were to visit the study sites at preliminary enrollment (visit 1), main enrollment (visit 2), week 1 of the treatment period (visit 3), week 2 of the treatment period (visit 4), week 4 of the treatment period (visit 5) and completion of the safety follow-up period (visit 6).

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Number of Patients (Planned, Enrolled and Analyzed):

Planned: 300 patients (100 patients in each treatment group)

Randomized: 320 patients (108, 106 and 106 in the placebo, ASP4901 400 mg and tamsulosin 0.2 mg groups, respectively)

Analyzed:

Full analysis set (FAS), pharmacokinetics analysis set (PKAS) and safety analysis set (SAF):

320 patients (108, 106 and 106 in the placebo, ASP4901 400 mg and tamsulosin 0.2 mg groups, respectively)

Per protocol set (PPS): 305 patients (100, 103 and 102 in the placebo, ASP4901 400 mg and tamsulosin 0.2 mg groups, respectively)

Diagnosis and Main Criteria for Inclusion:

The study population consisted of patients with BPH who had provided written informed consent and who satisfied all inclusion and exclusion criteria.

Inclusion Criteria:

A patient was eligible for the study if all of the following applied:

At Preliminary Enrollment (Visit 1)

1. Male patient aged 40 years or older and less than 75 years at the time of informed consent;
2. Patient who provided written informed consent;
3. Patient who was able to walk to the bathroom, to measure the voided volume and to keep a micturition diary without assistance;
4. Patient who had urination disorders associated with BPH for at least 12 weeks before giving informed consent;
5. Patient who had an International Prostate Symptom Score (IPSS) total score of 13 or higher;
6. Patient who had an IPSS quality of life (QOL) score of 3 or higher;
7. Patient who had a maximal urinary flow rate (Q_{max}) of ≥ 4 mL/sec and < 15 mL/sec, at which time voided volume was ≥ 150 mL (the latest data obtained within 12 weeks prior to visit 1 could be used);
8. Patient who had a prostate volume of ≥ 20 mL estimated by transabdominal or transrectal ultrasonography (the latest data obtained within 12 weeks prior to visit 1 could be used).

At Main Enrollment (Visit 2)

9. Patient who had an IPSS total score of 13 or higher;
10. Patient whose improvement rate in IPSS total score at visit 2 compared to visit 1 ([visit 1 - visit 2] / visit 1 x 100) was < 25%;
11. Patient with an IPSS QOL score of 3 or higher;

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12. Patient who had a Q_{max} of ≥ 4 mL/sec and < 15 mL/sec, at which time voided volume was ≥ 150 mL.

Exclusion Criteria:

A patient was excluded from participation if any of the following applied:

At Preliminary Enrollment (Visit 1)

1. Patient who had post-void residual volume (PVR) of > 350 mL as measured by ultrasonography;
2. Patient who had symptomatic urinary tract infection or had a history of such within 4 weeks prior to visit 1;
3. Patient who had one or more of diseases listed below or had a history of such:

- Recurrent urinary tract infection (≥ 3 episodes within 24 weeks prior to visit 1);
- Genitourinary or pelvic tumor (e.g., prostate tumor, bladder tumor, rectal tumor);
- Neurogenic bladder or a neurological disease which presents a risk of neurogenic bladder (e.g., Parkinson's disease, multiple sclerosis and diabetic complications);
- Cerebral infarction, spinal cord injury;
- Urethral stenosis, bladder neck stenosis;

Or patient who had undergone one or more of the following therapies:

- Pelvic radiation therapy;
- Surgical intervention for the bladder neck or prostate gland (e.g., prostatectomy, hyperthermia for BPH);

4. Patient who had chronic genitourinary inflammation or lower urinary tract pain syndrome (e.g., prostatitis, cystitis interstitial, bladder pain syndrome and chronic pelvic pain syndrome), or had a history of such within 24 weeks prior to visit 1;
5. Patient who had calculus of the lower urinary tract or had a history of such within 24 weeks prior to visit 1;
6. Patient who had clinically relevant cardiovascular or cerebrovascular disorders (e.g., myocardial infarction, uncontrollable angina pectoris, cardiac failure [New York Heart Association classification Class III or higher], stroke, uncontrolled hypertension [systolic blood pressure of 180 mmHg or higher or diastolic blood pressure of 110 mmHg or higher], and orthostatic hypotension), or had a history of such within 24 weeks prior to visit 1;
7. Patient who had a history of non-medication therapy for BPH (e.g., urethral stenting, intermittent self-catheterization, urethral catheterization and electric stimulation);
8. Patient who had a malignant tumor or had a history of such (excluding squamous cell carcinoma or basal cell carcinoma of skin tissue; including interventions to prevent recurrence) within 5 years prior to visit 1;
9. Patient who had received treatment with the following drugs during the specified period:

- Within 2 weeks prior to visit 1:
  BPH drugs such as α-blockers (excluding 5α-reductase inhibitors and antiandrogens), other drugs that affect the evaluation of ASP4901 or tamsulosin hydrochloride (αβ-blockers, αβ-agonists, α-blockers, α-agonists, cholinergic agonists, anticholinergics, drugs with anticholinergic effect [e.g., antidepressants, antihistamines, antiparkinsonian drugs, parasympathetic inhibitors/blockers including agents containing

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narcotic drugs], cholinesterase inhibitors, nitric acid preparations, diabetes insipidus drugs, loop diuretics, narcotics, phosphodiesterase [PDE] 5 inhibitors, Chinese herbal medicines for storage and voiding disorders);

- Within 24 weeks prior to visit 1: 5α-reductase inhibitors;
- Within 48 weeks prior to visit 1: antiandrogens;

10. Patient who was scheduled to undergo a cataract operation during the study period;
11. Patient who had serious hepatic diseases, renal diseases, immunological diseases or pulmonary diseases that were considered clinically relevant;
12. Patient who had hypersensitivity to ASP4901 or tamsulosin hydrochloride;
13. Patient who was judged by the investigator to be inappropriate as a study subject;
14. Patient who participated in any other clinical study or postmarketing clinical study (including those for medical devices) within 12 weeks prior to informed consent;
15. Patient who participated in any clinical study or postmarketing clinical study conducted in patients with BPH within 3 years prior to informed consent;
16. Patient who was employed by the sponsor, Contract Research Organization, Site Management Organization or study site involved in this clinical study.

<u>At Main Enrollment (Visit 2)</u>

17. Patient who had PVR of > 350 mL as measured by ultrasonography;
18. Patient who had aspartate aminotransferase (AST), alanine aminotransferase (ALT) or total bilirubin (TBL) levels exceeding the following criteria at visit 1:

- AST: 2 x upper limit of normal (ULN)
- ALT: 2 x ULN
- TBL: 1.5 x ULN

19. Patient who had a prostate specific antigen (PSA) level exceeding 10 ng/mL at visit 1;
20. Patient who had a 12-lead electrocardiogram (ECG) finding obtained at visit 1 that was judged by the investigator to be “abnormal–clinically significant”;
21. Patient who was judged by the investigator to be inappropriate as a study subject.

Test Product, Dose and Mode of Administration, Batch Numbers:

ASP4901 tablets 100 mg, each tablet containing 100 mg of ASP4901; Lot number, [redacted]

In the ASP4901 400 mg group, a total of 5 tablets (4 ASP4901 tablets 100 mg and 1 tamsulosin hydrochloride placebo tablet) were administered orally once daily after breakfast.

Duration of Treatment (or Duration of Study, if applicable):

Placebo run-in period: 4 weeks
Treatment period: 4 weeks

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Reference Product, Dose and Mode of Administration, Batch Numbers:

Placebo for ASP4901, indistinguishable tablet from ASP4901 tablets 100 mg in appearance; Lot number, [redacted]

Tamsulosin hydrochloride tablet 0.2 mg ([redacted] Tablet 0.2 mg), each tablet containing 0.2 mg of tamsulosin hydrochloride; Lot number, [redacted]

Placebo for tamsulosin hydrochloride, indistinguishable tablet from tamsulosin hydrochloride tablets 0.2 mg in appearance; Lot number, [redacted]

In the placebo group, a total of 5 tablets (4 ASP4901 placebo tablets and 1 tamsulosin hydrochloride placebo tablet) were administered orally once daily after breakfast.
In the tamsulosin 0.2 mg group, a total of 5 tablets (4 ASP4901 placebo tablets and 1 tamsulosin hydrochloride tablet 0.2 mg) were administered orally once daily after breakfast.

Drugs for the Placebo Run-in Period:

Placebo for ASP4901, indistinguishable tablet from ASP4901 tablets 100 mg in appearance; Lot number, [redacted]

Placebo for tamsulosin hydrochloride, indistinguishable tablet from tamsulosin hydrochloride tablets 0.2 mg in appearance; Lot number, [redacted]

During the placebo run-in period, a total of 5 tablets (4 ASP4901 placebo tablets and 1 tamsulosin hydrochloride placebo tablet) were administered orally once daily after breakfast.

Criteria for Evaluation:

Efficacy: Efficacy variables included:

1. Primary variable
- Change in total IPSS score from baseline to the final visit
2. Secondary variables
- Change from baseline in IPSS voiding symptom score
- Change from baseline in IPSS storage symptom score
- IPSS QOL score
- Change from baseline in each symptom score of IPSS
- IPSS responders
- Change from baseline in the mean number of micturitions per 24 hours
- Change from baseline in the mean number of urgency episodes per 24 hours
- Change from baseline in the mean number of incontinence episodes per 24 hours
- Change from baseline in the mean volume voided per micturition
- Change from baseline in the mean number of night time frequency per night
3. Other variables
- Urinary flow measurement: Q_{max}, average urinary flow rate (Q_{ave}), voided volume, voiding efficiency

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- PVR (measured by ultrasonography)
- BPH Impact Index
- Patient Global Impression
- Clinician Global Impression

Pharmacokinetics: Pharmacokinetic variables included:

- Plasma concentrations of the unchanged ASP4901 and ASP4901 glucuronide (URM-1) (only in the ASP4901 400 mg group)

Safety: Safety variables included:

- Adverse events (AEs)
- Laboratory test values (hematology, biochemistry, urinalysis)
- Vital signs (blood pressure and pulse ratein the sitting position)
- 12-lead ECG

Statistical Methods:

Efficacy: The following analyses were performed in the FAS as the main analysis set, and the PPS as the secondary analysis set. For each efficacy variable, adjusted changes from baseline to the final visit were generated from the analysis of covariance (ANCOVA) model with treatment group as a fixed factor, and baseline value as a covariate. Differences of the adjusted mean changes were calculated by subtracting the adjusted mean change in the placebo group from that in the treatment groups (ASP4901 400 mg or tamsulosin 0.2 mg groups). An IPSS responder was defined as a patient whose total IPSS score at the final visit improved by 25% or more from baseline, and the percentage of IPSS responders was compared between the ASP4901 and placebo groups using the chi-squared test. The improvement rates of Patient Global Impression and Clinician Global Impression at the final visit were compared between the ASP4901 and placebo groups using Fisher's exact test.

Pharmacokinetics: Scatter plots of plasma concentrations of unchanged ASP4901 and URM-1 vs elapsed time from last dosing were prepared.

Safety: An AE observed after the first administration of the study drugs for the treatment period was defined as a treatment-emergent AE (TEAE). The number and percentage of patients with TEAEs were summarized for each treatment group by SOC and preferred term (PT). Clinical laboratory parameters were summarized using summary statistics and shift tables for continuous data and frequency tables for categorical data. Vital signs were summarized using summary statistics. 12-lead ECGs were summarized in frequency tables.

Summary of Results/Conclusions:

Population:

A total of 504 patients gave informed consent and underwent screening procedures [Figure 1]. Among them, 397 patients entered the placebo run-in period, and 341 patients received the placebo for the placebo run-in

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period. A total of 320 patients underwent randomization to the placebo group (108 patients), ASP4901 400 mg group (106 patients) and tamsulosin 0.2 mg group (106 patients), and all randomized patients received the assigned study drug. Of these, 302 patients (101, 100 and 101 in the placebo, ASP4901 400 mg and tamsulosin 0.2 mg groups, respectively) completed the study, and 18 patients (7, 6 and 5 in the placebo, ASP4901 400 mg and tamsulosin 0.2 mg groups, respectively) discontinued the study.

Demographics and Other Baseline Characteristics:

No statistically significant imbalance across the 3 treatment groups was found in any demographic characteristics [Table 1]. The mean age in each treatment group ranged from 63.8 to 65.4 years. The percentage of patients aged 65 years or older was higher in the ASP4901 400 mg group compared with the placebo and tamsulosin 0.2 mg groups. The mean body mass index (BMI) ranged from 23.19 to 23.74 kg/m^2. The median duration of BPH was longer in the ASP4901 400 mg group compared with the placebo and tamsulosin 0.2 mg groups.

No statistically significant imbalance across the 3 treatment groups was found in any baseline characteristics, except for IPSS QOL score [Table 2]. A comparison for IPSS QOL score showed a statistically significant difference (P = 0.029, one way analysis of variance [ANOVA]), however, differences in the means between treatment groups on this parameter were not considered to be clinically relevant. The mean total IPSS score ranged from 18.1 to 18.7. The mean values of IPSS voiding symptom score, IPSS voiding symptom score (including Question 1) and IPSS storage symptom score ranged from 8.7 to 9.2, 10.8 to 11.3 and 6.8 to 7.4, respectively.

Efficacy Results:

- For the primary variable of reduction in total IPSS score, the difference [95% confidence interval (CI)] between the ASP4901 400 mg and placebo groups for the adjusted mean change from baseline to the final visit was -0.5 [-1.9, 0.8], which was not statistically significant (P = 0.433, ANCOVA) [Table 3]. The treatment effect of tamsulosin 0.2 mg was also not statistically significant compared with placebo (difference [95% CI] between the tamsulosin 0.2 mg and placebo groups, -1.1 [-2.5, 0.2], P = 0.103, ANCOVA). The magnitude of the treatment effect observed with ASP4901 400 mg was lower than observed with tamsulosin 0.2 mg, while there is no statistical evidence about the difference.
- Subgroup analyses on the primary variable of total IPSS score indicated that the treatment effects of ASP4901 400 mg may be larger in older patients, patients with larger prostates, higher PVRs and lower urinary flow rates.
- All IPSS symptom scores including IPSS voiding symptom score, IPSS voiding symptom score (including Question 1) and IPSS storage symptom score decreased from baseline at the final visit in all treatment groups [Table 4]. However, no statistically significant difference was found between the ASP4901 400 mg and placebo groups for adjusted mean changes from baseline to the final visit in any of the IPSS symptom scores (P = 0.584, 0.308 and 0.617, respectively, ANCOVA). Tamsulosin 0.2 mg showed a statistically significant difference for the adjusted mean change from baseline to the final visit compared

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with placebo for IPSS voiding symptom score (including Question1) but not on the IPSS voiding symptom score or IPSS storage symptom score.

- On the individual IPSS scores, ASP4901 400 mg demonstrated a statistically significant reduction from baseline compared with placebo on IPSS Question 1 (incomplete emptying) [Table 6]. Tamsulosin 0.2 mg demonstrated a statistically significant reduction from baseline compared with placebo on IPSS Questions 1 and 5 (weak urinary stream). None of the other individual IPSS scores were reduced to a statistically significant extent by either ASP4901 400 mg or tamsulosin 0.2 mg.
- ASP4901 400 mg demonstrated a statistically significant reduction from baseline in PVR compared with placebo and a statistically significant increase in the related variable of voiding efficiency [Table 9 and Table 10]. Tamsulosin 0.2 mg also demonstrated a statistically significant difference compared with placebo in these variables with a similar magnitude of treatment effect as ASP4901 400 mg.
- No significant difference was found between the ASP4901 400 mg and placebo groups in IPSS QOL score, BPH Impact Index, or improvement rates in any Global Impression instrument [Table 5, Table 11 and Table 12]. However, tamsulosin 0.2 mg showed a statistically significant difference in the adjusted mean change from baseline to the final visit compared with placebo on IPSS QOL score and improvement rates from baseline in Patient Global Impression (urinary symptoms) and Clinician Global Impression.
- None of the other efficacy variables were statistically significantly different between ASP4901 400 mg and placebo [Table 7 and Table 8]. However, tamsulosin 0.2 mg showed a statistically significant difference for the adjusted mean change from baseline to the final visit compared with placebo for mean volume voided per micturition and increase in percentage of IPSS responders in addition to the variables described earlier in this section.
- ASP4901 400 mg did not demonstrate proof of concept on efficacy variables in the treatment of patients with BPH, i.e., there was no statistically significant difference between ASP4901 400 mg and placebo treatments on the primary variable of total IPSS score. However ASP4901 400 mg demonstrated evidence of efficacy which was statistically significant on a number of secondary variables.
- The treatment effect size estimate for ASP4901 400 mg was lower than that of tamsulosin 0.2 mg on the primary variable and most other variables. However, there is no evidence that there is difference between the treatment effect of ASP4901 400 mg and tamsulosin 0.2 mg from a statistical perspective.

Pharmacokinetic Results:

At visit 3 and visit 5, plasma concentrations of ASP4901 ranged from 59.694 to 4135.759 ng/mL (with 2 samples < lower limit of quantification [LLOQ]) and plasma concentration of URM-1 ranged from 62.686 to 4473.211 ng/mL (with 2 samples < LLOQ). At visit 4, plasma concentrations of ASP4901 ranged from 2.644 to 650.740 ng/mL and plasma concentrations of URM-1 ranged from 6.406 to 2260.258 ng/mL.

Safety Results:

ASP4901 at a dose of 400 mg once daily for 4 weeks appeared to be safe and well tolerated in the majority of patients. However, a potential risk of renal impairment was identified.

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- There were no deaths in the study.
- The incidence of serious TEAEs was 1.9% in the placebo group and 0.9% in the ASP4901 400 mg group, and no serious TEAE was reported in the tamsulosin 0.2 mg group. There was 1 serious TEAE reported in the ASP4901 400 mg group (thalamus hemorrhage), which was considered by the investigator to be not related to the study drug [Table 15].
- The incidence of TEAEs was 50.0%, 45.3% and 39.6% in the placebo, ASP4901 400 mg and tamsulosin 0.2 mg groups, respectively, and that of drug-related TEAEs was 27.8%, 28.3% and 17.9% in the placebo, ASP4901 400 mg and tamsulosin 0.2 mg groups, respectively [Table 13 and Table 14]. Thus the incidence of TEAEs and drug-related TEAEs was similar between the placebo and ASP4901 400 mg groups.
- All TEAEs reported in the ASP4901 400 mg group were mild in severity, except for the severe event of thalamus hemorrhage referred to above.
- TEAEs reported in ≥ 2% of patients in the ASP4901 400 mg group were residual urine volume increased (8.5% in the ASP4901 400 mg group vs 10.2% in the placebo group), atrioventricular block first degree (6.6% vs 3.7%), blood urea increased (5.7% vs 0%), blood triglycerides increased (3.8% vs 6.5%), electrocardiogram T wave amplitude decreased (3.8% vs 2.8%), conduction disorder (2.8% vs 6.5%), nasopharyngitis (2.8% vs 5.6%), blood creatinine increased (2.8% vs 0%) and white blood cell count increased (2.8% vs 0%) [Table 13].
- Drug-related TEAEs reported in ≥ 2% of patients in the ASP4901 400 mg group were blood urea increased (4.7% in the ASP4901 400 mg group vs 0% in the placebo group), residual urine volume increased (4.7% vs 7.4%), atrioventricular block first degree (3.8% vs 2.8%), electrocardiogram T wave amplitude decreased (2.8% vs 2.8%), conduction disorder (2.8% vs 4.6%) and blood creatinine increased (2.8% vs 0%) [Table 14].
- The incidence of TEAEs leading to permanent discontinuation was 4.6%, 3.8% and 1.9% in the placebo, ASP4901 400 mg and tamsulosin 0.2 mg groups, respectively. TEAEs leading to permanent discontinuation reported in the ASP4901 400 mg group were blood creatinine increased, pyrexia, electrocardiogram ST segment depression and hydronephrosis (1 patient each) [Table 16].
- TEAEs related to PVR were reported in 9 patients (9 events of residual urine volume increased) in the ASP4901 400 mg group.
- No TEAEs related to effects on blood pressure were reported in the ASP4901 400 mg group.
- No TEAEs related to hypersensitivity were reported in the ASP4901 400 mg group.
- TEAEs related to gastrointestinal effects were reported in 3 patients (nausea, dyspepsia and diarrhea) in the ASP4901 400 mg group.
- In the ASP4901 400 mg group, no notable change from baseline was found in the mean values of any laboratory test parameter throughout the treatment period.
- TEAEs related to liver function abnormalities were reported in 2 patients (2 events of hepatic enzyme increased) in the ASP4901 400 mg group. In the ASP4901 400 mg group, there were no patients who

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exhibited potentially clinically significant values in liver function tests (AST or ALT > 3 x ULN, TBL > 2 x ULN, or alkaline phosphatase [ALP] > 1.5 x ULN) during the treatment period.

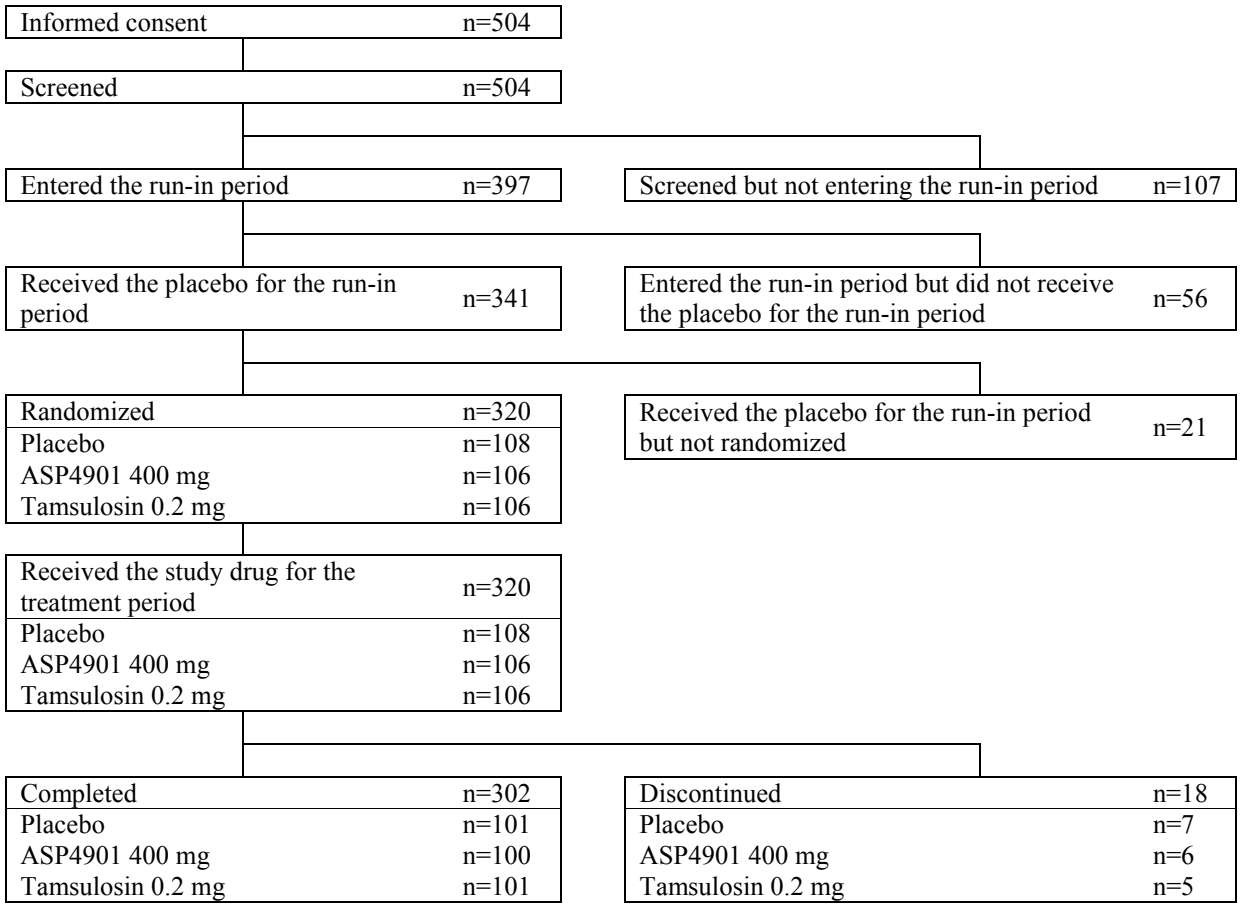
- TEAEs related to renal function impairment were reported in 1, 7 and 3 patients in the placebo, ASP4901 400 mg and tamsulosin 0.2 mg groups, respectively, and the frequency in the ASP4901 400 mg group was higher compared with the other treatment groups [Table 17]. TEAEs related to renal function impairment reported in the ASP4901 400 mg group were 6 events of blood urea increased, 3 events of blood creatinine increased and 1 event of hydronephrosis. One patient had serum creatinine level exceeding > 1.5 x ULN at the first post-baseline laboratory evaluation time point. The magnitude and timing of the increase in creatinine which was accompanied by an increase in blood urea represents moderate renal impairment consistent with an acute kidney injury.
- No clinically relevant changes in systolic blood pressure, diastolic blood pressure or pulse rate were observed during treatment with ASP4901 400 mg.
- There was no evidence to suggest that ASP4901 400 mg caused a clinically relevant increased risk of ECG abnormalities in comparison to placebo.
- TEAEs suggestive of bleeding events or decreases in hemoglobin level were reported in 2 patients (thalamus hemorrhage and anemia) in the ASP4901 400 mg group.

CONCLUSIONS:

- ASP4901 at a dose of 400 mg once daily for 4 weeks provided improvement in both voiding and storage symptoms in patients with BPH although statistically significant differences vs placebo were not shown.
- Whilst ASP4901 appeared safe and well tolerated in most patients, there is a clear signal of renal impairment with ASP4901 including a case of potential acute renal injury. This should be regarded as a significant safety finding with ASP4901.

Date of Report: 1 September 2014

Figure 1 Patient Disposition



Source: Table 12.1.1.1, Table 12.1.1.2 and Table 12.1.1.3

Table 1 Demographic Characteristics (FAS)

		Placebo (n=108)	ASP4901 400 mg (n=106)	Tamsulosin 0.2 mg (n=106)	P-value
Age (years)	Mean (SD)	63.8 (6.9)	65.4 (6.5)	64.4 (7.4)	0.244†
	Min, Max	44, 74	45, 74	41, 74	
Age group	< 65 years	52 (48.1%)	37 (34.9%)	45 (42.5%)	-
	≥ 65 years	56 (51.9%)	69 (65.1%)	61 (57.5%)	
Race	Asian	108 (100.0%)	106 (100.0%)	106 (100.0%)	-
Height (cm) [Visit 1]	Mean (SD)	167.20 (6.27)	167.15 (6.30)	167.78 (5.95)	0.706†
	Min, Max	151.0, 184.0	154.0, 181.5	153.0, 180.5	
Weight (kg) [Visit 1]	Mean (SD)	66.19 (9.87)	64.89 (8.01)	66.98 (10.65)	0.278†
	Min, Max	48.5, 105.3	45.5, 86.0	47.0, 108.8	
BMI (kg/m^2) [Visit 1]	Mean (SD)	23.63 (2.89)	23.19 (2.25)	23.74 (3.18)	0.316†
	Min, Max	18.5, 35.0	16.9, 29.1	17.5, 37.7	
BPH disease duration (months)	Mean (SD)	63.4 (64.9)	69.3 (54.7)	67.2 (62.4)	0.765†
	Median	48.0	56.0	47.0	
	Min, Max	2, 534	3, 368	4, 371	
BPH disease duration group	< 6 months	7 (6.5%)	4 (3.8%)	8 (7.5%)	0.352‡
	≥ 6 months, < 1 year	9 (8.3%)	4 (3.8%)	10 (9.4%)	
	≥ 1 year, < 3 years	24 (22.2%)	23 (21.7%)	23 (21.7%)	
	≥ 3 years, < 5 years	29 (26.9%)	24 (22.6%)	17 (16.0%)	
	≥ 5 years	39 (36.1%)	51 (48.1%)	48 (45.3%)	
Medical conditions	No	17 (15.7%)	18 (17.0%)	19 (17.9%)	0.912‡
	Yes	91 (84.3%)	88 (83.0%)	87 (82.1%)	

Full analysis set (FAS): patients who received the study drug for the treatment period at least once and in whom at least 1 or more evaluable efficacy variables were measured prior to and after the beginning of the treatment period.

n (%)

ANOVA: analysis of variance, BMI: body mass index, BPH: benign prostatic hyperplasia

† One way ANOVA, ‡ Chi-squared test

Source: Table 12.1.2.1.1

Table 2 Baseline Characteristics (FAS)

		Placebo	ASP4901 400 mg	Tamsulosin 0.2 mg	P-value
Total IPSS score	n	108	106	106	-
	Mean (SD)	18.7 (4.5)	18.1 (4.1)	18.1 (4.1)	0.438§
	Min, Max	13, 32	13, 32	13, 31	
IPSS voiding symptom score	n	108	106	106	-
	Mean (SD)	9.1 (3.0)	9.2 (3.0)	8.7 (2.9)	0.478§
	Min, Max	3, 15	0, 15	1, 15	
IPSS voiding symptom score (including Question 1)	n	108	106	106	-
	Mean (SD)	11.3 (3.7)	11.3 (3.6)	10.8 (3.4)	0.487§
	Min, Max	4, 20	0, 20	4, 20	
IPSS storage symptom score	n	108	106	106	-
	Mean (SD)	7.4 (2.6)	6.8 (2.6)	7.3 (2.6)	0.220§
	Min, Max	0, 13	0, 14	1, 13	
IPSS QOL score	n	108	106	106	-
	Mean (SD)	4.6 (1.0)	4.2 (1.0)	4.3 (1.0)	0.029§
	Min, Max	3, 6	3, 6	3, 6	
Mean number of micturitions per 24 hours†	n	108	106	106	-
	Mean (SD)	9.87 (2.74)	9.48 (2.43)	9.80 (2.85)	0.533§
	Min, Max	4.0, 18.3	4.7, 16.7	4.7, 19.0	
Mean number of urgency episodes per 24 hours†	n	79	77	75	-
	Mean (SD)	3.32 (3.22)	2.85 (2.51)	3.36 (3.17)	0.501§
	Min, Max	0.3, 14.3	0.3, 11.3	0.3, 13.3	
Mean number of incontinence episodes per 24 hours†	n	15	14	14	-
	Mean (SD)	1.00 (0.79)	0.81 (1.51)	1.07 (1.13)	0.829§
	Min, Max	0.3, 2.7	0.3, 6.0	0.3, 4.7	
Mean volume voided per micturition (mL)†	n	108	106	106	-
	Mean (SD)	178.985 (59.258)	177.411 (51.428)	179.324 (49.794)	0.962§
	Min, Max	73.09, 514.50	74.24, 341.82	78.18, 341.67	
Mean number of night time frequency per night†	n	96	87	94	-
	Mean (SD)	1.50 (0.96)	1.68 (0.87)	1.70 (1.12)	0.302§
	Min, Max	0.5, 4.5	0.5, 5.0	0.5, 5.0	
Q_{max} (mL/sec)	n	108	106	106	-
	Mean (SD)	10.06 (2.77)	10.37 (2.40)	9.96 (2.78)	0.510§
	Min, Max	4.4, 14.7	4.7, 14.9	4.3, 14.9	
Q_{ave} (mL/sec)	n	108	106	106	-
	Mean (SD)	4.23 (1.69)	4.24 (1.41)	4.10 (1.49)	0.738§
	Min, Max	1.0, 8.5	1.4, 8.5	0.9, 7.9	
Voided volume (uroflowmetry) (mL)	n	108	106	106	-
	Mean (SD)	240.26 (70.40)	245.62 (84.66)	241.91 (81.42)	0.879§
	Min, Max	154.0, 527.0	151.0, 581.0	151.0, 580.0	
Voiding efficiency‡ (%)	n	108	106	106	-
	Mean (SD)	86.61 (13.87)	87.59 (12.93)	86.90 (13.20)	0.859§
	Min, Max	45.8, 100.0	42.6, 100.0	40.4, 100.0	
PVR (mL)	n	108	106	106	-
	Mean (SD)	43.70 (53.70)	41.39 (53.38)	42.89 (54.03)	0.950§
	Min, Max	0.0, 255.4	0.0, 263.7	0.0, 264.1	
BPH Impact Index total score	n	108	106	106	-
	Mean (SD)	5.2 (2.9)	4.9 (3.1)	5.0 (3.1)	0.840§
	Min, Max	0, 13	0, 12	0, 12	

Full analysis set (FAS): patients who received the study drug for the treatment period at least once and in whom at least 1 or more evaluable efficacy variables were measured prior to and after the beginning of the treatment period.

ANOVA: analysis of variance, BPH: benign prostatic hyperplasia, IPSS: International Prostate Symptom Score, PVR: post-void residual volume, Q_{ave}: average urinary flow rate, Q_{max}: maximal urinary flow rate, QOL: quality of life

† The mean variables were calculated based on the micturition diary data for 3 days immediately before visit 2 (week 0). For the mean number of urgency episodes per 24 hours, the mean number of incontinence episodes per 24 hours and the mean number of night time frequency per night, patients who did not have the symptom at baseline were excluded from the analysis.

‡ Voiding efficiency (%): [voided volume / (voided volume + PVR)] x 100

§ One way ANOVA

Source: Table 12.1.2.2.1

Table 3 Adjusted Mean Changes from Baseline to the Final Visit in Total IPSS Score, LOCF (FAS)

Treatment Group	Adjusted Mean Change (SE) [95% CI]	Difference of Adjusted Mean Changes (SE) [95% CI]	P-value
Placebo	-5.2 (0.5) [-6.1, -4.2]	-	-
ASP4901 400 mg	-5.7 (0.5) [-6.6, -4.7]	-0.5 (0.7) [-1.9, 0.8]	0.433
Tamsulosin 0.2 mg	-6.3 (0.5) [-7.2, -5.3]	-1.1 (0.7) [-2.5, 0.2]	0.103

Full analysis set (FAS): patients who received the study drug for the treatment period at least once and in whom at least 1 or more evaluable efficacy variables were measured prior to and after the beginning of the treatment period.

Adjusted mean changes from baseline were generated from the ANCOVA model with treatment group as a fixed factor, and baseline value as a covariate. Differences of the adjusted mean changes were calculated by subtracting the adjusted mean change in the placebo group from that in the treatment group. P-values were from pairwise comparison vs placebo within the ANCOVA model. Statistical results were considered significant at the P = 0.05 level.

ANCOVA: analysis of covariance, CI: confidence interval, IPSS: International Prostate Symptom Score, LOCF: last observation carried forward

Source: Table 12.3.1.1.1

Table 4 Adjusted Mean Changes from Baseline to the Final Visit in IPSS Symptom Scores, LOCF (FAS)

Treatment Group	Adjusted Mean Change (SE) [95% CI]	Difference of Adjusted Mean Changes (SE) [95% CI]	P-value
IPSS voiding symptom score†			
Placebo	-2.8 (0.3) [-3.4, -2.3]	-	-
ASP4901 400 mg	-3.1 (0.3) [-3.7, -2.5]	-0.2 (0.4) [-1.1, 0.6]	0.584
Tamsulosin 0.2 mg	-3.5 (0.3) [-4.1, -2.9]	-0.7 (0.4) [-1.5, 0.1]	0.101
IPSS voiding symptom score (including Question 1‡)			
Placebo	-3.2 (0.3) [-3.9, -2.6]	-	-
ASP4901 400 mg	-3.7 (0.3) [-4.4, -3.1]	-0.5 (0.5) [-1.5, 0.5]	0.308
Tamsulosin 0.2 mg	-4.2 (0.3) [-4.9, -3.5]	-1.0 (0.5) [-1.9, -0.0]	0.048
IPSS storage symptom score§			
Placebo	-1.9 (0.2) [-2.3, -1.5]	-	-
ASP4901 400 mg	-2.0 (0.2) [-2.4, -1.6]	-0.2 (0.3) [-0.7, 0.4]	0.617
Tamsulosin 0.2 mg	-2.0 (0.2) [-2.5, -1.6]	-0.2 (0.3) [-0.8, 0.4]	0.591

Full analysis set (FAS): patients who received the study drug for the treatment period at least once and in whom at least 1 or more evaluable efficacy variables were measured prior to and after the beginning of the treatment period.

Adjusted mean changes from baseline were generated from the ANCOVA model with treatment group as a fixed factor, and baseline value as a covariate. Differences of the adjusted mean changes were calculated by subtracting the adjusted mean change in the placebo group from that in the treatment group. P-values were from pairwise comparison vs placebo within the ANCOVA model. Statistical results were considered significant at the P = 0.05 level.

ANCOVA: analysis of covariance, CI: confidence interval, IPSS: International Prostate Symptom Score, LOCF: last observation carried forward

† Voiding symptoms included intermittency (Question 3), weak urinary stream (Question 5) and hesitancy (Question 6).
‡ Question1: incomplete emptying
§ Storage symptoms included frequency (Question 2), urgency (Question 4) and nocturia (Question 7).

Source: Table 12.3.2.1.1.1

Table 5 Adjusted Mean Changes from Baseline to the Final Visit in IPSS QOL Score, LOCF (FAS)

Treatment Group	Adjusted Mean Change (SE) [95% CI]	Difference of Adjusted Mean Changes (SE) [95% CI]	P-value
Placebo	-0.7 (0.1) [-0.9, -0.5]	-	-
ASP4901 400 mg	-0.8 (0.1) [-1.0, -0.6]	-0.1 (0.2) [-0.4, 0.2]	0.477
Tamsulosin 0.2 mg	-1.1 (0.1) [-1.3, -0.9]	-0.4 (0.2) [-0.7, -0.1]	0.016

Full analysis set (FAS): patients who received the study drug for the treatment period at least once and in whom at least 1 or more evaluable efficacy variables were measured prior to and after the beginning of the treatment period.

Adjusted mean changes from baseline were generated from the ANCOVA model with treatment group as a fixed factor, and baseline value as a covariate. Differences of the adjusted mean changes were calculated by subtracting the adjusted mean change in the placebo group from that in the treatment group. P-values were from pairwise comparison vs placebo within the ANCOVA model. Statistical results were considered significant at the P = 0.05 level.

ANCOVA: analysis of covariance, CI: confidence interval, IPSS: International Prostate Symptom Score, LOCF: last observation carried forward, QOL: quality of life

Source: Table 12.3.2.2.1.1

Table 6 Adjusted Mean Changes from Baseline to the Final Visit in Each IPSS Question, LOCF (FAS)

Variable	Treatment Group	Adjusted Mean Change (SE) [95% CI]	Difference of Adjusted Mean Changes (SE) [95% CI]	P-value
Question 1	Placebo	-0.4 (0.1) [-0.6, -0.2]	-	-
	ASP4901 400 mg	-0.7 (0.1) [-0.9, -0.5]	-0.3 (0.1) [-0.6, -0.0]	0.044
	Tamsulosin 0.2 mg	-0.7 (0.1) [-0.9, -0.5]	-0.3 (0.1) [-0.6, -0.1]	0.020
Question 2	Placebo	-0.9 (0.1) [-1.1, -0.7]	-	-
	ASP4901 400 mg	-1.0 (0.1) [-1.3, -0.8]	-0.1 (0.2) [-0.5, 0.2]	0.374
	Tamsulosin 0.2 mg	-1.0 (0.1) [-1.3, -0.8]	-0.1 (0.2) [-0.5, 0.2]	0.347
Question 3	Placebo	-0.9 (0.1) [-1.1, -0.6]	-	-
	ASP4901 400 mg	-0.9 (0.1) [-1.1, -0.7]	-0.0 (0.2) [-0.3, 0.3]	0.952
	Tamsulosin 0.2 mg	-1.1 (0.1) [-1.3, -0.8]	-0.2 (0.2) [-0.5, 0.1]	0.234
Question 4	Placebo	-0.6 (0.1) [-0.8, -0.4]	-	-
	ASP4901 400 mg	-0.8 (0.1) [-1.0, -0.6]	-0.2 (0.1) [-0.5, 0.1]	0.236
	Tamsulosin 0.2 mg	-0.7 (0.1) [-0.9, -0.5]	-0.1 (0.1) [-0.4, 0.2]	0.594
Question 5	Placebo	-1.1 (0.1) [-1.4, -0.8]	-	-
	ASP4901 400 mg	-1.3 (0.1) [-1.6, -1.1]	-0.2 (0.2) [-0.6, 0.1]	0.223
	Tamsulosin 0.2 mg	-1.5 (0.1) [-1.8, -1.3]	-0.5 (0.2) [-0.8, -0.1]	0.022
Question 6	Placebo	-0.9 (0.1) [-1.1, -0.6]	-	-
	ASP4901 400 mg	-0.8 (0.1) [-1.1, -0.6]	0.0 (0.2) [-0.3, 0.4]	0.797
	Tamsulosin 0.2 mg	-1.0 (0.1) [-1.2, -0.7]	-0.1 (0.2) [-0.4, 0.2]	0.599
Question 7	Placebo	-0.3 (0.1) [-0.5, -0.2]	-	-
	ASP4901 400 mg	-0.2 (0.1) [-0.4, -0.1]	0.1 (0.1) [-0.1, 0.3]	0.251
	Tamsulosin 0.2 mg	-0.3 (0.1) [-0.5, -0.2]	0.0 (0.1) [-0.2, 0.2]	0.939

Full analysis set (FAS): patients who received the study drug for the treatment period at least once and in whom at least 1 or more evaluable efficacy variables were measured prior to and after the beginning of the treatment period.

Adjusted mean changes from baseline were generated from the ANCOVA model with treatment group as a fixed factor, and baseline value as a covariate. Differences of the adjusted mean changes were calculated by subtracting the adjusted mean change in the placebo group from that in the treatment group. P-values were from pairwise comparison vs placebo within the ANCOVA model. Statistical results were considered significant at the P = 0.05 level.

Question 1: incomplete emptying, Question 2: frequency, Question 3: intermittency, Question 4: urgency, Question 5: weak urinary stream, Question 6: hesitancy, Question 7: nocturia

ANCOVA: analysis of covariance, CI: confidence interval, IPSS: International Prostate Symptom Score, LOCF: last observation carried forward

Source: Table 12.3.2.3.1.1

Table 7 Number and Percentage of IPSS Responders (FAS)

Treatment Group	Percentage of IPSS Responders [95% CI]	P-value
Placebo	57/108 (52.8%) [42.9, 62.5]	-
ASP4901 400 mg	67/106 (63.2%) [53.3, 72.4]	0.122
Tamsulosin 0.2 mg	73/106 (68.9%) [59.1, 77.5]	0.016

Full analysis set (FAS): patients who received the study drug for the treatment period at least once and in whom at least 1 or more evaluable efficacy variables were measured prior to and after the beginning of the treatment period.

IPSS responder: patient who had 25% or more improvement in total IPSS score from visit 2 (week 0) at the final visit.

P-values were from chi-squared test comparison vs placebo. Statistical results were considered significant at the P = 0.05 level.

CI: confidence interval, IPSS: International Prostate Symptom Score

Source: Table 12.3.2.3.4.1

Table 8 Adjusted Mean Changes from Baseline to the Final Visit in Micturition Diary Parameters, LOCF (FAS)

Treatment Group	Adjusted Mean Change (SE) [95% CI]	Difference of Adjusted Mean Changes (SE) [95% CI]	P-value
Mean number of micturitions per 24 hours			
Placebo	0.02 (0.17) [-0.32, 0.36]	-	-
ASP4901 400 mg	-0.01 (0.17) [-0.36, 0.33]	-0.03 (0.25) [-0.52, 0.45]	0.892†
Tamsulosin 0.2 mg	-0.33 (0.17) [-0.67, 0.01]	-0.35 (0.25) [-0.84, 0.13]	0.153†
Mean number of urgency episodes per 24 hours			
Placebo	-0.70 (0.27) [-1.23, -0.17]	-	-
ASP4901 400 mg	-1.21 (0.27) [-1.74, -0.68]	-0.51 (0.38) [-1.26, 0.24]	0.182†
Tamsulosin 0.2 mg	-1.04 (0.27) [-1.58, -0.50]	-0.34 (0.38) [-1.10, 0.41]	0.371†
Mean number of incontinence episodes per 24 hours			
Placebo	-0.18 (0.32) [-0.82, 0.46]	-	-
ASP4901 400 mg	-0.66 (0.33) [-1.33, -0.00]	-0.49 (0.46) [-1.41, 0.43]	0.575‡
Tamsulosin 0.2 mg	-0.55 (0.33) [-1.21, 0.11]	-0.38 (0.46) [-1.30, 0.55]	0.733‡
Mean volume voided per micturition (mL)			
Placebo	2.180 (3.055) [-3.829, 8.190]	-	-
ASP4901 400 mg	3.923 (3.083) [-2.144, 9.989]	1.742 (4.340) [-6.797, 10.282]	0.688†
Tamsulosin 0.2 mg	13.565 (3.083) [7.498, 19.631]	11.384 (4.340) [2.845, 19.923]	0.009†
Mean number of night time frequency per night			
Placebo	-0.13 (0.08) [-0.30, 0.03]	-	-
ASP4901 400 mg	-0.21 (0.09) [-0.38, -0.03]	-0.07 (0.12) [-0.31, 0.16]	0.538†
Tamsulosin 0.2 mg	-0.07 (0.08) [-0.24, 0.09]	0.06 (0.12) [-0.17, 0.29]	0.619†

Full analysis set (FAS): patients who received the study drug for the treatment period at least once and in whom at least 1 or more evaluable efficacy variables were measured prior to and after the beginning of the treatment period.

Adjusted mean changes from baseline were generated from the ANCOVA model with treatment group as a fixed factor, and baseline value as a covariate. Differences of the adjusted mean changes were calculated by subtracting the adjusted mean change in the placebo group from that in the treatment group.

Statistical results were considered significant at the P = 0.05 level.

The mean variables were calculated based on the micturition diary data for 3 days immediately before visit 2 (week 0).

ANCOVA: analysis of covariance, CI: confidence interval, LOCF: last observation carried forward

† P-values were from pairwise comparison vs placebo within the ANCOVA model.

‡ P-values were from pairwise comparison vs placebo within rank ANCOVA.

Source: Table 12.3.2.4.1.1

Table 9 Adjusted Mean Changes from Baseline to the Final Visit in Urinary Flow Measurements, LOCF (FAS)

Variable/ Treatment Group	Adjusted Mean Change (SE) [95% CI]	Difference of Adjusted Mean Changes (SE) [95% CI]	P-value
Q_{max} (mL/sec)			
Placebo	2.42 (0.47) [1.49, 3.35]	-	-
ASP4901 400 mg	2.08 (0.48) [1.14, 3.01]	-0.35 (0.67) [-1.66, 0.97]	0.607
Tamsulosin 0.2 mg	2.49 (0.47) [1.56, 3.43]	0.07 (0.67) [-1.25, 1.39]	0.916
Q_{ave} (mL/sec)			
Placebo	0.76 (0.19) [0.39, 1.14]	-	-
ASP4901 400 mg	0.72 (0.19) [0.35, 1.10]	-0.04 (0.27) [-0.57, 0.49]	0.875
Tamsulosin 0.2 mg	1.05 (0.19) [0.68, 1.42]	0.29 (0.27) [-0.24, 0.81]	0.289
Voided volume (mL)			
Placebo	31.71 (9.52) [12.97, 50.44]	-	-
ASP4901 400 mg	13.27 (9.57) [-5.56, 32.09]	-18.44 (13.50) [-45.01, 8.13]	0.173
Tamsulosin 0.2 mg	26.27 (9.57) [7.44, 45.09]	-5.44 (13.50) [-32.00, 21.12]	0.687
Voiding efficiency† (%)			
Placebo	-0.51 (0.86) [-2.20, 1.18]	-	-
ASP4901 400 mg	2.08 (0.86) [0.38, 3.78]	2.59 (1.22) [0.19, 4.99]	0.034
Tamsulosin 0.2 mg	2.99 (0.86) [1.29, 4.69]	3.50 (1.22) [1.10, 5.89]	0.004

Full analysis set (FAS): patients who received the study drug for the treatment period at least once and in whom at least 1 or more evaluable efficacy variables were measured prior to and after the beginning of the treatment period.

Adjusted mean changes from baseline were generated from the ANCOVA model with treatment group as a fixed factor, and baseline value as a covariate. Differences of the adjusted mean changes were calculated by subtracting the adjusted mean change in the placebo group from that in the treatment group. P-values were from pairwise comparison vs placebo within the ANCOVA model.

Statistical results were considered significant at the P = 0.05 level.

ANCOVA: analysis of covariance, CI: confidence interval, LOCF: last observation carried forward, PVR: post-void residual volume, Q_{ave}: average urinary flow rate, Q_{max}: maximal urinary flow rate

† Voiding efficiency (%): [voided volume / (voided volume + PVR)] x 100

Source: Table 12.3.3.3.1.1

Table 10 Adjusted Mean Changes from Baseline to the Final Visit in PVR, LOCF (FAS)

Treatment Group	Adjusted Mean Change (SE) [95% CI]	Difference of Adjusted Mean Changes (SE) [95% CI]	P-value
Placebo	6.69 (4.07) [-1.32, 14.70]	-	-
ASP4901 400 mg	-8.56 (4.11) [-16.64, -0.47]	-15.25 (5.78) [-26.63, -3.87]	0.009
Tamsulosin 0.2 mg	-12.13 (4.11) [-20.21, -4.04]	-18.82 (5.78) [-30.20, -7.44]	0.001

Full analysis set (FAS): patients who received the study drug for the treatment period at least once and in whom at least 1 or more evaluable efficacy variables were measured prior to and after the beginning of the treatment period.

Unit: mL

Adjusted mean changes from baseline were generated from the ANCOVA model with treatment group as a fixed factor, and baseline value as a covariate. Differences of the adjusted mean changes were calculated by subtracting the adjusted mean change in the placebo group from that in the treatment group. P-values were from pairwise comparison vs placebo within the ANCOVA model. Statistical results were considered significant at the P = 0.05 level.

ANCOVA: analysis of covariance, CI: confidence interval, LOCF: last observation carried forward, PVR: post-void residual volume

Source: Table 12.3.3.2.1.1

Table 11 Adjusted Mean Change from Baseline to the Final Visit in BPH Impact Index, LOCF (FAS)

Treatment Group	Adjusted Mean Change (SE) [95% CI]	Difference of Adjusted Mean Changes (SE) [95% CI]	P-value
Placebo	-0.7 (0.2) [-1.2, -0.3]	-	-
ASP4901 400 mg	-1.1 (0.2) [-1.6, -0.7]	-0.4 (0.3) [-1.1, 0.2]	0.197
Tamsulosin 0.2 mg	-1.2 (0.2) [-1.7, -0.8]	-0.5 (0.3) [-1.1, 0.1]	0.122

Full analysis set (FAS): patients who received the study drug for the treatment period at least once and in whom at least 1 or more evaluable efficacy variables were measured prior to and after the beginning of the treatment period.

Adjusted mean changes from baseline were generated from the ANCOVA model with treatment group as a fixed factor, and baseline value as a covariate. Differences of the adjusted mean changes are calculated by subtracting the adjusted mean change in the placebo group from that in the treatment group. P-values were from pairwise comparison vs placebo within the ANCOVA model. Statistical results were considered significant at the P = 0.05 level.

ANCOVA: analysis of covariance, BPH: benign prostatic hyperplasia, CI: confidence interval, LOCF: last observation carried forward

Source: Table 12.3.3.1.1.1

Table 12 Number and Percentage of Patients who Achieved Improvement in Global Impression, LOCF (FAS)

Variable/Treatment Group	Percentage of Improved Patients [95% CI]	P-value
Patient Global Impression (urinary symptoms)		
Placebo	17/108 (15.7%) [9.4, 24.0]	-
ASP4901 400 mg	18/106 (17.0%) [10.4, 25.5]	0.855
Tamsulosin 0.2 mg	33/106 (31.1%) [22.5, 40.9]	0.010
Patient Global Impression (current health status)		
Placebo	5/108 (4.6%) [1.5, 10.5]	-
ASP4901 400 mg	6/106 (5.7%) [2.1, 11.9]	0.767
Tamsulosin 0.2 mg	12/106 (11.3%) [6.0, 18.9]	0.081
Clinician Global Impression		
Placebo	18/108 (16.7%) [10.2, 25.1]	-
ASP4901 400 mg	22/106 (20.8%) [13.5, 29.7]	0.486
Tamsulosin 0.2 mg	32/106 (30.2%) [21.7, 39.9]	0.024

Full analysis set (FAS): patients who received the study drug for the treatment period at least once and in whom at least 1 or more evaluable efficacy variables were measured prior to and after the beginning of the treatment period.

Patients who had achieved a “very much improved” or “much improved” were defined as “improved patients”, and the percentage of the patients was defined as the improvement rate.

P-values were from Fisher’s exact test comparison vs placebo. Statistical results were considered significant at the P = 0.05 level.

CI: confidence interval, LOCF: last observation carried forward

Source: Table 12.3.3.4.1

Table 13 Incidence of Treatment-emergent Adverse Events (SAF)

MedDRA (version 16.0) System Organ Class Preferred Term	Placebo (n=108)	ASP4901 400 mg (n=106)	Tamsulosin 0.2 mg (n=106)
Overall	**54 (50.0%)**	**48 (45.3%)**	**42 (39.6%)**
Blood and lymphatic system disorders	**0**	**1 (0.9%)**	**0**
Anaemia	0	1 (0.9%)	0
Cardiac disorders	**15 (13.9%)**	**14 (13.2%)**	**13 (12.3%)**
Atrioventricular block first degree	4 (3.7%)	7 (6.6%)	6 (5.7%)
Bundle branch block left	2 (1.9%)	1 (0.9%)	1 (0.9%)
Bundle branch block right	0	0	2 (1.9%)
Conduction disorder	7 (6.5%)	3 (2.8%)	2 (1.9%)
Sinus bradycardia	0	1 (0.9%)	1 (0.9%)
Sinus tachycardia	1 (0.9%)	0	0
Supraventricular extrasystoles	1 (0.9%)	2 (1.9%)	0
Ventricular extrasystoles	1 (0.9%)	1 (0.9%)	3 (2.8%)
Ear and labyrinth disorders	**1 (0.9%)**	**0**	**0**
Vertigo	1 (0.9%)	0	0
Eye disorders	**1 (0.9%)**	**0**	**1 (0.9%)**
Conjunctival haemorrhage	1 (0.9%)	0	0
Conjunctivitis	1 (0.9%)	0	0
Conjunctivitis allergic	0	0	1 (0.9%)
Eyelids pruritus	0	0	1 (0.9%)
Gastrointestinal disorders	**4 (3.7%)**	**3 (2.8%)**	**5 (4.7%)**
Abdominal discomfort	0	0	3 (2.8%)
Abdominal pain lower	1 (0.9%)	0	0
Diarrhoea	0	1 (0.9%)	1 (0.9%)
Diverticulum intestinal haemorrhagic	1 (0.9%)	0	0
Dyspepsia	0	1 (0.9%)	0
Gastritis	1 (0.9%)	0	0
Nausea	0	1 (0.9%)	0
Paraesthesia oral	1 (0.9%)	0	0
Stomatitis	0	0	1 (0.9%)
General disorders and administration site conditions	**0**	**2 (1.9%)**	**0**
Pyrexia	0	2 (1.9%)	0
Infections and infestations	**8 (7.4%)**	**6 (5.7%)**	**6 (5.7%)**
Cystitis	1 (0.9%)	0	0
Gastroenteritis viral	0	1 (0.9%)	0
Keratitis herpetic	0	0	1 (0.9%)
Nasopharyngitis	6 (5.6%)	3 (2.8%)	5 (4.7%)
Pharyngitis	1 (0.9%)	1 (0.9%)	0
Sinusitis	0	1 (0.9%)	0
Injury, poisoning and procedural complications	**1 (0.9%)**	**0**	**0**
Thermal burn	1 (0.9%)	0	0
Investigations	**34 (31.5%)**	**31 (29.2%)**	**19 (17.9%)**
Aspartate aminotransferase increased	1 (0.9%)	0	1 (0.9%)
Beta 2 microglobulin increased	2 (1.9%)	0	0
Beta 2 microglobulin urine increased	1 (0.9%)	1 (0.9%)	2 (1.9%)
Blood alkaline phosphatase increased	0	0	2 (1.9%)
Blood bilirubin increased	1 (0.9%)	0	0
Blood creatine increased	0	1 (0.9%)	0

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MedDRA (version 16.0) System Organ Class Preferred Term	Placebo (n=108)	ASP4901 400 mg (n=106)	Tamsulosin 0.2 mg (n=106)
Blood creatine phosphokinase increased	3 (2.8%)	2 (1.9%)	5 (4.7%)
Blood creatinine increased	0	3 (2.8%)	1 (0.9%)
Blood triglycerides increased	7 (6.5%)	4 (3.8%)	1 (0.9%)
Blood urea increased	0	6 (5.7%)	2 (1.9%)
Blood urine present	0	0	1 (0.9%)
Electrocardiogram PR prolongation	0	1 (0.9%)	0
Electrocardiogram QT prolonged	3 (2.8%)	0	0
Electrocardiogram ST segment depression	5 (4.6%)	2 (1.9%)	1 (0.9%)
Electrocardiogram T wave amplitude decreased	3 (2.8%)	4 (3.8%)	0
Electrocardiogram T wave biphasic	1 (0.9%)	2 (1.9%)	1 (0.9%)
Glucose urine present	2 (1.9%)	2 (1.9%)	0
Heart rate increased	1 (0.9%)	0	0
Hepatic enzyme increased	0	2 (1.9%)	1 (0.9%)
Platelet count decreased	1 (0.9%)	0	0
Protein urine present	0	0	1 (0.9%)
Residual urine volume increased	11 (10.2%)	9 (8.5%)	7 (6.6%)
Urinary casts	0	1 (0.9%)	0
White blood cell count decreased	0	1 (0.9%)	0
White blood cell count increased	0	3 (2.8%)	1 (0.9%)
Metabolism and nutrition disorders	**1 (0.9%)**	**0**	**0**
Hypertriglyceridaemia	1 (0.9%)	0	0
Musculoskeletal and connective tissue disorders	**1 (0.9%)**	**1 (0.9%)**	**2 (1.9%)**
Back pain	0	1 (0.9%)	1 (0.9%)
Groin pain	1 (0.9%)	0	0
Myalgia	0	0	1 (0.9%)
Nervous system disorders	**1 (0.9%)**	**2 (1.9%)**	**1 (0.9%)**
Headache	1 (0.9%)	0	0
Somnolence	0	1 (0.9%)	1 (0.9%)
Thalamus haemorrhage	0	1 (0.9%)	0
Psychiatric disorders	**0**	**0**	**1 (0.9%)**
Anxiety	0	0	1 (0.9%)
Renal and urinary disorders	**2 (1.9%)**	**1 (0.9%)**	**1 (0.9%)**
Calculus ureteric	1 (0.9%)	0	0
Hydronephrosis	1 (0.9%)	1 (0.9%)	0
Renal impairment†	0	0	1 (0.9%)
Respiratory, thoracic and mediastinal disorders	**2 (1.9%)**	**1 (0.9%)**	**0**
Laryngeal discomfort	1 (0.9%)	0	0
Oropharyngeal pain	1 (0.9%)	0	0
Upper respiratory tract inflammation	0	1 (0.9%)	0
Vascular disorders	**0**	**2 (1.9%)**	**0**
Hypertension	0	2 (1.9%)	0

Safety analysis set (SAF): patients who received the study drug for the treatment period at least once.

n (%)

† One patient ([redacted]) in the ASP4901 400 mg group experienced an increase in serum creatine level, which was assessed by the sponsor as a case of considerable renal impairment. However, as the investigator reported the event as a preferred term of "blood creatine increased," this case is not included in the category of "renal impairment."

Source: Table 12.6.1.2

Table 14 Incidence of Drug-related Treatment-emergent Adverse Events (SAF)

MedDRA (version 16.0) System Organ Class Preferred Term	Placebo (n=108)	ASP4901 400 mg (n=106)	Tamsulosin 0.2 mg (n=106)
Overall	**30 (27.8%)**	**30 (28.3%)**	**19 (17.9%)**
Blood and lymphatic system disorders	**0**	**1 (0.9%)**	**0**
Anaemia	0	1 (0.9%)	0
Cardiac disorders	**12 (11.1%)**	**10 (9.4%)**	**6 (5.7%)**
Atrioventricular block first degree	3 (2.8%)	4 (3.8%)	2 (1.9%)
Bundle branch block left	2 (1.9%)	1 (0.9%)	0
Bundle branch block right	0	0	1 (0.9%)
Conduction disorder	5 (4.6%)	3 (2.8%)	0
Sinus bradycardia	0	0	1 (0.9%)
Sinus tachycardia	1 (0.9%)	0	0
Supraventricular extrasystoles	1 (0.9%)	2 (1.9%)	0
Ventricular extrasystoles	0	1 (0.9%)	2 (1.9%)
Gastrointestinal disorders	**4 (3.7%)**	**2 (1.9%)**	**3 (2.8%)**
Abdominal discomfort	0	0	2 (1.9%)
Abdominal pain lower	1 (0.9%)	0	0
Diverticulum intestinal haemorrhagic	1 (0.9%)	0	0
Dyspepsia	0	1 (0.9%)	0
Gastritis	1 (0.9%)	0	0
Nausea	0	1 (0.9%)	0
Paraesthesia oral	1 (0.9%)	0	0
Stomatitis	0	0	1 (0.9%)
General disorders and administration site conditions	**0**	**1 (0.9%)**	**0**
Pyrexia	0	1 (0.9%)	0
Infections and infestations	**1 (0.9%)**	**0**	**0**
Cystitis	1 (0.9%)	0	0
Investigations	**18 (16.7%)**	**20 (18.9%)**	**9 (8.5%)**
Aspartate aminotransferase increased	0	0	1 (0.9%)
Beta 2 microglobulin increased	1 (0.9%)	0	0
Beta 2 microglobulin urine increased	1 (0.9%)	1 (0.9%)	2 (1.9%)
Blood alkaline phosphatase increased	0	0	2 (1.9%)
Blood bilirubin increased	1 (0.9%)	0	0
Blood creatine phosphokinase increased	1 (0.9%)	0	1 (0.9%)
Blood creatinine increased	0	3 (2.8%)	1 (0.9%)
Blood triglycerides increased	1 (0.9%)	1 (0.9%)	1 (0.9%)
Blood urea increased	0	5 (4.7%)	2 (1.9%)
Blood urine present	0	0	1 (0.9%)
Electrocardiogram PR prolongation	0	1 (0.9%)	0
Electrocardiogram QT prolonged	2 (1.9%)	0	0
Electrocardiogram ST segment depression	3 (2.8%)	1 (0.9%)	0
Electrocardiogram T wave amplitude decreased	3 (2.8%)	3 (2.8%)	0
Electrocardiogram T wave biphasic	1 (0.9%)	1 (0.9%)	1 (0.9%)
Heart rate increased	1 (0.9%)	0	0
Hepatic enzyme increased	0	2 (1.9%)	1 (0.9%)
Residual urine volume increased	8 (7.4%)	5 (4.7%)	1 (0.9%)
White blood cell count decreased	0	1 (0.9%)	0
White blood cell count increased	0	1 (0.9%)	1 (0.9%)

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MedDRA (version 16.0) System Organ Class Preferred Term	Placebo (n=108)	ASP4901 400 mg (n=106)	Tamsulosin 0.2 mg (n=106)
Nervous system disorders	**1 (0.9%)**	**0**	**1 (0.9%)**
Headache	1 (0.9%)	0	0
Somnolence	0	0	1 (0.9%)
Renal and urinary disorders	**1 (0.9%)**	**1 (0.9%)**	**1 (0.9%)**
Hydronephrosis	1 (0.9%)	1 (0.9%)	0
Renal impairment†	0	0	1 (0.9%)
Respiratory, thoracic and mediastinal disorders	**1 (0.9%)**	**0**	**0**
Laryngeal discomfort	1 (0.9%)	0	0

Safety analysis set (SAF): patients who received the study drug for the treatment period at least once.

n (%)

† One patient ([redacted]) in the ASP4901 400 mg group experienced an increase in serum creatine level, which was assessed by the sponsor as a case of considerable renal impairment. However, as the investigator reported the event as a preferred term of "blood creatine increased," this case is not included in the category of "renal impairment."

Source: Table 12.6.1.3

Table 15 Serious Treatment-emergent Adverse Events without an Outcome of Death

Patient Number	Age	MedDRA Preferred Term (Reported Term)	Onset/End Day† (Last Dose Day†)	Severity	Outcome	Relationship to Study Drug
Placebo						
[redacted]	[redacted]	Diverticulum intestinal haemorrhagic‡ ([redacted])	19/- (18)	Severe	Not recovered	Possible
[redacted]	[redacted]	Residual urine volume increased ([redacted])	30/- (30)	Mild	Not recovered	Possible
ASP4901 400 mg						
[redacted]	[redacted]	Thalamus haemorrhage ([redacted])	32/- (29)	Severe	Not recovered	Not related

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TEAE: treatment-emergent adverse event

† The day of the prescribing of the study drugs for the treatment period was defined as day 1.

‡ TEAE leading to permanent discontinuation

Source: Appendix 13.2.5.1 and Appendix 13.2.7.4

Table 16 Treatment-emergent Adverse Events Leading to Permanent Discontinuation

Patient Number	Age	MedDRA Preferred Term (Reported Term)	Onset/End Day† (Last Dose Day†)	Severity	Outcome	Relationship to Study Drug
Placebo						
[redacted]	[redacted]	Abdominal pain lower ([redacted])	18/21 (20)	Moderate	Recovered	Possible
[redacted]	[redacted]	Diverticulum intestinal haemorrhagic‡ ([redacted])	19/- (18)	Severe	Not recovered	Possible
[redacted]	[redacted]	Electrocardiogram QT prolonged ([redacted])	15/22 (18)	Mild	Recovered	Probable
[redacted]	[redacted]	Electrocardiogram ST segment depression ([redacted])	10/15 (14)	Mild	Recovered	Possible
[redacted]	[redacted]	Bundle branch block left ([redacted])	8/- (9)	Mild	Not recovered	Possible
ASP4901 400 mg						
[redacted]	[redacted]	Blood creatinine increased ([redacted])	10/-§ (27)	Mild	Not recovered§	Possible
[redacted]	[redacted]	Pyrexia ([redacted])	2/- (8)	Mild	Not recovered	Possible
[redacted]	[redacted]	Electrocardiogram ST segment depression ([redacted])	9/15 (14)	Mild	Recovered	Possible
[redacted]	[redacted]	Hydronephrosis ([redacted])	15/- (22)	Mild	Not recovered	Probable
Tamsulosin 0.2 mg						
[redacted]	[redacted]	Electrocardiogram ST segment depression ([redacted])	8/15 (14)	Mild	Recovered	Not related
[redacted]	[redacted]	Stomatitis ([redacted])	12/27 (20)	Mild	Recovered	Possible

MedDRA version16.0

TEAE: treatment-emergent adverse event

† The day of the prescribing of the study drugs for the treatment period was defined as day 1.

‡ Serious TEAE

§ According to follow-up observation, the event resolved on day 92.

Source: Appendix 13.2.5.1 and Appendix 13.2.7.5

Table 17 Treatment-emergent Adverse Events Related to Renal Function Impairment

Patient Number	Age	MedDRA Preferred Term (Reported Term)	Onset/End Day† (Last Dose Day†)	Severity	Outcome	Relationship to Study Drug
Placebo						
[redacted]	[redacted]	Hydronephrosis ([redacted])	37/- (30)	Mild	Not recovered	Possible
ASP4901 400 mg						
[redacted]	[redacted]	Blood creatinine increased‡ ([redacted])	10/-§ (27)	Mild	Not recovered§	Possible
		Blood urea increased ([redacted])	16/29 (27)	Mild	Recovered	Possible
[redacted]	[redacted]	Blood urea increased ([redacted])	8/29 (29)	Mild	Recovered	Not related
[redacted]	[redacted]	Blood urea increased ([redacted])	15/- (32)	Mild	Recover-ing	Possible
[redacted]	[redacted]	Blood urea increased ([redacted])	29/37 (29)	Mild	Recovered	Possible
[redacted]	[redacted]	Blood creatine increased ([redacted])	8/18 (28)	Mild	Recovered	Not related
		Blood urea increased ([redacted])	8/- (28)	Mild	Not recovered	Possible
[redacted]	[redacted]	Blood creatinine increased ([redacted])	29/- (29)	Mild	Not recovered	Possible
		Blood urea increased ([redacted])	29/39 (29)	Mild	Recovered	Possible
[redacted]	[redacted]	Hydronephrosis‡ ([redacted])	15/- (22)	Mild	Not recovered	Probable
		Blood creatinine increased ([redacted])	15/- (22)	Mild	Not recovered	Probable
Tamsulosin 0.2 mg						
[redacted]	[redacted]	Blood creatinine increased ([redacted])	9/16 (30)	Mild	Recovered	Possible
		Blood urea increased ([redacted])	9/36 (30)	Mild	Recovered	Possible
		Blood creatinine increased ([redacted])	30/36 (30)	Mild	Recovered	Possible
[redacted]	[redacted]	Blood urea increased ([redacted])	29/36 (29)	Mild	Recovered	Possible
[redacted]	[redacted]	Renal impairment ([redacted])	8/36 (29)	Mild	Recovered	Possible

MedDRA version16.0

BUN: blood urea nitrogen, TEAE: treatment-emergent adverse event

† The day of the prescribing of the study drugs for the treatment period was defined as day 1.

‡ TEAE leading to permanent discontinuation

§ According to follow-up observation, the event resolved on day 92.

Source: Appendix 13.2.5.1 and Appendix 13.2.7.1