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Name of Active Ingredient: tamsulosin/solifenacin		

SYNOPSIS

Title of Study: An open-label, long term, multi-center study to assess the safety and efficacy of fixed dose combinations of solifenacin succinate (6 mg and 9 mg) with tamsulosin hydrochloride OCAS 0.4 mg, in male subjects with lower urinary tract symptoms (LUTS) associated with benign prostatic hyperplasia (BPH) with a substantial storage component

Coordinating Investigator: [redacted], [redacted], [redacted] United Kingdom (UK)

Study Center(s): A total of 82 centers in 12 countries participated in the study

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

Study Period: April 2010 – December 2011

Study Initiation Date (Date of First Enrollment): 26 April 2010

Study Completion Date (Date of Last Evaluation): 14 December 2011

Phase of Development: 3

Objectives:

Primary

- To assess the safety and tolerability of long-term treatment of the fixed dose combination (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.

Secondary

- To assess the efficacy of long-term treatment 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.

Methodology: This was an open-label extension study following the double-blind Study 905-CL-055. In Study 905-CL-055 patients were randomized to one of the following treatments: placebo, tamsulosin oral controlled absorption system (TOCAS) 0.4 mg, FDC tamsulosin/solifenacin 0.4 mg/6 mg or FDC tamsulosin/solifenacin 0.4 mg/9 mg. Patients were considered eligible for the extension study if they completed 12 weeks of double-blind treatment in Study 905-CL-055, complied with inclusion criteria and no exclusion criteria were met. Patients who completed Study 905-CL-055 were thereafter treated with the FDC tamsulosin/solifenacin 0.4 mg/6 mg or 0.4 mg/9 mg for maximally 40 weeks. The mean exposure to the FDC for the total population was 305.3 days (median 287.0 days).

Patients were seen at the final visit of the double-blind study (visit 5A). If they were willing to participate in the long-term study, the first visit of the long-term study (visit 5B) was completed immediately after completing Study 905-CL-055. All eligible patients started with 4 weeks of open-label FDC tamsulosin/solifenacin 0.4 mg/6 mg. Patients returned to the clinic after 4 weeks (visit 6) and then 3 times more at intervals of 12 weeks (visits 7–9). Patients were given the opportunity to request a dose increase to FDC tamsulosin/solifenacin 0.4 mg/9 mg at visits 6–8. At visits 7 and 8, patients on the FDC tamsulosin/solifenacin

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0.4 mg/9 mg had the opportunity to request a dose reduction to the FDC tamsulosin/solifenacin 0.4 mg/6 mg. At visit 9 the patients were asked whether the dose would have been changed if the study had continued after visit 9.

Number of Patients (Planned, Enrolled and Analyzed): It was originally expected that approximately 800 patients who completed Study 905-CL-055 would agree to participate in Study 905-CL-057; however, this estimate was increased to approximately 1000 patients during conduct of the study. It was calculated that with 800 patients, the Blyth-Still-Casella 95% CI for the estimate of patients with adverse events (AEs) that appear with a relative frequency of 1.0% was 0.43% - 1.93%, which was considered an acceptable precision for such AEs. With respect to less frequent AEs, with the expected number of 800 patients, the probability to detect AEs with a frequency of 0.3% (at least 1 occurrence of the AE) was 91%.

A total of 1066 patients who completed Study 905-CL-055 were willing to participate in the long-term extension study and took at least one dose of open-label study medication. The safety analysis set (SAF) consisted of 1066 patients and the full analysis set (FAS) consisted of 1009 patients.

Diagnosis and Main Criteria for Inclusion: Male patients with LUTS associated with BPH with a substantial storage component who had completed 12 weeks of double-blind treatment in Study 905-CL-055 and fulfilled the in- and exclusion criteria were included.

Test Product, Dose and Mode of Administration, Batch Numbers: Throughout the study, each patient took 1 tablet per day (the FDC tamsulosin/solifenacin 0.4 mg/6 mg or the FDC tamsulosin/solifenacin 0.4 mg/9 mg). 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.

FDC tamsulosin/solifenacin 0.4 mg/6 mg, batch [redacted]

FDC tamsulosin/solifenacin 0.4 mg/9 mg, batch [redacted]

Duration of Study: The study was a 40-week extension study of a 12-week double-blind study. Patients who received the FDC in Study 905-CL-055 had a maximum treatment duration of 52 weeks while patients who were treated with placebo or TOCAS in Study 905-CL-055 had a maximum treatment duration of 40 weeks.

Reference Product, Dose and Mode of Administration, Batch Numbers: Not applicable

Criteria for Evaluation: Efficacy: There were two primary efficacy variables:

- Change from baseline to endpoint in total international prostate symptom score (IPSS)
- Change from baseline to endpoint in total urgency score (TUS) per 24 hours (calculated from PPIUS [patient perception of the intensity of urgency scale] urgency grades recorded in the micturition diary).

Secondary efficacy variables were change from baseline to endpoint in:

- From IPSS questionnaire: IPSS voiding score, IPSS storage score, IPSS quality of life (QoL) score, individual IPSS items
- 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,

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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

- From overactive bladder questionnaire (OAB-q): total and subscores
- European quality of life-5 dimensions questionnaire (EQ-5D) scores
- Increase/decrease in FDC dose and reason for dose change

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

Statistical Methods: Efficacy: Efficacy data was presented using several groups of patients, which include the 905-CL-057 Dose Taken groups, which were defined as:

- Pure_6: the group of patients who received only the FDC tamsulosin/solifenacin 0.4 mg/6 mg between visits 5B and visit 9 in study 905-CL-057 (and in Study 905-CL-055 did not receive the FDC tamsulosin/solifenacin 0.4 mg/9 mg)
- Pure_9: the group of patients who received the open-label FDC tamsulosin/solifenacin 0.4 mg/6 mg between visit 5B and visit 6 and only the FDC tamsulosin/solifenacin 0.4 mg/9 mg at all visits attended thereafter (and in Study 905-CL-055 did not receive the FDC tamsulosin/solifenacin 0.4 mg/6 mg)
- Mixed: the complement of Pure_6 and Pure_9 (i.e., included all dose sequences not included in Pure_6 and Pure_9)
- End_6: the group of patients whose last dose taken in Study 905-CL-057 was FDC tamsulosin/solifenacin 0.4 mg/6 mg
- End_9: the group of patients whose last dose taken in Study 905-CL-057 was FDC tamsulosin/solifenacin 0.4 mg/9 mg
- Total: all patients included in the FAS of Study 905-CL-057

No formal statistical testing was performed for the efficacy variables. All primary and secondary efficacy variables were summarized using descriptive statistics. Continuous variables were summarized using the descriptive statistical mean, standard deviation (SD), minimum, median and maximum by visit and FDC treatment duration. Change from baseline was also summarized. Categorical variables were described using absolute and relative frequency and shift tables were provided for some categorical variables per visit. For the total IPSS and TUS a repeated measures model was fitted to data having a response vector of change from baseline to each week. The model contained covariates baseline, factors treatment, week and country, and interaction terms week by treatment, week by country and week by baseline. The adjusted mean change from baseline and associated two-sided 95% CI was summarized by week and treatment group, but no formal comparisons were made.

Safety: Safety data was presented using several groups of patients, which were the Pure_6, Pure_9, Mixed and Total Dose Taken analysis groups as defined above.

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For the Dose Taken groups all AEs a patient had reported were included, but if an AE was reported more than once for the same patient, the AE was categorized only once, under the most severe intensity or most related causality category.

AEs were also reported by the FDC treatment the patient was receiving at the time the AE started. For this analysis, the Dose Taken Anytime groups, Re_6 and Re_9 populations were defined. The denominators used for estimation of these AE frequencies were defined as:

- Re_6: the group of patients who received the FDC tamsulosin/solifenacin 0.4 mg/6 mg anytime during studies 905-CL-055 or 905-CL-057
- Re_9: the group of patients who received the FDC tamsulosin/solifenacin 0.4 mg/9 mg anytime during studies 905-CL-055 or 905-CL-057

For the Dose Taken Anytime groups, AEs were reported in a summary table only once under the most severe or most related (i.e., treatment emergent to FDC tamsulosin/solifenacin 0.4 mg/6 mg or 0.4 mg/9 mg). An AE was counted twice if the severity or relationship changed under the new FDC dose taken, once for the Re_6 group and once for the Re_9 group.

Safety data were summarized using descriptive statistics. Continuous variables were summarized using the descriptive statistical mean, SD, minimum, median, maximum. Categorical variables were described using absolute and relative frequency and shift tables were provided for some categorical variables.

Summary of Results/Conclusions:

Subject Disposition and Analysis Sets:

A total of 1334 patients were randomized in Study 905-CL-055 and 1199 patients were seen at the final visit of this study. A total of 1066 patients were willing to participate in the long-term extension study and took at least 1 dose of open-label study medication. The SAF consisted of 1066 patients who received at least 1 dose of the FDC tamsulosin/solifenacin 0.4 mg/6 mg or 0.4 mg/9 mg during the open-label treatment period and who had any data reported after first dose of the FDC during the open-label treatment period. A total of 106 patients (9.9%) from the SAF discontinued from the study. The main reason for treatment discontinuation was an AE (n=43, 4.0%) followed by withdrawal of consent (n=23, 2.2%) and lack of efficacy (n=19, 1.8%). The FAS consisted of 1009 patients who took at least 1 dose of the FDC tamsulosin/solifenacin 0.4 mg/6 mg or 0.4 mg/9 mg during the open-label study, had a total IPSS or TUS at baseline and had at least one total IPSS or TUS after first dose of the FDC in the open-label study.

Demographics (SAF):

Almost 100% of the patients were White. The mean age of the patients at screening was 65.1 years and their mean body mass index (BMI) was 28.4 kg/m^2.

Disease Characteristics (FAS, SAF):

The mean total IPSS was 18.7 points with a mean IPSS storage score of 8.9 points and a mean IPSS QoL score of 4.1 points. The mean TUS for the entire population was 27.18 points; the mean number of urgency episodes (PPIUS grade 3 or 4) was 5.38. Patients had a mean of 11.44 micturitions/24 h. The mean Q_{max} was 8.91 mL/s,

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the mean PVR 36.0 mL and the mean prostate weight 37.8 g. Since patients were assigned to analysis groups based on their self-selected dosage of the FDC and were not randomized, the analysis groups were not balanced in terms of baseline disease characteristics. The majority of patients (77.7%) used concomitant medication while taking the FDC, which were mainly those used for cardiovascular disorders.

Study Drug Exposure: Patients in the Total group had a mean of 305.3 days of treatment with the FDC. The mean exposure durations to the FDC tamsulosin/solifenacin 0.4 mg/6 mg and 0.4 mg/9 mg were 219.0 days and 165.2 days, respectively. A total of 1013 patients (95.0%) had a FDC duration of at least 6 months and 407 patients (38.2%) of at least 1 year.

Efficacy Results: The Total group was considered the most relevant analysis group as patients self selected their FDC dosage, which may have affected results in the 905-CL-057 Dose Taken analysis groups. As patients were not randomized, the analysis groups cannot be compared. Therefore the results of only the Total group are discussed. Details on the other Dose Taken groups can be found in the full report.

Primary efficacy variables: A reduction in mean total IPSS and mean TUS was observed at 4 weeks of FDC treatment, which was maintained up to 52 weeks of FDC treatment [Figure 2, Figure 3]. The mean (SD) total IPSS was reduced from 18.7 (4.41) points at baseline by 9.0 (5.69) points to 9.7 (5.94) points at endpoint in the Total group. The mean (SD) TUS was reduced from 27.2 (8.59) points at baseline by 10.1 (9.23) points to 17.1 (9.47) at endpoint in the Total group.

Secondary efficacy variables: The results of the secondary efficacy variables support the results of the primary efficacy variables. Mean IPSS storage and voiding scores, and mean micturition diary variables (e.g. the mean number of micturitions/24 h, mean voided volume per micturition and the mean number of urgency episodes [PPIUS grade 3-4]/24 h) improved after 4 weeks of FDC treatment, which was maintained up to 52 weeks of FDC treatment. QoL related to LUTS/BPH, and bother due to storage symptoms was also improved by the FDC as shown by an improvement in the IPSS QoL score, OAB-q symptom bother score and HRQL total score after 4 weeks of FDC treatment, which was maintained up to 52 weeks of FDC treatment. Other OAB-q subscales were also improved with a similar pattern showing maintenance of efficacy. About 91% of the patients taking the FDC tamsulosin/solifenacin 0.4 mg/6 mg in the period before visit 6 indicated that efficacy was "satisfactory". The figure was about 89% for the period before visit 7 and about 92% for the periods before visit 8 and visit 9. About 84-91% of the patients taking the FDC tamsulosin/solifenacin 0.4 mg/6 mg in the period before visits 6, 7, 8 and 9 indicated that safety was "satisfactory".

Safety Results: The Total group was again considered the most relevant analysis group as patients self select their FDC dosage, which may affect results in the Pure_6, Pure_9 and Mixed analysis groups. The latter groups can therefore also not be compared. The results of the Total group are discussed in the text, and for completeness the results of the Pure_6, Pure_9 and Mixed analysis groups are presented in the tables.

The FDC was well tolerated. The majority of treatment emergent AEs (TEAEs) were of mild to moderate intensity. Three patients died during the study due to serious AEs (SAEs) while taking the FDC tamsulosin/solifenacin 0.4 mg/6 mg. No patients died while taking the FDC tamsulosin/solifenacin 0.4 mg/9 mg. The 3 fatal cases, all of which were considered unrelated to study medication by the investigator, were a suicide, a myocardial infarction and a cerebral disorder (cerebrovascular accident).

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The frequency of SAEs was low (64 patients or 6.0% in the Total group). During double-blind and open-label treatment with the FDC, 86 SAEs were reported. A total of 12 SAEs in 12 patients (1.1%) were considered possibly or probably related to treatment by the investigator. When considering AEs while the patients were taking FDC tamsulosin/solifenacin 0.4 mg/6 mg or 0.4 mg/9 mg (i.e., the Dose Taken Anytime groups) 3.9% of patients experienced at least 1 treatment-emergent SAE while taking the FDC tamsulosin/solifenacin 0.4 mg/6 mg (i.e., Re_6) and 4.4% of patients experienced a SAE while taking the FDC tamsulosin/solifenacin 0.4 mg/9 mg (i.e., Re_9). These SAEs were considered possibly or probably related to treatment by the investigator for 7 patients (0.7%) while taking the FDC tamsulosin/solifenacin 0.4 mg/6 mg and 5 patients (0.9%) while taking the FDC tamsulosin/solifenacin 0.4 mg/9 mg.

Permanent discontinuations due to TEAEs were infrequent: 42 patients or 3.9% in the Total group. A total of 28 patients (2.6%) in the Total group discontinued due to drug-related TEAEs. The frequency of treatment discontinuations due to TEAEs was 3.3% while taking the FDC tamsulosin/solifenacin 0.4 mg/6 mg and 1.3% while taking the FDC tamsulosin/solifenacin 0.4 mg/9 mg. The frequency of discontinuations due to drug-related AEs was 2.4% while taking the FDC tamsulosin/solifenacin 0.4 mg/6 mg and 0.4% while taking the FDC tamsulosin/solifenacin 0.4 mg/9 mg.

The frequency of TEAEs was 46.8% for the total population. The frequency of TEAEs was comparable while taking FDC tamsulosin/solifenacin 0.4 mg/6 mg (35.9%) and 0.4 mg/9 mg (34.3%). The majority of TEAEs were of mild to moderate intensity (only 3.8% were of severe intensity) and considered not related to study medication by the investigator. The percentage of patients with possibly or probably drug-related AEs was 23.9% in the Total group. The frequency of drug-related TEAEs while taking the FDC tamsulosin/solifenacin 0.4 mg/6 mg or 0.4 mg/9 mg was similar for both FDCs: 17.6% and 17.0%, respectively.

The most commonly reported TEAEs with the FDC were in line with those mentioned in the Summary of Product Characteristics for solifenacin, i.e., dry mouth, constipation and dyspepsia [Table 2, Table 3]. The frequencies of dry mouth, constipation and dyspepsia were 12.4%, 5.2% and 2.7% in the total population. Dry mouth, constipation and dyspepsia were also the most common drug-related TEAEs [Table 4 and Table 5].

Most cases of dry mouth, constipation and dyspepsia were of mild or moderate intensity. Discontinuations due to these TEAEs were also infrequent; this included 1 patient with dry mouth, constipation and dyspepsia, 2 patients with both constipation and dry mouth, 1 patient with both dyspepsia and dry mouth, 2 patients with dry mouth, 2 patients with constipation and 2 patients with dyspepsia.

Four patients treated with the FDC tamsulosin/solifenacin 0.4 mg/6 mg and 4 patients treated with the FDC tamsulosin/solifenacin 0.4 mg/9 mg experienced urinary retention. Three patients each treated with FDC tamsulosin/solifenacin 0.4 mg/6 mg and 0.4 mg/9 mg had urinary retention reported as an SAE, which required catheterization. One patient each treated with FDC tamsulosin/solifenacin 0.4 mg/6 mg and 0.4 mg/9 mg had urinary retention reported as an SAE in Study 905-CL-055. In 2 out of 3 patients treated with FDC tamsulosin/solifenacin 0.4 mg/6 mg and 2 out of 3 patients treated with 0.4 mg/9 mg who had a urinary retention SAE, the event was considered possibly or probably related to study medication. Three patients

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(2 with SAEs) treated with FDC tamsulosin/solifenacin 0.4 mg/6 mg discontinued the study because of urinary retention, as did 1 patient (with an SAE) treated with FDC tamsulosin/solifenacin 0.4 mg/9 mg.

There was an increase of 10.7 mL in mean PVR from baseline (mean 36.0 mL) to endpoint in the Total group.

Both mean Q_{max} and Q_{mean} increased during 52-week treatment with the FDC. The mean Q_{max} at baseline was 8.9 mL/s. During FDC treatment, Q_{max} increased from baseline to endpoint by 4.5 mL/s. The increase in Q_{max} was maintained during 52 weeks of FDC treatment duration. The mean Q_{mean} at baseline was 4.9 mL/s. The mean Q_{mean} increased by 2.1 mL/s from baseline to endpoint.

The incidence of biochemistry, hematology, urinalysis variables, vital signs and electrocardiogram (ECG) recordings reported as TEAEs was < 1.0%.

Six patients (0.6%) had at least one value of creatinine above 2 x ULN, of whom 2 (FDC tamsulosin/solifenacin 0.4 mg/9 mg) had mild acute renal failure reported as a TEAE based on laboratory results without clinical symptoms. Increased blood creatinine and hypercreatininemia was reported as a TEAE for 3 patients, 2 taking the FDC tamsulosin/solifenacin 0.4 mg/6 mg (1 not related and 1 possibly related to study medication) and 1 taking the FDC tamsulosin/solifenacin 0.4 mg/9 mg (not related to study medication). Four patients (0.4%) had increased GGT reported as a TEAE: 3 taking the FDC tamsulosin/solifenacin 0.4 mg/6 mg (not related to study medication) and 1 taking the FDC tamsulosin/solifenacin 0.4 mg/9 mg (not related to study medication).

No patients fulfilled the biochemical criteria of a Hy's law case, with an ALT and/or AST > 3 times ULN with a total bilirubin > 2 times ULN.

There were isolated instances (1 patient) of other biochemistry parameters reported as a TEAE: of blood alkaline phosphatase increased, blood creatinine increased, blood urea increased, blood bilirubin increased, blood creatine increased, blood glucose increased, blood lactate dehydrogenase increased, and blood uric acid increased

Two (0.4%) patients (Pure_6) had WBC count increased reported as a TEAE (not related to study medication) and 1 patient (Pure_6) had WBC count decreased reported as a TEAE (probably related to study medication).

There were no clinically significant changes in urine pH or qualitative urinalysis results.

The percentage of patients meeting predefined outlier criteria for vital signs (SBP ≥ 180 mmHg and ≥ 20 mmHg change from baseline, DBP ≥ 105 mmHg and a ≥ 15 mmHg change from baseline, and pulse rate ≥ 120 bpm and ≥ 15 mmHg change from baseline) was low (≤ 0.4%). One patient (0.8%) in the Pure_9 group had blood pressure increased reported as a TEAE, not related to study medication.

Abnormal clinically significant ECG measurements at endpoint were reported for 5 (0.5%) patients: 2 (0.4%) Pure_6, 1 (0.8%) Pure_9, and 2 (0.5%) Mixed. In addition, there were few patients at endpoint with a shift from normal to abnormal clinically significant post-baseline ECG measurements (≤0.3%): 1 (0.3%) Pure_6 and 1 (0.4%) Mixed. One patient (Pure_9) had PR prolongation reported as a TEAE, not related to study medication. One patient (Pure_6) had QT prolongation reported as a TEAE, possibly related to study medication. One patient (Pure_6) had T-wave amplitude decreased reported as a TEAE, possibly related to study medication.

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CONCLUSIONS: This long-term extension study of the 12-week, double-blind Study 905-CL-055 in male patients with LUTS associated with BPH with a substantial storage component shows a further improvement in IPSS, micturition diary variables and QoL variables after 4 weeks of FDC treatment, which is maintained up to 52 weeks of FDC treatment. The significant improvement in total IPSS and TUS achieved during 12 weeks of FDC treatment in the double-blind, randomized Study 905-CL-055 was maintained throughout the long-term, follow-up Study 905-CL-057.

Long-term treatment with the FDCs tamsulosin/solifenacin 0.4 mg/6 mg and 0.4 mg/9 mg appeared to be safe and was well tolerated. Three patients treated with the FDC tamsulosin/solifenacin 0.4 mg/6 mg died but these were considered not drug-related by the investigator. The frequency of (drug-related) SAEs was low, and discontinuations due to TEAEs were infrequent. The most frequently reported TEAEs and drug-related TEAEs were in line with those mentioned in the summary of product characteristics for solifenacin (dry mouth and constipation and to a lesser extent dyspepsia) and tamsulosin. There were a few cases of AUR, as can be expected in a population of patients with LUTS associated with BPH.

Date of Report: 13 August 2012

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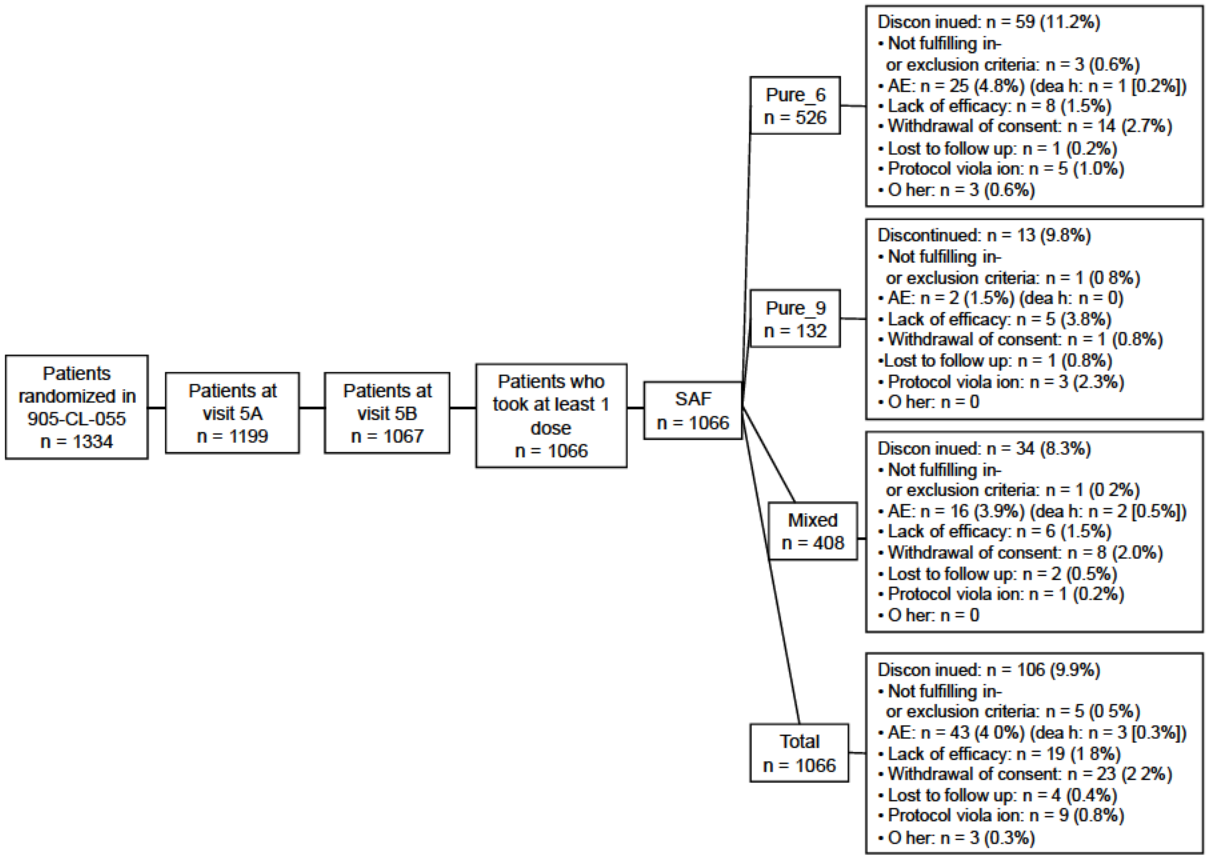
Figure 1: Disposition of Subjects



AE: adverse event; FDC: fixed dose combination; Mixed, Pure_6, Pure_9, Total: defined in Sections 5.5.3.3 and 5.5.3.4; SAF: safety analysis set-patients who received at least 1 dose of the FDC tamsulosin/solifenacin 0.4 mg/6 mg or 0.4 mg/9 mg during the open-label treatment period and had any data reported after the first dose of the FDC during the open-label treatment period
Source: Tables 12.1.1, 12.1.2.2 & 12.1.4.3

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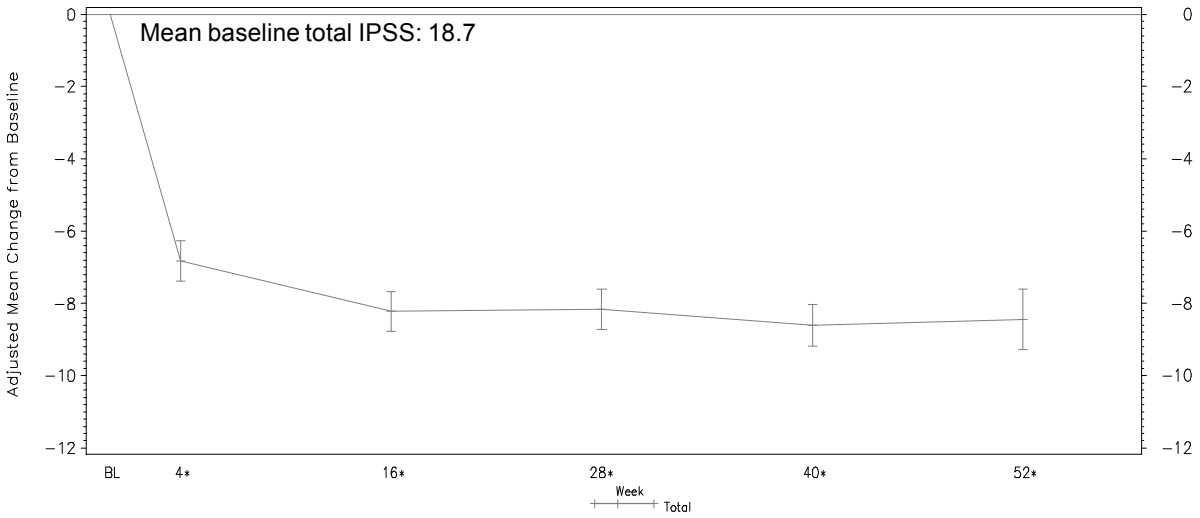
Figure 2 **Change from Baseline in Mean (± SE) Total IPSS by FDC Treatment Duration for the Total Group (FAS)**



FAS: full analysis set-patients who took at least 1 dose of the FDC tamsulosin/solifenacin 0.4 mg/6 mg or 0.4 mg/9 mg during the open-label study, had a total IPSS or TUS at baseline and had at least one total IPSS or TUS after the first dose of the FDC in study 905-CL-057, with the exclusion of 5 patients with invalid questionnaires; FDC: fixed dose combination; IPSS: international prostate symptom score; Total: all patients; TUS: total urgency score

*Since exposure to FDC depends on the treatment the patient received in the double-blind Study 905-CL-055, visits were re-mapped to the exposure time to FDC

Source: Table 12.3.3.1.2 and Figure 12.3.1.8

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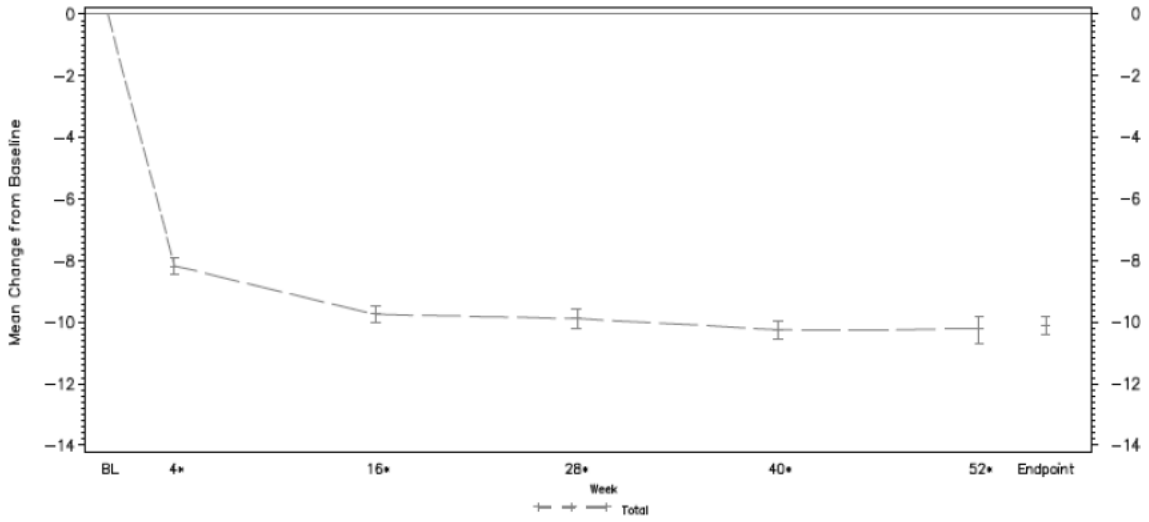
Figure 3 Change from Bas T a t on for the Total Group (FAS)



FAS: full analysis set-patients who tc t m mg/6 mg or 0.4 mg/9 mg during the open- udy, had a total IPSS or TUS at b l one total IPSS or dos D n study 905-CL-057; C f e c na on; : international om e l tients; TUS: total urgency score x ur pe the treatment the patient received in the double- nd dy 905-CL-055, visits were re-m e time to FDC bl e 12.3.2.6

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Table 1 Patient Disposition

	Pure_6	Pure_9	Mixed	End_6	End_9	Total	Re_6	Re_9
Randomized in Study 905-CL-055						1334		
Visit 5A						1199		
Visit 5B						1067		
Took ≥ 1 dose of open-label study drug	526 (100%)	132 (100%)	408 (100%)	745 (100%)	309 (100%)	1066 (100%)	1066 (100%)	540 (100%)
SAF	526 (100%)	132 (100%)	408 (100%)	745 (100%)	309 (100%)	1066 (100%)	1066 (100%)	540 (100%)
Discontinued (SAF)†	59 (11.2%)	13 (9.8%)	34 (8.3%)			106 (9.9%)	106 (9.9%)	47 (8.7%)
Not fulfilling in/exclusion criteria	3 (0.6%)	1 (0.8%)	1 (0.2%)			5 (0.5%)	5 (0.5%)	2 (0.4%)
Adverse event	25 (4.8%)	2 (1.5%)	16 (3.9%)			43 (4.0%)	43 (4.0%)	18 (3.3%)
Resulted in death	1 (0.2%)	0	2 (0.5%)			3 (0.3%)	3 (0.3%)	2 (0.4%)
Lack of efficacy	8 (1.5%)	5 (3.8%)	6 (1.5%)			19 (1.8%)	19 (1.8%)	11 (2.0%)
Withdrawal of consent	14 (2.7%)	1 (0.8%)	8 (2.0%)			23 (2.2%)	23 (2.2%)	9 (1.7%)
Lost to follow up	1 (0.2%)	1 (0.8%)	2 (0.5%)			4 (0.4%)	4 (0.4%)	3 (0.6%)
Protocol violation	5 (1.0%)	3 (2.3%)	1 (0.2%)			9 (0.8%)	9 (0.8%)	4 (0.7%)
Other	3 (0.6%)	0	0			3 (0.3%)	3 (0.3%)	0
FAS	489 (93.0%)	131 (99.2%)	389 (95.3%)	702 (94.2%)	303 (98.1%)	1009 (94.7%)		

End_6, End_9: defined in Section 5.5.3.3; FAS: full analysis set-patients who took at least 1 dose of the FDC tamsulosin/solifenacin 0.4 mg/6 mg or 0.4 mg/9 mg during the open-label study, had a total IPSS or TUS at baseline and had at least one total IPSS or TUS after first dose of the FDC in Study 905-CL-057; FDC: fixed dose combination; IPSS: international prostate symptom score; Mixed, Pure_6, Pure_9, Total: defined in Sections 5.5.3.3 and 5.5.3.4; Re_6, Re_9: defined in Section 5.5.3.4; SAF: safety analysis set-patients who received at least 1 dose of the FDC tamsulosin/solifenacin 0.4 mg/6 mg or 0.4 mg/9 mg during the open-label treatment period and had any data reported after the first dose of the FDC during the open-label treatment period; TUS: total urgency score

†: Primary reason for discontinuation

Source: Tables 12.1.1, 12.1.2.2, 12.1.2.3, 12.1.4.3 & 12.1.4.4

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

Table 2 TEAEs Reported by at Least 1.0% of Patients in any Treatment Group by Dose Taken Groups (SAF)

PT: n (%)	Pure_6 (n = 526)	Pure_9 (n = 132)	Mixed (n = 408)	Total (n = 1066)
Dry mouth	56 (10.6%)	12 (9.1%)	64 (15.7%)	132 (12.4%)
Constipation	21 (4.0%)	4 (3.0%)	30 (7.4%)	55 (5.2%)
Dyspepsia	15 (2.9%)	3 (2.3%)	11 (2.7%)	29 (2.7%)
Hypertension	8 (1.5%)	7 (5.3%)	11 (2.7%)	26 (2.4%)
Urinary tract infection	14 (2.7%)	1 (0.8%)	9 (2.2%)	24 (2.3%)
Back pain	11 (2.1%)	0	10 (2.5%)	21 (2.0%)
Bronchitis	7 (1.3%)	2 (1.5%)	3 (0.7%)	12 (1.1%)
Erectile dysfunction	3 (0.6%)	2 (1.5%)	6 (1.5%)	11 (1.0%)
Nasopharyngitis	6 (1.1%)	3 (2.3%)	2 (0.5%)	11 (1.0%)
Faeces hard	4 (0.8%)	0	6 (1.5%)	10 (0.9%)
Urinary hesitation	8 (1.5%)	0	2 (0.5%)	10 (0.9%)
Haematuria	7 (1.3%)	2 (1.5%)	1 (0.2%)	10 (0.9%)
Osteoarthritis	4 (0.8%)	0	6 (1.5%)	10 (0.9%)
Viral infection	7 (1.3%)	0	3 (0.7%)	10 (0.9%)
Residual urine volume increased	6 (1.1%)	0	3 (0.7%)	9 (0.8%)
Headache	3 (0.6%)	0	5 (1.2%)	8 (0.8%)
Hypercholesterolaemia	3 (0.6%)	2 (1.5%)	3 (0.7%)	8 (0.8%)
Arthralgia	1 (0.2%)	2 (1.5%)	6 (1.5%)	9 (0.8%)
Influenza	6 (1.1%)	1 (0.8%)	2 (0.5%)	9 (0.8%)
Urinary retention	2 (0.4%)	0	6 (1.5%)	8 (0.8%)
Pharyingitis	3 (0.6%)	2 (1.5%)	3 (0.7%)	8 (0.8%)
Dysuria	2 (0.4%)	0	5 (1.2%)	7 (0.7%)
Retrograde ejaculation	1 (0.2%)	1 (0.8%)	5 (1.2%)	7 (0.7%)
Fatigue	2 (0.4%)	0	5 (1.2%)	7 (0.7%)
Vertigo	3 (0.6%)	0	4 (1.0%)	7 (0.7%)
Depression	2 (0.4%)	3 (2.3%)	2 (0.5%)	7 (0.7%)
Vision blurred	2 (0.4%)	0	4 (1.0%)	6 (0.6%)
Musculoskeletal pain	1 (0.2%)	0	5 (1.2%)	6 (0.6%)
Bone pain	1 (0.2%)	0	4 (1.0%)	5 (0.5%)
Neck pain	0	0	4 (1.0%)	4 (0.4%)
Hypermetropia	0	2 (1.5%)	0	2 (0.2%)
Rhinitis allergic	0	2 (1.5%)	0	2 (0.2%)
Rhinitis	0	2 (1.5%)	0	2 (0.2%)
Intervertebral disc disorder	0	2 (1.5%)	0	2 (0.2%)

FDC: fixed dose combination; Mixed: the complement of Pure_6 and Pure_9; Pure_6: : the group of patients who only received the FDC tamsulosin/solifenacin 0.4 mg/6 mg between visits 5B and 9 in Study 905-CL-057 (and in Study 905-CL-055 did not receive the FDC tamsulosin/solifenacin 0.4 mg/9 mg); Pure_9: the group of patients who received the open-label FDC tamsulosin/solifenacin 0.4 mg/6 mg between visit 5B and visit 6 and only the FDC tamsulosin/solifenacin 0.4 mg/9 mg at all visits attended thereafter (and in Study 905-CL-055 did

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Name of Active Ingredient: tamsulosin/solifenacin		

not receive the FDC tamsulosin/solifenacin 0.4 mg/6 mg; PT: preferred term; SAF: safety analysis set-patients who received at least 1 dose of the FDC tamsulosin/solifenacin 0.4 mg/6 mg or 0.4 mg/9 mg during the open-label treatment period and had any data reported after the first dose of the FDC during the open-label treatment period; TEAEs: treatment-emergent adverse event (i.e., AEs treatment emergent to FDC) occurring during Studies 905-CL-055 and 905-CL-057; Total: all patients included in the SAF
Source: Table 12.6.1.2.1

Table 3 TEAEs that Started while Taking the FDC Tamsulosin/Solifenacin 0.4 mg/6 mg or 0.4 mg/9 mg Reported by at Least 1.0% of Patients (SAF))

PT: n (%)	Re_6 (n = 1066)	Re_9 (n = 540)
Dry mouth	86 (8.1%)	49 (9.1%)
Constipation	36 (3.4%)	22 (4.1%)
Dyspepsia	21 (2.0%)	9 (1.7%)
Hypertension	15 (1.4%)	11 (2.0%)
Back pain	19 (1.8%)	3 (0.6%)
Urinary tract infection	18 (1.7%)	6 (1.1%)
Erectile dysfunction	6 (0.6%)	6 (1.1%)

AE: adverse event; FDC: fixed dose combination; PT: preferred term; Re_6: the group of patients who received the FDC tamsulosin/solifenacin 0.4 mg/6 mg at anytime during the double-blind or open-label treatment period; Re_9: the group of patients who received the FDC tamsulosin/solifenacin 0.4 mg/9 mg at anytime during the double-blind or open-label treatment period; SAF: safety analysis set-patients who received at least 1 dose of the FDC tamsulosin/solifenacin 0.4 mg/6 mg or 0.4 mg/9 mg during the open-label treatment period and had any data reported after the first dose of the FDC during the open-label treatment period; TEAEs: treatment-emergent adverse event (i.e., AEs treatment emergent to FDC) occurring during Studies 905-CL-055 and 905-CL-057
Source: Table 12.6.1.2.2

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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 by Dose Taken Groups (SAF)

PT: n (%)	Pure_6 (n = 526)	Pure_9 (n = 132)	Mixed (n = 408)	Total (n = 1066)
Dry mouth	55 (10.5%)	12 (9.1%)	64 (15.7%)	131 (12.3%)
Constipation	20 (3.8%)	3 (2.3%)	28 (6.9%)	51 (4.8%)
Dyspepsia	9 (1.7%)	1 (0.8%)	7 (1.7%)	17 (1.6%)
Faeces hard	4 (0.8%)	0	6 (1.5%)	10 (0.9%)
Urinary hesitation	8 (1.5%)	0	2 (0.5%)	10 (0.9%)
Residual urine volume increased	6 (1.1%)	0	3 (0.7%)	9 (0.8%)
Retrograde ejaculation	1 (0.2%)	1 (0.8%)	5 (1.2%)	7 (0.7%)
Dysuria	2 (0.4%)	0	4 (1.0%)	6 (0.6%)
Erectile dysfunction	1 (0.2%)	1 (0.8%)	4 (1.0%)	6 (0.6%)

FDC: fixed dose combination; Mixed: the complement of Pure_6 and Pure_9; PT: preferred term; Pure_6: the group of patients who only received the FDC tamsulosin/solifenacin 0.4 mg/6 mg between visits 5B and 9 in Study 905-CL-057 (and in Study 905-CL-055 did not receive the FDC tamsulosin/solifenacin 0.4 mg/9 mg); Pure_9: the group of patients who received the open-label FDC tamsulosin/solifenacin 0.4 mg/6 mg between visit 5B and visit 6 and only the FDC tamsulosin/solifenacin 0.4 mg/9 mg at all visits attended thereafter (and in Study 905-CL-055 did not receive the FDC tamsulosin/solifenacin 0.4 mg/6 mg); SAF: safety analysis set-patients who received at least 1 dose of the FDC tamsulosin/solifenacin 0.4 mg/6 mg or 0.4 mg/9 mg during the open-label treatment period and had any data reported after the first dose of the FDC during the open-label treatment period; TEAEs: treatment-emergent adverse event (i.e., AEs treatment emergent to FDC) occurring during Studies 905-CL-055 and 905-CL-057; Total: all patients included in the SAF
Source: Table 12.6.1.5.1

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Name of Finished Product: Vesomni®		
Name of Active Ingredient: tamsulosin/solifenacin		

Table 5 Drug-related TEAEs that Started while Taking the FDC Tamsulosin/Solifenacin 0.4 mg/6 mg or 0.4 mg/9 mg Reported by at Least 1.0% of Patients (SAF)

PT: N (%)	Re_6 (n = 1066)	Re_9 (n = 540)
Dry mouth	85 (8.0%)	49 (9.1%)
Constipation	35 (3.3%)	19 (3.5%)
Dyspepsia	14 (1.3%)	4 (0.7%)

AE: adverse event; PT: preferred term; Re_6: the group of patients who received the FDC tamsulosin/solifenacin 0.4 mg/6 mg at anytime during the double-blind or open-label treatment period; Re_9: the group of patients who received the FDC tamsulosin/solifenacin 0.4 mg/9 mg at anytime during the double-blind or open-label treatment period; FDC: fixed dose combination; SAF: safety analysis set-patients who received at least 1 dose of the FDC tamsulosin/solifenacin 0.4 mg/6 mg or 0.4 mg/9 mg during the open-label treatment period and had any data reported after the first dose of the FDC during the open-label treatment period; TEAEs: treatment-emergent adverse event (i.e., AEs treatment emergent to FDC) occurring during Studies 905-CL-055 and Study 905-CL-057
Source: Table 12.6.1.5.2

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

Table 6 Summary of Serious Treatment-Emergent Adverse Events

System Organ Class Preferred Term	**Pure_6 (n = 526)**	**Pure_9 (n = 132)**	**Mixed (n = 408**	**Total (n = 1066)**
Overall	**26 (4.9%)**	**7 (5.3%)**	**31 (7.6%)**	**64 (6.0%)**
Neoplasms, benign, malignant and unspecified (inc. cysts and polyps)	**5 (1.0%)**	**1 (0.8%)**	**7 (1.7%)**	**13 (1.2%)**
Basal cell carcinoma	1 (0.2%)	0	1 (0.2%)	2 (0.2%)
Bladder cancer	1 (0.2%)	1 (0.8%)	0	2 (0.2%)
Colon cancer	1 (0.2%)	0	1 (0.2%)	2 (0.2%)
Bladder transitional cell carcinoma	1 (0.2%)	0	0	1 (0.1%)
Malignant melanoma	0	0	1 (0.2%)	1 (0.1%)
Malignant peritoneal neoplasm	0	0	1 (0.2%)	1 (0.1%)
Neoplasm skin	0	0	1 (0.2%)	1 (0.1%)
Neuroendocrine tumour	0	0	1 (0.2%)	1 (0.1%)
Prostatic adenoma	0	0	1 (0.2%)	1 (0.1%)
Rectal cancer	1 (0.2%)	0	0	1 (0.1%)
Renal neoplasm	0	0	1 (0.2%)	1 (0.1%)
Cardiac disorders	**2 (0.4%)**	**0**	**7 (1.7%)**	**9 (0.8%)**
Angina pectoris	1 (0.2%)	0	1 (0.2%)	2 (0.2%)
Atrial fibrillation	0	0	2 (0.5%)	2 (0.2%)
Myocardial infarction	1 (0.2%)	0	1 (0.2%)	2 (0.2%)
Cardiac failure	0	0	1 (0.2%)	1 (0.1%)
Coronary artery disease	0	0	1 (0.2%)	1 (0.1%)
Coronary artery stenosis	0	0	1 (0.2%)	1 (0.1%)
Sick sinus syndrome	0	0	1 (0.2%)	1 (0.1%)
Musculoskeletal and connective tissue disorders	**3 (0.6%)**	**1 (0.8%)**	**5 (1.2%)**	**9 (0.8%)**
Intervertebral disc protrusion	2 (0.4%)	0	1 (0.2%)	3 (0.3%)
Back pain	0	0	1 (0.2%)	1 (0.1%)
Intervertebral disc disorder	0	1 (0.8%)	0	1 (0.1%)
Lumbar spinal stenosis	0	0	1 (0.2%)	1 (0.1%)
Osteoarthritis	0	0	1 (0.2%)	1 (0.1%)
Osteonecrosis	0	0	1 (0.2%)	1 (0.1%)
Spondylolisthesis	1 (0.2%)	0	0	1 90.1%)
Nervous system disorders	**2 (0.4%)**	**2 (1.5%)**	**4 (1.0%)**	**8 (0.8%)**
Transient ischaemic attack	1 (0.2%)	1 (0.8%)	0	2 (0.2%)
Cerebral disorder	0	0	1 (0.2%)	1 (0.1%)
Cerebrovascular accident	0	0	1 (0.2%)	1 (0.1%)
Cerebrovascular disorder	0	1 (0.8%)	0	1 (0.1%)
Lateral medullary syndrome	0	0	1 (0.2%)	1 (0.1%)
Parkinsonism	1 (0.2%)	0	0	1 (0.1%)
Spinal cord compression	0	0	1 (0.2%)	1 (0.1%)
Renal and urinary disorders	**1 (0.2%)**	**0**	**8 (2.0%)**	**9 (0.8%)**
Urinary retention	1 (0.2%)	0	5 (1.2%)	6 (0.6%)
Renal failure acute	0	0	2 (0.5%)	2 (0.2%)
Calculus ureteric	0	0	1 (0.2%)	1 (0.1%)
Urinary tract obstruction	0	0	1 (0.2%)	1 (0.1%)
Injury, poisoning and procedural complications	**3 (0.6%)**	**1 (0.8%)**	**3 (0.7%)**	**7 (0.7%)**
Ankle fracture	1 (0.2%)	0	1 (0.2%)	2 (0.2%)
Femur fracture	1 (0.2%)	0	0	1 (0.1%)

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Name of Finished Product: Vesomni®		
Name of Active Ingredient: tamsulosin/solifenacin		

System Organ Class Preferred Term	**Pure_6 (n = 526)**	**Pure_9 (n = 132)**	**Mixed (n = 408**	**Total (n = 1066)**
Table continued on next page				
Post procedural haematoma	1 (0.2%)	0	0	1 (0.1%)
Post procedural haematuria	0	0	1 (0.2%)	1 (0.1%)
Procedural pain	0	0	1 (0.2%)	1 (0.1%)
Radius fracture	0	1 (0.8%)	0	1 (0.1%)
Gastrointestinal disorders	**3 (0.6%)**	**0**	**1 (0.2%)**	**4 (0.4%)**
Gastric ulcer	1 (0.2%)	0	0	1 (0.1%)
Haemorrhoidal haemorrhage	1 (0.2%)	0	0	1 (0.1%)
Haemorrhoids	1 (0.2%)	0	0	1 (0.1%)
Inguinal hernia	1 (0.2%)	0	0	1 (0.1%)
Proctalgia	0	0	1 (0.2%)	1 (0.1%)
Infections and infestations	**2 (0.4%)**	**0**	**2 (0.5%)**	**4 (0.4%)**
Anal abscess	0	0	1 (0.2%)	1 (0.1%)
Appendicitis	1 (0.2%)	0	0	1 (0.1%)
Bronchiectasis	0	0	1 (0.2%)	1 (0.1%)
Lobar pneumonia	1 (0.2%)	0	0	1 (0.1%)
Vascular disorders	**1 (0.2%)**	**2 (1.5%)**	**0**	**3 (0.3%)**
Aortic aneurysm	1 (0.2%)	0	0	1 (0.1%)
Deep vein thrombosis	0	1 (0.8%)	0	1 (0.1%)
Femoral arterial stenosis	1 (0.2%)	0	0	1 (0.1%)
Iliac artery occlusion	1 (0.2%)	0	0	1 (0.1%)
Orthostatic hypotension	0	1 (0.8%)	0	1 (0.1%)
Eye disorders	**2 (0.4%)**	**0**	**0**	**2 (0.2%)**
Cataract	1 (0.2%)	0	0	1 (0.1%)
Macular degeneration	1 (0.2%)	0	0	1 (0.1%)
Hepatobiliary disorders	**1 (0.2%)**	**1 (0.8%)**	**0**	**2 (0.2%)**
Cholangitis	1 (0.2%)	0	0	1 (0.1%)
Cholelithiasis	0	1 (0.8%)	0	1 (0.1%)
Respiratory, thoracic and mediastinal disorders	**1 (0.2%)**	**0**	**1 (0.2%)**	**2 (0.2%)**
Chronic obstructive pulmonary disease	0	0	1 (0.2%)	1 (0.1%)
Pulmonary embolism	1 (0.2%)	0	0	1 (0.1%)
Blood and lymphatic disorders	**1 (0.2%)**	**0**	**0**	**1 (0.1%)**
Anaemia	1 (0.2%)	0	0	1 (0.1%)
Immune system disorders	**1 (0.2%)**	**0**	**0**	**1 (0.1%)**
Allergy to arthropod sting	1 (0.2%)	0	0	1 (0.1%)
Investigations	**0**	**0**	**1 (0.2%)**	**1 (0.1%)**
Hepatic enzyme increased	0	0	1 (0.2%)	1 (0.1%)
Metabolism and nutrition disorders	**1 (0.2%)**	**0**	**0**	**1 (0.1%)**
Hypokalaemia	1 (0.2%)	0	0	1 (0.1%)
Psychiatric disorders	**0**	**0**	**1 (0.2%)**	**1 (0.1%)**
Completed suicide	0	0	1 (0.2%)	1 (0.1%)
Depression	0	0	1 (0.1%)	1 (0.1%)
Reproductive system and breast disorders	**0**	**0**	**1 (0.2%)**	**1 (0.1%)**
Prostatomegaly	0	0	1 (0.2%)	1 (0.1%)

SAEs are sorted in descending order of incidence of the total group by system organ class and preferred term, and within system organ class in descending order by preferred term

Source: Table 12.6.1.10.1

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