Name of Sponsor/Company: Astellas Pharma Europe B.V.		
Name of Finished Product: Vesomni®		
Name of Active Ingredient: tamsulosin/solifenacin		

SYNOPSIS

Title of Study: A randomized, double-blind, parallel group, placebo-controlled, multi-center study of fixed dose combinations of solifenacin succinate (6 mg and 9 mg) with tamsulosin hydrochloride OCAS 0.4 mg and tamsulosin hydrochloride OCAS 0.4 mg monotherapy, in male subjects with lower urinary tract symptoms (LUTS) associated with benign prostatic hyperplasia (BPH) with a substantial storage component.

Coordinating investigator: [redacted], [redacted] in the Netherlands

Responsible Medical Officer: [redacted]

Study Center(s): A total of 112 centers in 13 European countries participated in the study

Publication (reference): Not applicable at the time of the synopsis

Study Period: January 2010-March 2011

Date of first enrollment (Study initiation date): 11 January 2010

Date of last evaluation (Study completion date): 1 March 2011

Phase of Development: 3

Objectives:

Primary

- To assess the efficacy of the fixed-dose combination (FDC) tamsulosin/solifenacin 0.4 mg/6 mg and 0.4 mg/9 mg in comparison with tamsulosin oral controlled absorption system (TOCAS) 0.4 mg monotherapy in male patients with LUTS associated with BPH with a substantial storage component.

Secondary

- To assess the safety and tolerability of the FDC tamsulosin/solifenacin 0.4 mg/6 mg and 0.4 mg/9 mg in male patients with LUTS associated with BPH with a substantial storage component.
- To assess the efficacy of the FDC tamsulosin/solifenacin 0.4 mg/6 mg and 0.4 mg/9 mg in comparison with placebo in male patients with LUTS associated with BPH with a substantial storage component.

Methodology: This was a randomized, double-blind, placebo-controlled, parallel group, multicenter study. The study comprised a single-blind, 2-week placebo run-in period followed by a randomized, double-blind, placebo-controlled, 12-week treatment period. Patients visited the clinic at screening (visit 1), at the end of the placebo run-in period (visit 2, i.e., baseline visit), and after 4, 8 and 12 weeks of double-blind treatment (visits 3, 4, and 5). After the placebo run-in period, patients were randomized to one of the following treatments: placebo, TOCAS 0.4 mg, FDC tamsulosin/solifenacin 0.4 mg/6 mg or FDC tamsulosin/solifenacin 0.4 mg/9 mg in a 1:1:1:1 ratio.

Name of Sponsor/Company: Astellas Pharma Europe B.V.		
Name of Finished Product: Vesomni®		
Name of Active Ingredient: tamsulosin/solifenacin		

Number of Patients (planned, enrolled and analyzed): A sample size of 274 patients per treatment group or a total sample size of 1096 patients was planned. Assuming that 10% of the randomized patients would be excluded from the per protocol set (PPS) (used for statistical testing), a total of 1220 patients were to be randomized. Assuming a drop-out rate of 16% during the placebo run-in, approximately 1452 patients were expected to be enrolled.

A total of 1334 patients were randomized. Four analysis populations were used for statistical analysis: the safety analysis set (SAF; n=1328), the intention-to-treat (ITT) population (n=1275), the full analysis set (FAS; n=1235), and the PPS (n=1086).

Diagnosis and Main Criteria for Inclusion: Male patients aged ≥ 45 years fulfilling the following criteria: voiding symptoms (including incomplete emptying of the bladder, intermittency, weak stream or hesitancy) and storage symptoms (including frequency and urgency), diagnosed as LUTS associated with BPH for ≥ 3 months, a total international prostate symptom score (IPSS) of ≥ 13, a substantial amount of storage symptoms for ≥ 3 months (a micturition frequency of ≥ 8 and at least 2 episodes of urgency with a patient perception of the intensity of urgency scale [PPIUS] grade 3 or 4 per day), a maximum flow rate (Q_{max}) of ≥ 4.0 mL/s and ≤ 12.0 mL/s, with a voided volume of ≥ 120 mL during free flow.

Test Product, Dose and Mode of Administration, Batch Numbers: Throughout the study, the patient took 3 tablets per day: TOCAS 0.4 mg tablet or matching placebo tablet, FDC tamsulosin/solifenacin 0.4 mg/6 mg tablet or matching placebo tablet, or FDC tamsulosin/solifenacin 0.4 mg/9 mg tablet or matching placebo tablet. Study medication was taken orally once daily in the morning. Medication was taken with a glass of water and swallowed whole. The medication intake could take place with or without food.

Lot Numbers: TOCAS 0.4 mg tablets, lot [redacted]; placebo for TOCAS, lot [redacted]

FDC tamsulosin/solifenacin 0.4 mg/6 mg, lot [redacted]; placebo for FDC 0.4 mg/6 mg, lot [redacted]

FDC tamsulosin/solifenacin 0.4 mg/9 mg, lot [redacted]; placebo for FDC 0.4 mg/9 mg, lot [redacted]

Duration of Treatment: The study comprised a single-blind, 2-week placebo run-in period followed by a randomized, double-blind, placebo-controlled, 12-week treatment period.

Criteria for Evaluation: Efficacy: There were two primary efficacy variables: change from baseline to endpoint in total IPSS, and change from baseline to endpoint in total urgency score per 24 hours (TUS, calculated from PPIUS urgency grades recorded in the micturition diary).

Secondary efficacy variables were change from baseline to endpoint in:

- From micturition diary: Mean number of micturitions/24 h, mean voided volume/micturition, maximum volume voided/micturition, mean number of urgency episodes (PPIUS grade 3 or 4)/24 h, mean number of urgency incontinence episodes/24 h, mean number of incontinence episodes/24 h, mean number of nocturia episodes/24 h, mean number of pads used/24 h

Name of Sponsor/Company: Astellas Pharma Europe B.V.		
Name of Finished Product: Vesomni®		
Name of Active Ingredient: tamsulosin/solifenacin		

- From IPSS questionnaire: IPSS voiding score, IPSS storage score, IPSS quality of life (QoL) score, individual IPSS scores
- From overactive bladder questionnaire (OAB-q): total and subscores
- European quality of life-5 dimensions questionnaire (EQ-5D) scores
- Patient global impression question (PGI): overall bladder symptoms score, general health score
- Clinician global impression question (CGI): overall bladder symptoms score

Safety: Safety was assessed from adverse events (AEs), safety laboratory assessments, vital signs, electrocardiogram (ECG), physical examination, post void residual (PVR) volume and free flow measurements (Q_{max} and Q_{mean}).

Statistical Methods: The primary analysis for total IPSS was done in two stages. First, superiority of the FDCs tamsulosin/solifenacin 0.4 mg/6 mg and 0.4 mg/9 mg versus placebo was tested in total IPSS. If superiority was achieved for a given FDC arm versus placebo, then the noninferiority of that FDC arm versus TOCAS alone was tested using a noninferiority margin of 0.5 points in total IPSS. If a FDC showed noninferiority in total IPSS versus TOCAS alone, the superiority of that FDC versus TOCAS alone was further investigated.

Superiority of the FDCs tamsulosin/solifenacin 0.4 mg/6 mg and 0.4 mg/9 mg versus TOCAS alone for TUS was tested on the change from baseline to endpoint in the FAS.

The study was regarded successful if at least 1 FDC had shown superiority to placebo for total IPSS (in FAS), noninferiority versus TOCAS alone for total IPSS (in both the FAS and PPS), along with superiority versus TOCAS alone for TUS (in FAS).

The primary analysis was adjusted for the multiplicity of the combination regimes using the Hochberg procedure, so that the two-sided significance level was 0.05 for the overall procedure for superiority testing and a one-sided significance level of 0.025 for non-inferiority testing. Both primary variables were analyzed by means of a mixed model including fixed factors for treatment group and country. Site nested within country was included as a random effect and the baseline value as a covariate. All primary and secondary analysis variables were summarized using descriptive statistics. Continuous variables were summarized using the descriptive statistical mean, standard deviation (SD), minimum, median, maximum. For continuous variables that have a skewed distribution (continuous laboratory variables, ECG, PVR, mean number of (urgency) incontinence episodes/ 24 h and EQ-5D VAS), quartiles were also provided. Categorical variables were described using absolute and relative frequency and shift tables were provided for some categorical variables.

Summary of Results:

Subject Disposition and Analysis Sets: A total of 2141 patients were screened, of whom 1690 took at least 1 dose of placebo run-in medication. A total of 1334 patients were randomized of whom 1329 (99.6%) took at least one dose of the double-blind study medication and of these 1328 had any data reported after the first dose

Name of Sponsor/Company: Astellas Pharma Europe B.V.		
Name of Finished Product: Vesomni®		
Name of Active Ingredient: tamsulosin/solifenacin		

of double-blind study medication (i.e., the SAF). A total of 129 (9.7%) patients discontinued in the SAF. The main reason for treatment discontinuation was an AE (2.8%) followed by withdrawal of consent (2.3%) and protocol violations (2.1%).

- The SAF consisted of 1328 patients who received at least one dose of double-blind study drug and for whom any data was reported after intake of the first dose of study drug.
- The ITT consisted of 1275 patients who received at least one dose of double-blind study drug and who had either a total IPSS at baseline or a TUS at baseline.
- The FAS consisted of 1235 patients who received at least one dose of double-blind study drug and who had either a total IPSS at baseline and at least 1 postbaseline total IPSS during the double-blind treatment period or a TUS at baseline and at least 1 postbaseline TUS during the double-blind treatment period.
- The PPS included 1086 patients of the FAS without major protocol violations

Demographics (SAF): Almost 100% of the patients were Caucasian males. The mean age of the patients was 65.4 years (range 45-86 years) and their mean BMI was 28.1 kg/m^2.

Disease Characteristics (FAS, SAF): The mean total IPSS was 18.6 with a mean IPSS storage score of 8.8 and a mean IPSS voiding score of 9.8. The mean TUS for the entire population was 27.1 and the mean number (PPIUS grade 3 or 4) urgency episodes was 5.4. The mean number of micturitions/24 h was 11.4. The majority of patients had ≥ 3 (PPIUS grade 3 or 4) urgency episodes/24 h (79.9%) and experienced at least 1 nocturia episode (96.1%). The mean Q_{max} was 8.9 mL/s, the mean PVR 36.5 mL and the mean prostate weight 38.1 g. There were no relevant differences between the treatment groups with respect to the baseline disease characteristics. Approximately half of the patients (55.8%) had previously used medical treatment for LUTS associated with BPH, these were mostly $alpha_1$-adrenoceptor antagonists (49.2%) and antimuscarinics agents (14.3%). Prior medications used for conditions other than LUTS associated with BPH were used by 71.1% of patients and were mainly those used for cardiovascular disorders (e.g. ACE inhibitors, selective beta blocking agents). A total of 72.7% of patients used concomitant medication during the study, which were comparable to those used prior to the study.

Study Drug Exposure: The mean exposure ranged from 80.1 to 81.7 days across treatment arms. The majority of patients had a treatment exposure 71-98 days. The median treatment duration was 84.0 days in all treatment arms.

Efficacy Results: Primary efficacy variables: The mean total IPSS was reduced from baseline to endpoint in the FDC tamsulosin/solifenacin 0.4 mg/6 mg group by 7.0 and in the FDC tamsulosin/solifenacin 0.4 mg/9 mg groups by 6.5 [Table 1]. The mean reduction in total IPSS from baseline to endpoint with both FDCs was statistically significantly greater than the reduction of 5.4 with placebo. The reduction in total IPSS with the FDC tamsulosin/solifenacin 0.4 mg/6 mg was proven noninferior to the reduction with TOCAS 0.4 mg (6.2);

Name of Sponsor/Company: Astellas Pharma Europe B.V.		
Name of Finished Product: Vesomni®		
Name of Active Ingredient: tamsulosin/solifenacin		

superiority vs TOCAS 0.4 mg was not shown. Although the improvement with the FDC tamsulosin/solifenacin 0.4 mg/9 mg was numerically better than with TOCAS 0.4 mg, the reduction in total IPSS with the FDC 0.4 mg/9 mg was not proven non-inferior to the reduction with TOCAS 0.4 mg. The results in the FAS were confirmed by those in the PPS.

Table 1 Change from Baseline to Endpoint in Total IPSS (FAS)

	Placebo (n = 318)	**TOCAS 0.4 mg (n = 298)**	**FDC 0.4/6 (n = 313)**	**FDC 0.4/9 (n = 301)**
Baseline				
n	318	297	311	299
Mean (SD)	19.0 (4.48)	18.7 (4.63)	18.3 (4.31)	18.6 (4.31)
Endpoint†				
n	316	297	312	297
Mean (SD)	12.8 (6.51)	11.7 (6.07)	10.7 (5.82)	11.4 (6.15)
Mean change from baseline (SE)	-5.4 (0.41)	-6.2 (0.42)	-7.0 (0.41)	-6.5 (0.42)
Mean change vs placebo (SE)		-0.8 (0.41)	-1.6 (0.40)	-1.1 (0.41)
95% CI		(-1.6, -0.0)	(-2.4, -0.9)	(-1.9, -0.3)
P-value vs placebo		0.039‡	<0.001§	0.006§
Mean change vs TOCAS 0.4 mg (SE)			-0.8 (0.41)	-0.3 (0.41)
95% CI			(-1.61, -0.01)	(-1.10, 0.52)
97.5% CI			(-1.73, 0.11)§	(-1.22, 0.64)
P-value vs TOCAS 0.4 mg noninferiority testing			0.001§	0.028
P-value vs TOCAS 0.4 mg superiority testing			0.048	0.483

FAS: full analysis set - patients who received at least one dose of double-blind study drug and who had either a total IPSS at baseline and at least 1 postbaseline total IPSS during the double-blind treatment period or a TUS at baseline and at least 1 postbaseline TUS during the double-blind treatment period with the exclusion of 5 patients with invalid questionnaires

FDC 0.4/6: fixed-dose combination tamsulosin/solifenacin 0.4 mg/6 mg;
FDC 0.4/9: fixed-dose combination tamsulosin/solifenacin 0.4 mg/9 mg;
TOCAS: tamsulosin oral controlled absorption system; IPSS: international prostate symptom score; TUS: total urgency score

† All variables are adjusted estimates from mixed model, including treatment group and country as fixed factors, centre as a random effect and baseline as a covariate, except for mean (SD) total IPSS at endpoint.
‡ Statistically significant not multiplicity adjusted

§ Statistically significant with multiplicity adjustments

Source: Tables 12.3.1.1.1, 12.3.3.1.1 & 12.3.4.1.1

The FDC tamsulosin/solifenacin 0.4 mg/6 mg and the FDC tamsulosin/solifenacin 0.4 mg/9 mg reduced TUS from baseline to endpoint by 8.1 and 7.6, respectively [Table 2]. The reduction in TUS with both FDCs was statistically significantly greater than that with placebo (-4.4). The reduction in TUS with the FDC tamsulosin/solifenacin 0.4 mg/6 mg was also statistically significantly greater than that with TOCAS 0.4 mg (-6.7). This was not the case for the FDC tamsulosin/solifenacin 0.4 mg/9 mg.

Name of Sponsor/Company: Astellas Pharma Europe B.V.		
Name of Finished Product: Vesomni®		
Name of Active Ingredient: tamsulosin/solifenacin		

Table 2 Change from Baseline to Endpoint in TUS (FAS)

	Placebo (n = 320)	TOCAS 0.4 mg (n = 299)	FDC 0.4/6 (n = 314)	FDC 0.4/9 (n = 302)
Baseline				
n	318	299	314	302
Mean (SD)	27.1 (8.80)	27.8 (9.02)	27.0 (8.66)	26.4 (8.34)
Endpoint†				
n	315	295	313	302
Mean (SD)	22.3 (11.39)	20.4 (9.54)	18.5 (9.13)	18.7 (9.51)
Mean change from baseline (SE)	-4.4 (0.68)	-6.7 (0.69)	-8.1 (0.67)	-7.6 (0.69)
Mean change vs placebo (SE)		-2.3 (0.64)	-3.7 (0.62)	-3.2 (0.63)
95% CI		(-3.5, -1.0)	(-4.9, -2.5)	(-4.4, -1.9)
P-value vs placebo		< 0.001‡	< 0.001‡	< 0.001‡
Mean change vs TOCAS 0.4 mg (SE)			-1.4 (0.64)	-0.9 (0.64)
95% CI			(-2.7, -0.2)	(-2.2, 0.4)
97.5% CI			(-2.9, 0.0)	(-2.3, 0.5)
P-value vs TOCAS 0.4 mg			0.025§	0.162

FAS: full analysis set - patients who received at least one dose of double-blind study drug and who had either a total IPSS at baseline and at least 1 postbaseline total IPSS during the double-blind treatment period or a TUS at baseline and at least 1 postbaseline TUS during the double-blind treatment period

FDC 0.4/6: fixed-dose combination tamsulosin/solifenacin 0.4 mg/6 mg;
FDC 0.4/9: fixed-dose combination tamsulosin/solifenacin 0.4 mg/9 mg;
TOCAS: tamsulosin oral controlled absorption system;
IPSS: international prostate symptom score; TUS: total urgency score

† All variables are adjusted estimates from mixed model, including treatment group and country as fixed factors, centre as a random effect and baseline as a covariate, except for mean (SD) TUS at endpoint.
‡ Statistically significant not multiplicity adjusted
§ Statistically significantly superior with multiplicity adjustment.

Source: Tables 12.3.1.2.1, 12.3.3.2.1 & 12.3.4.2.1

Secondary efficacy variables:

The FDC tamsulosin/solifenacin 0.4 mg/6 mg improved the mean IPSS storage score from baseline to endpoint (-3.5) to a statistically significantly greater extent than both placebo (-2.4) and TOCAS 0.4 mg (-2.9). It also improved the mean IPSS voiding score (-3.7) to a statistically greater extent than placebo (-3.0). The FDC tamsulosin/solifenacin 0.4 mg/9 mg improved the mean IPSS storage score (-3.3) to a statistically significantly greater extent than placebo, but not the mean IPSS voiding score (-3.2).

The FDC tamsulosin/solifenacin 0.4 mg/6 mg improved the micturition diary parameters number of micturitions/24 h, number of (PPIUS grade 3 or 4) urgency episodes/24 h, number of nocturia episodes/24 h, mean voided volume per micturition and maximum voided volume per micturition to a statistically significantly greater extent than placebo. The mean reduction in number of micturitions/24 h and the mean increase in mean

Name of Sponsor/Company: Astellas Pharma Europe B.V.		
Name of Finished Product: Vesomni®		
Name of Active Ingredient: tamsulosin/solifenacin		

voided volume per micturition with the FDC tamsulosin/solifenacin 0.4 mg/6 mg were also statistically significantly greater than with TOCAS 0.4 mg.

The FDC tamsulosin/solifenacin 0.4 mg/9 mg improved the micturition diary parameters number of micturitions/24 h, mean number of (PPIUS grade 3 or 4) urgency episodes/24 h, mean voided volume per micturition and maximum voided volume per micturition to a statistically significantly greater extent than placebo. The mean increase in mean voided volume per micturition with the FDC tamsulosin/solifenacin 0.4 mg/9 mg was also statistically significantly greater than with TOCAS 0.4 mg.

QoL related to LUTS/BPH was improved by both FDCs as shown by a statistically significantly greater decrease in IPSS QoL score with both FDCs compared to placebo and TOCAS 0.4 mg.

In addition, bother due to storage symptoms was improved by the FDC tamsulosin/solifenacin 0.4 mg/6 mg. The OAB-q symptom bother score was improved by the FDC tamsulosin/solifenacin 0.4 mg/6 mg to a statistically significantly greater extent than placebo; the greater improvement compared to TOCAS 0.4 mg did not reach statistical significance (P=0.068). The HRQoL total score and the HRQoL coping, concern, sleep and social subscale scores were improved to a statistically significantly greater extent than with either placebo and TOCAS 0.4 mg.

The FDC tamsulosin/solifenacin 0.4 mg/9 mg improved the OAB-q symptom bother score, the HRQoL total score and the HRQoL coping and concern subscale scores to a statistically significantly greater extent than with both placebo and TOCAS 0.4 mg. The HRQoL social score was improved to a statistically significantly greater extent than with placebo, but not compared with TOCAS 0.4 mg.

Significantly more patients treated with the FDC tamsulosin/solifenacin 0.4 mg/6 mg and 0.4 mg/9 mg reported an improvement in overall bladder symptoms since the start of the study compared to patients treated with placebo and TOCAS 0.4 mg. This was confirmed by the clinicians who also reported a significant improvement in overall bladder symptoms in comparison with placebo. In addition, significantly more patients treated with either FDC reported an improvement in general health since the start of the study compared to patients treated with placebo. The difference between the FDC tamsulosin/solifenacin 0.4 mg/9 mg and TOCAS 0.4 mg was also statistically significant (P=0.031) whereas that between the FDC tamsulosin/solifenacin 0.4 mg/6 mg and TOCAS 0.4 mg approached statistical significance (P=0.053).

Statistically significant correlations ($P < 0.001$) were observed between change from baseline to endpoint in TUS score and the PGI, CGI, IPSS QoL score and OAB-q symptom bother score at endpoint irrespective of treatment.

None of the efficacy variables showed a dependency on age at baseline (> 65 years ≤ 65 years) or the number of (PPIUS grade 3 or 4) urgency episodes/24 h at baseline (< 3 vs ≥ 3).

Safety Results: The FDCs tamsulosin/solifenacin 0.4 mg/6 mg and 0.4 mg/9 mg were generally well tolerated. The majority of the TEAEs were of mild to moderate intensity. Two patients died during the study. One patient

Name of Sponsor/Company: Astellas Pharma Europe B.V.		
Name of Finished Product: Vesomni®		
Name of Active Ingredient: tamsulosin/solifenacin		

in the TOCAS 0.4 mg group died due to intestinal ischemia and myocardial infarction, which the investigator considered as not related to study medication. One patient in the FDC tamsulosin/solifenacin 0.4 mg/6 mg group died because of small cell lung cancer, which the investigator also considered as not related to study medication.

Serious AEs (SAEs) were experienced by 0.9% of patients in the placebo group, 3.1% of patients in the TOCAS 0.4 mg group, 1.5% of patients in the FDC tamsulosin/solifenacin 0.4 mg/6 mg group and 2.8% of patients in the FDC tamsulosin/solifenacin 0.4 mg/9 mg group. A total of 42 SAEs were reported of which 19 were considered possibly or probably related to treatment by the investigator. The incidence of treatment-related SAEs was 0.3% on placebo, 1.2% on TOCAS 0.4 mg, 0% on the FDC tamsulosin/solifenacin 0.4 mg/6 mg and 1.5% on the FDC tamsulosin/solifenacin 0.4 mg/9 mg. Discontinuations due to TEAEs were infrequent. The incidence of treatment discontinuations due to TEAEs was 1.5% in the placebo group, 2.8% in TOCAS 0.4 mg group, 3.9% in the FDC tamsulosin/solifenacin 0.4 mg/6 mg group and 3.1% in the FDC tamsulosin/solifenacin 0.4 mg/9 mg group. The incidence of treatment emergent AEs (TEAEs) was slightly higher in the FDC tamsulosin/solifenacin 0.4 mg/6 mg group (29.4%) and in the FDC tamsulosin/solifenacin 0.4 mg/9 mg group (30.9%) than in the placebo group (25.5%) and in the TOCAS 0.4 mg group (22.7%). The majority of TEAEs were of mild to moderate intensity and considered not related to study medication. The percentage of patients with possibly or probably treatment-related TEAEs was 8.8% in the placebo group and 8.3% in the TOCAS group, 16.9% in the FDC tamsulosin/solifenacin 0.4 mg/6 mg group and 20.1% in the FDC tamsulosin/solifenacin 0.4 mg/9 mg group.

The incidence of most commonly reported TEAEs with the FDC tamsulosin/solifenacin 0.4 mg/6 mg and 0.4 mg/9 mg was in line with those mentioned in the SPCs for solifenacin, i.e., dry mouth, constipation and dyspepsia [Table 3]. The incidence of dry mouth was 1.2% in the placebo arm, 0.6% in the TOCAS 0.4 mg arm, 8.6% in the FDC tamsulosin/solifenacin 0.4 mg/6 mg arm and 10.5% in the FDC tamsulosin/solifenacin 0.4 mg/9 mg. The incidence of constipation was 0.3% in the placebo group, 0.3% in the TOCAS 0.4 mg group, 3.6% in the FDC tamsulosin/solifenacin 0.4 mg/6 mg group and 5.6% in the FDC tamsulosin/solifenacin 0.4 mg/9 mg group. Dry mouth and constipation were also the most common treatment-related TEAEs [Table 4]. The incidences of these TEAEs were slightly higher in the FDC tamsulosin/solifenacin 0.4 mg/9 mg group compared to the FDC tamsulosin/solifenacin 0.4 mg/6 mg group. Most cases of dry mouth, constipation and dyspepsia were of mild or moderate intensity; none of the cases of dry mouth, 1 case of constipation (on the FDC 0.4 mg/6 mg) and 1 case of dyspepsia (on the FDC 0.4 mg/9 mg) were of severe intensity. Discontinuations due to these TEAEs were also infrequent, i.e., did not occur in more than 2 patients (0.6%) on each FDC.

One patient (0.3%) in the TOCAS 0.4 mg group, 1 patient (0.3%) in the FDC tamsulosin/solifenacin 0.4 mg/6 mg group and 3 patients (0.9%) in the FDC tamsulosin/solifenacin 0.4 mg/9 mg group experienced acute urinary retention (AUR) which required catheterization. Two patients on the FDC tamsulosin/solifenacin 0.4 mg/9 mg discontinued the study because of AUR.

Name of Sponsor/Company: Astellas Pharma Europe B.V.		
Name of Finished Product: Vesomni®		
Name of Active Ingredient: tamsulosin/solifenacin		

There was a small increase in mean PVR for patients treated with the FDC tamsulosin/solifenacin 0.4 mg/6 mg (mean change from baseline 3.8 mL) and with the FDC tamsulosin/solifenacin 0.4 mg/9 mg (mean change from baseline 12.3 mL). These increases in PVR were considered not clinically significant and not related to the incidence of AUR.

There were no clinically relevant changes or differences between treatment groups in biochemistry variables, hematology or urinalysis variables, vital signs, ECGs or free flow measurements during the study.

Table 3 TEAEs Reported by at Least 1.0% of Patients in Any Treatment Group (SAF)

PT: n (%)	Placebo (n=341)	TOCAS 0.4 mg (n=326)	FDC 0.4/6 (n=337)	FDC 0.4/9 (n=324)
Dry mouth	4 (1.2%)	2 (0.6%)	29 (8.6%)	34 (10.5%)
Constipation	1 (0.3%)	1 (0.3%)	12 (3.6%)	18 (5.6%)
Dyspepsia	2 (0.6%)	1 (0.3%)	8 (2.4%)	11 (3.4%)
Nausea	3 (0.9%)	5 (1.5%)	1 (0.3%)	1 (0.3%)
Influenza	0	5 (1.5%)	3 (0.9%)	3 (0.9%)
Bronchitis	4 (1.2%)	2 (0.6%)	2 (0.6%)	1 (0.3%)
Back pain	4 (1.2%)	3 (0.9%)	4 (1.2%)	0
Headache	3 (0.9%)	2 (0.6%)	5 (1.5%)	1 (0.3%)
Hypertension	8 (2.3%)	2 (0.6%)	7 (2.1%)	5 (1.5%)
Urinary retention	0	1 (0.3%)	3 (0.9%)	4 (1.2%)
Retrograde ejaculation	0	0	1 (0.3%)	4 (1.2%)
Vision blurred	0	0	4 (1.2%)	1 (0.3%)
Fatigue	2 (0.6%)	4 (1.2%)	4 (1.2%)	1 (0.3%)

SAF: safety analysis set - patients who received at least one dose of double blind study drug and for whom any data was reported after intake of the first dose of study drug

FDC 0.4/6: fixed-dose combination tamsulosin/solifenacin 0.4 mg/6 mg; FDC 0.4/9: fixed-dose combination tamsulosin/solifenacin 0.4 mg/9 mg; TOCAS: tamsulosin oral controlled absorption system; PT: preferred term; TEAE: treatment-emergent adverse event

Source: Table 12.6.1.3

Name of Sponsor/Company: Astellas Pharma Europe B.V.		
Name of Finished Product: Vesomni®		
Name of Active Ingredient: tamsulosin/solifenacin		

Table 4 Drug-related AEs Reported by at Least 1.0% of Patients in Any Treatment Group (SAF)

PT: n (%)	Placebo (n=341)	TOCAS 0.4 mg (n=326)	FDC 0.4/6 (n=337)	FDC 0.4/9 (n=324)
Dry mouth	4 (1.2%)	1 (0.3%)	27 (8.0%)	34 (10.5%)
Constipation	1 (0.3%)	1 (0.3%)	9 (2.7%)	16 (4.9%)
Dyspepsia	1 (0.3%)	1 (0.3%)	6 (1.8%)	4 (1.2%)
Nausea	1 (0.3%)	4 (1.2%)	1 (0.3%)	0
Headache	2 (0.6%)	2 (0.6%)	4 (1.2%)	0
Urinary retention	0	1 (0.3%)	2 (0.6%)	4 (1.2%)
Fatigue	2 (0.6%)	2 (0.6%)	4 (1.2%)	1 (0.3%)
Retrograde ejaculation	0	0	1 (0.3%)	4 (1.2%)

SAF: safety analysis set - patients who received at least one dose of double blind study drug and for whom any data was reported after intake of the first dose of study drug

FDC 0.4/6: fixed-dose combination tamsulosin/solifenacin 0.4 mg/6 mg; FDC 0.4/9: fixed-dose combination tamsulosin/solifenacin 0.4 mg/9 mg; TOCAS: tamsulosin oral controlled absorption system; AE: adverse event; PT: preferred term

Source: Table 12.6.1.4

CONCLUSIONS: The FDC tamsulosin/solifenacin 0.4 mg/6 mg was statistically significantly superior to placebo in reducing the total IPSS from baseline to endpoint and noninferior to TOCAS 0.4 mg. In addition, the FDC tamsulosin/solifenacin 0.4 mg/6 mg was statistically significantly superior to both placebo and TOCAS 0.4 mg in reducing the mean TUS from baseline to endpoint. The FDC tamsulosin/solifenacin 0.4 mg/6 mg therefore fulfilled the predefined criteria for success and it can thus be concluded that the FDC tamsulosin/solifenacin 0.4 mg/6 mg is successful in improving LUTS associated with BPH with a substantial storage component. The FDC tamsulosin/solifenacin 0.4 mg/9 mg did not fulfill the predefined success criteria.

The results of the primary efficacy variables were supported by the results of the secondary efficacy variables.

Treatment with tamsulosin/solifenacin 0.4 mg/6 mg and 0.4 mg/9 mg appeared to be safe and was generally well tolerated in men with LUTS associated with BPH with a substantial storage component. The most common TEAEs were in line with or lower than those reported in the summary of product characteristics for solifenacin and tamsulosin as the most frequently reported TEAEs and treatment-related TEAEs were dry mouth and constipation. Cases of AUR were reported, as can be expected in a population of patients with LUTS associated with BPH.

It can be concluded that the FDC tamsulosin/solifenacin 0.4 mg/6 mg is an effective treatment for LUTS associated with BPH, having added value compared to TOCAS 0.4 mg monotherapy. It achieved the predefined success criteria for the 2 primary efficacy variables which was supported by the results on the secondary efficacy variables, and was well tolerated.

Name of Sponsor/Company: Astellas Pharma Europe B.V.		
Name of Finished Product: Vesomni®		
Name of Active Ingredient: tamsulosin/solifenacin		

The FDC tamsulosin/solifenacin 0.4 mg/9 mg did not achieve the predefined success criteria, there was no clear additional benefit in efficacy compared with the FDC tamsulosin/solifenacin 0.4 mg/6 mg and it was associated with a slightly less favorable tolerability profile.

Date of Report: October 2011