SYNOPSIS

Name of Sponsor/Company: Astellas Pharma Europe B.V.		
Name of Finished Product: NA		
Name of Active Ingredient: Solifenacin/Tamsulosin OCAS		

Title of Study:
A randomized, double-blind, parallel group, placebo controlled, multi-center dose ranging study of solifenacin succinate (3 mg, 6 mg and 9 mg) in combination with tamsulosin OCAS 0.4 mg compared with solifenacin succinate monotherapy (3 mg, 6 mg and 9 mg) and tamsulosin OCAS 0.4 mg monotherapy in males with lower urinary tract symptoms (LUTS) associated with benign prostatic hyperplasia (BPH) - (SATURN)

Coordinating Investigator:
[redacted], MD, PhD, Fellow EBU, [redacted], The Netherlands

Study Center(s):
A total of 102 centers in 17 European countries participated in the study.

Publication (reference):
Not applicable at the time of this report

Study Period: **Date of First Enrollment:** 08 January 2007 **Date of Last Evaluation:** 06 September 2007	**Phase of Development:** II

Objectives:

Primary objective:

- To assess whether the combination of solifenacin (3 mg, 6 mg, 9 mg) and tamsulosin OCAS 0.4 mg would provide improved efficacy compared to tamsulosin OCAS 0.4 mg alone in males with LUTS associated with BPH.

Secondary objectives:

- To assess the safety and the tolerability of the combination of different doses of solifenacin (0 [placebo], 3 mg, 6 mg and 9 mg) and tamsulosin OCAS (0 [placebo] and 0.4 mg) in males with LUTS associated with BPH;
- To assess the dose-response relationship of the combination of different doses of solifenacin (0 [placebo], 3 mg, 6 mg and 9 mg) and tamsulosin OCAS (0 [placebo] and 0.4 mg) in relieving voiding and storage symptoms in males with LUTS associated with BPH;
- To assess the efficacy of the combination of solifenacin (3 mg, 6 mg, 9 mg) and tamsulosin OCAS 0.4 mg compared with solifenacin (3 mg, 6 mg, 9 mg) alone in males with LUTS associated with BPH;
- To evaluate the pharmacokinetics (PK) of the combination of different doses of solifenacin (0 [placebo], 3 mg, 6 mg and 9 mg) and tamsulosin OCAS (0 [placebo] and 0.4 mg) in males with LUTS associated with BPH;
- To assess the exposure (area under the plasma drug concentration-time curve [AUC]) response relationship of the combination of different doses of solifenacin (0 [placebo], 3 mg, 6 mg and 9 mg) and tamsulosin OCAS (0 [placebo] and 0.4 mg) in relieving voiding and storage symptoms in males with LUTS associated with BPH;
- To select one or more doses of solifenacin in combination with tamsulosin OCAS 0.4 mg for further clinical development.

Study Design:
Randomized, double-blind, parallel-group, placebo-controlled, multi-center dose-ranging 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. Subjects visited the clinic at screening (Visit 1), at the end of the placebo run-in period (Visit 2), and after 2, 4, 8 and 12 weeks of double-blind treatment (Visits 3, 4, 5 and 6).
After the placebo run-in period, subjects were randomized to one of the following treatment arms: placebo, tamsulosin OCAS 0.4 mg monotherapy, solifenacin succinate monotherapy (3 mg, 6 mg, or 9 mg), or tamsulosin OCAS 0.4 mg in combination with solifenacin succinate (3 mg, 6 mg, or 9 mg).

Diagnosis and Main Criteria for Inclusion:
Males aged ≥45 years with LUTS associated with BPH fulfilling the following criteria: with voiding symptoms (including incomplete emptying of the bladder, intermittency, weak stream or hesitancy) and storage symptoms (including frequency, urgency or nocturia) for ≥3 months, a total International Prostate Symptom Score (IPSS) of ≥13, and a maximum urinary flow rate of ≥4.0 mL/s and ≤15.0 mL/s with a voided volume ≥120 mL.

Number of Subjects (planned and analyzed):
Planned: a total of 840 subjects were planned to be randomized to have 756 evaluable subjects. The planned numbers per treatment arm were as follows: placebo 80; solifenacin monotherapy, 40 per arm; tamsulosin monotherapy and combination treatment, 160 per arm. Assuming a drop-out rate of 10% during the placebo run-in period, it was anticipated that 933 subjects would need to be enrolled into the study.
Analyzed: N=930 for safety (SAF); N=919 for full analysis set (FAS); N=814 for per protocol set (PPS); and PK: N=676 for tamsulosin and N=628 for solifenacin.

Test Product, Dose And Mode of Administration:
Throughout the placebo run-in period, subjects took 2 placebo tablets once daily. Throughout the 12-week double-blind treatment period, subjects took 2 tablets once daily (tamsulosin OCAS 0.4 mg or placebo and solifenacin succinate 3 mg, 6 mg or 9 mg or placebo). Study medication was taken orally in the morning with or without food. Medication was taken with a glass of water and was swallowed as a whole.

Lot Numbers:
Batch numbers for tamsulosin OCAS tablets were: [redacted] and [redacted]
Solifenacin succinate batch numbers were: 3 mg: [redacted] 6 mg: [redacted] and 9 mg: [redacted]
Batch numbers for placebo matching tamsulosin OCAS were: [redacted] and [redacted]
Batch number for placebo matching solifenacin succinate was: [redacted]

Duration of Study and 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: The primary efficacy variable was the change from baseline to endpoint in total IPSS. Secondary efficacy variables were the change from baseline to endpoint from the IPSS questionnaire in: IPSS voiding scores, IPSS storage scores, individual IPSS item scores, and number of IPSS responders; and from the micturition diary: change from baseline to endpoint in mean number of urgency episodes of grade 3 or 4 per 24 hours (Patient Perception of Intensity of Urgency Severity [PPIUS]), mean number of micturitions per 24 hours, mean number of incontinence episodes per 24 hours, mean number of urge incontinence episodes per 24 hours, mean number of nocturia episodes per 24 hours, mean level of urgency (PPIUS), and mean volume voided per micturition.
Other efficacy variables were symptom and bother scores as assessed by International Consultation on Incontinence Questionnaire – Male Lower Urinary Tract Symptoms Module (ICIQ-MLUTS), IPSS Quality of Life (QoL), Patient Perception of Bladder Condition (PPBC), Visual Analogue Scale – Treatment Satisfaction (VAS-TS), and Q_{max}.

Safety: Incidence and severity of adverse events (AEs), ECG, laboratory parameters, vital signs, post void residual volume (PVR; as measured by ultrasonography or bladder scan) and physical examination.
Pharmacokinetics: The following population PK parameters were calculated: t_{lag}, t_{max}, C_{max}, C_{trough}, AUC_{tau}, $t_{1/2}$, k_a, CL/F, and V/F.

Statistical Methods:
The primary analysis was performed on the change from baseline to endpoint in total IPSS. Only subjects receiving active tamsulosin OCAS 0.4 mg were included in this analysis. The primary efficacy analysis was performed on the FAS.
To investigate whether solifenacin had an additional benefit (in addition to that of tamsulosin OCAS) with regard to the total IPSS, it was tested if the slope with increasing solifenacin doses differed statistically significantly from 0.
The analysis was based on a general linear model including solifenacin dose as a covariate, country as a fixed factor and the baseline total IPSS as a covariate. The slope represented the expected increase of change from baseline in total IPSS when the dose of solifenacin (in combination with tamsulosin OCAS) was increased by 1 mg.
The primary analysis as described for the endpoint was also performed for the total IPSS at Weeks 2, 4, 8 and 12 for both FAS and PPS. Secondary variables were all analyzed in the same way as described for the primary and secondary analyses for the primary variable.
Safety variables were descriptively summarized by treatment. Plasma concentration data of tamsulosin and solifenacin were subjected to population PK analysis.

RESULTS:

Analysis Sets and Subject Disposition:
A total of 1163 subjects were screened, of whom 1079 subjects entered the study and 1067 (98.9%) took at least 1 dose of placebo run-in medication. The number and percentage of subjects prematurely discontinuing during the run-in period was 142 (13.2%). Most subjects were discontinued during the run-in period because they did not fulfill the inclusion or exclusion criteria (8.5%). A total of 937 subjects were randomized and entered the double-blind treatment period, of whom 930 (99.3%) took at least 1 dose of the double-blind study medication. A total of 878 (93.7%) subjects completed the study.

- The Safety Analysis Set (SAF) comprised 930 randomized subjects who received at least 1 dose of randomized study drug and for whom any data was reported after first dose of study drug.
- The Full Analysis Set (FAS) consisted of 919 randomized subjects who received at least 1 dose of randomized study drug and who had a total IPSS at baseline and at least 1 post-randomization total IPSS.
- The Per-Protocol Set (PPS) included 814 subjects (88.6%) of the FAS without major protocol violations.
- The Pharmacokinetic Analysis Set (PKAS) consisted of 676 subjects who received tamsulosin OCAS and 628 subjects who received solifenacin and for whom at least 1 quantifiable plasma concentration of tamsulosin and/or solifenacin was obtained and for whom the dosing and sampling history was recorded for at least 1 sample with a quantifiable plasma concentration.

Demographics and Baseline Symptoms:
All subjects were men with LUTS associated with BPH. Subjects were predominantly of Caucasian origin. The mean age across the treatment arms ranged from 65.0 to 66.0 years. There were no obvious imbalances between the treatment arms with respect to demographic characteristics.
The mean total IPSS at baseline was 18.3, while the mean voiding and storage scores were 10.3 and 7.9, respectively. 67.7% of the subjects had urgency episodes of grade 3 or 4 at baseline, 21.3% of subjects had incontinence episodes and 16.5% urge incontinence episodes, while most subjects had nocturia episodes (89.6%) at baseline. The mean PVR volume at baseline was 40.5 mL.
The study population was comparable with the study population studied in the tamsulosin OCAS registration study 02-OMN-02.

Study Drug Exposure:
The mean exposure ranged from 78.6 to 83.6 days across treatment arms. The overall mean exposure was 81.4 days. The median treatment duration was 84.0 days in all treatment arms. The target exposure was 12 weeks (84 days).

Efficacy Results:
Primary efficacy variable:
Parametric modeling results for the change from baseline to endpoint in total IPSS for solifenacin - tamsulosin OCAS combination versus tamsulosin OCAS alone indicated that there was no additional benefit from increasing doses of solifenacin (in combination with tamsulosin OCAS) on the change from baseline in total IPSS compared to tamsulosin OCAS alone.

Main secondary variables:

For the diary parameters frequency, urgency, total urgency score, voided volume, incontinence and urge incontinence, additional improvements were seen for the solifenacin 3 mg, 6 mg and 9 mg - tamsulosin OCAS combinations compared to 0.4 mg tamsulosin OCAS alone in the total study population, although not all were statistically significant. For micturition frequency per 24 hours, total urgency score and volume voided there was a statistically significant improvement (slope) with increasing dosages of solifenacin (when combined with tamsulosin) ($p=0.0008$, $p=0.0437$ and $p<0.0001$, for the solifenacin 3 mg, 6mg, 9 mg – tamsulosin combinations, respectively).

Main secondary comparison:

The comparison of the combinations of solifenacin - tamsulosin OCAS versus solifenacin alone showed statistically significant improvements for the change from baseline to endpoint on total IPSS, IPSS storage score, urgency, frequency and voided volume. On the IPSS voiding score a numerical improvement was seen when comparing the solifenacin alone arms with the combination arms.

Post hoc Efficacy Analyses Results:
The study data were further investigated in order to increase the understanding of the results. As solifenacin is expected to improve the storage symptoms of patients with LUTS/BPH, post hoc efficacy analyses were carried out on several subpopulations based on the severity of baseline storage symptoms. The subpopulations investigated were Storage Symptoms subgroups 1, 2 and 3, with a daily micturition frequency ≥8 and ≥1, 2 or 3 urgency episodes of grade 3 and 4 (PPIUS) per day, respectively (50%, 40% and 33% of all subjects in the FAS, respectively). The fourth subgroup was the Limited Storage Symptoms subgroup, consisting of subjects whose baseline symptoms did not meet the criteria for Storage Symptoms subgroup 1 (included 50% of the subjects). Thus, the Limited Storage Symptoms subgroup and the Storage Symptoms subgroup 1 together comprise all study subjects treated with tamsulosin OCAS alone or in combination with solifenacin. Storage Symptoms subgroups 2 and 3 are subgroups of Storage Symptoms subgroup 1. Total urgency score (the mean sum of all urgency grades [PPIUS**]** per day) was added as an additional variable.

- The 3 subgroups with storage symptoms showed improvements in the various storage measures. On the IPSS storage scores additional improvements of 2.58, 2.27, and 2.34 IPSS points were observed in Storage Symptoms subgroups 1, 2 and 3; ($p=0.0003$, $p=0.0042$ and $p=0.0067$) when comparing the combination arms with tamsulosin OCAS alone. This improvement was considered to be clinically relevant. Clinically relevant and statistically significant improvements were also observed in the diary parameters (such as micturition frequency, total urgency score, urgency grades 3 and 4, voided volume). The total IPSS showed a numerical improvement. The IPSS voiding score only deteriorated slightly and all 3 Storage Symptom subgroups showed a statistically significant improvement in the IPSS QoL score.
- In contrast, in the Limited Storage symptom subgroup statistically significant deteriorations in total IPSS and IPSS voiding score were shown. No statistically significant improvements in diary parameters were shown, with the exception of voided volume. IPSS QoL and PPBC showed a

statistically significant deterioration.

- Q_{max} increased compared to baseline in all study arms. The increase in Q_{max} was smaller in the solifenacin – tamsulosin OCAS combination arms (in all 4 subgroups) than in the tamsulosin OCAS alone arm.

Pharmacokinetic Results:
Population pharmacokinetic analysis was performed on the plasma concentration data of tamsulosin and solifenacin. The PK of both compounds was described by a linear 1-compartment model. Relevant covariates that affected the PK were α_1-AGP, age, and creatinine clearance for tamsulosin and α_1-AGP, height and age for solifenacin. The population PK models were used to derive the mean estimates of exposure parameters. Results were in line with data previously obtained for solifenacin and tamsulosin.

Safety Results:
Most treatment-emergent AEs (TEAEs) were of mild or moderate intensity. There were no deaths during the trial. The incidence of TEAEs was highest in the 2 arms with solifenacin 9 mg (both 32.6%). The incidence of treatment-related AEs was highest in the solifenacin 9 mg combination arm (24.6%). The incidence of solifenacin and tamsulosin-related TEAEs was in line with the SPCs for solifenacin and tamsulosin. The most common AEs were gastrointestinal disorders, in particular dry mouth and constipation.
Six subjects had a serious adverse event (SAE) that was considered possibly or probably related to treatment by the investigator. These events involved 3 subjects with urinary retention (1 subject in the solifenacin 9 mg arm, 1 subject in the tamsulosin OCAS only arm, and 1 subject in the solifenacin 3 mg – tamsulosin OCAS combination arm), 1 subject with dizziness and cerebrovascular accident in the tamsulosin OCAS only arm (onset 3 and 62 days after start of treatment, respectively), 1 subject with syncope in the tamsulosin OCAS arm, and 1 subject with duplicate events of acute myocardial infarction and myocardial infarction in the solifenacin 9 mg – tamsulosin OCAS combination arm. All other SAEs were considered not related to treatment.
Discontinuations due to AEs were infrequent. The highest incidence (5.7%) was observed in the solifenacin 9 mg – tamsulosin OCAS combination arm.
Acute urinary retention occurred in 6 randomized subjects: 1 (2.3%) in the solifenacin 9 mg arm, 1 (0.6%) in the tamsulosin OCAS arm, 2 (1.1%) in the solifenacin 3 mg - tamsulosin OCAS combination arm and 2 (1.1%) in the solifenacin 9 mg - tamsulosin OCAS combination arm. Four of these subjects needed catheterization; No catheterization was needed in the 1 subject in the solifenacin 9 mg - tamsulosin OCAS combination arm and in the second subject in the solifenacin 3 mg - tamsulosin OCAS combination arm. 1 subject in the solifenacin 3 mg - tamsulosin OCAS combination arm experienced the acute urinary retention 3 days after stop of study medication.
There was a dose-dependent increase in PVR (up to 31.8 mL) in the solifenacin alone arms. The maximum mean increase was lower (up to 16.9 mL) in the solifenacin - tamsulosin OCAS combination arms than in the solifenacin alone arms. The mean increase in PVR was considered not clinically relevant and was not accompanied by an increase in AUR.
There were no clinically relevant changes from baseline, or differences between treatment arms in ECGs, laboratory parameters, vital signs, and physical examination.

CONCLUSIONS:

Efficacy

Solifenacin - tamsulosin OCAS combination versus tamsulosin OCAS alone

- Parametric modeling results for the change from baseline to endpoint in total IPSS for solifenacin - tamsulosin OCAS combination versus tamsulosin OCAS alone indicated that there was no additional benefit from increasing doses of solifenacin (in combination with tamsulosin OCAS) on the change from baseline in total IPSS compared to tamsulosin OCAS alone.
- For the diary parameters frequency, urgency, total urgency score, voided volume, incontinence and urge incontinence, additional improvements were seen for the solifenacin 3 mg, 6 mg and 9 mg - tamsulosin OCAS combinations compared to 0.4 mg tamsulosin OCAS alone in the total study population, although not all were statistically significant.

Solifenacin - tamsulosin OCAS combination versus solifenacin alone

- Comparison of combination treatment versus treatment with solifenacin alone showed statistically significant improvements in favor of combination treatment compared with solifenacin alone on total IPSS, IPSS storage score, urgency, frequency of micturitions, and on voided volume. On the IPSS voiding score a numerical improvement was seen when comparing the solifenacin alone arms with the combination arms. This indicates that patients with LUTS associated with BPH experience greater clinical improvement when being treated with the combination than with solifenacin alone. This is in line with expectations based on the pharmacology of solifenacin.

Subgroup analyses

- The study population appeared to be a heterogeneous population.
- In all 3 **Storage Symptoms subgroups** a numerical improvement was seen on total IPSS and statistically significant improvements were observed in the IPSS storage scores. The IPSS voiding score only deteriorated slightly and a statistically significant improvement in the IPSS QoL score was shown in all 3 Storage Symptoms subgroups.
- Furthermore, consistent clinically relevant and statistically significant positive effects were seen in the Storage Symptoms subgroups on the diary parameters frequency, urgency, total urgency score and voided volume when comparing the combination arms with tamsulosin OCAS alone.
- The results observed in the Storage Symptom subgroups suggests that the addition of solifenacin to the treatment of tamsulosin OCAS provides clinically relevant additional benefit for patients with LUTS associated with BPH who have voiding symptoms as well as a substantial level of storage symptoms.
- In contrast, in the **Limited Storage Symptom subgroup** statistically significant deteriorations in total IPSS and IPSS voiding score were shown. No statistically significant improvements in diary parameters were observed, with the exception of voided volume. IPSS QoL and PPBC showed a statistically significant deterioration. Combination treatment is therefore not of benefit for the subjects in the Limited Storage Symptoms subgroup.
- Q_{max} increased compared to baseline in all study arms. The increase in Q_{max} was smaller in the solifenacin – tamsulosin OCAS combination arms (in all 4 subgroups) than in the tamsulosin OCAS alone arm.

Pharmacokinetic Results

Population pharmacokinetic analysis was performed on the plasma concentration data of tamsulosin and solifenacin. Results were in line with data previously obtained for solifenacin and tamsulosin.

Safety

- Treatment with 0.4 mg tamsulosin OCAS in combination with 3 mg, 6 mg or 9 mg solifenacin was safe and well tolerated in males with LUTS associated with BPH.
- There were no deaths and the incidence of SAEs and AEs leading to study discontinuation was low (1.6% and 2.7%, respectively). The incidence of solifenacin and tamsulosin-related TEAEs was in line with the SPCs for solifenacin and tamsulosin. The most frequently observed AEs with solifenacin and the solifenacin - tamsulosin OCAS combinations were dry mouth and constipation, as expected.
- Cases of acute urinary retention were reported, as can be expected in a population of patients with LUTS associated with BPH. The incidence of AUR was low and there was no apparent dose relationship with increasing doses of solifenacin in the combination with tamsulosin OCAS. (0.6%, 1.1%, 0% and 1.1% in the tamsulosin OCAS monotherapy arm and the combination arms with 3 mg, 6 mg, 9 mg solifenacin, respectively).
- There were no clinically relevant changes from baseline, or differences between treatment arms in ECGs, laboratory parameters, vital signs, and physical examination.

Overall conclusion

This study demonstrated that combination treatment of solifenacin and tamsulosin OCAS is expected to be an efficacious and well tolerated treatment for patients with LUTS associated with BPH who have voiding symptoms as well as a substantial level of storage symptoms. The 6 mg and 9 mg solifenacin – tamsulosin OCAS combination arms seem to have the best benefit-risk ratio and will be further investigated in a phase 3 study in patients with LUTS associated with BPH with a substantial level of storage symptoms in addition to voiding symptoms.

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Date of Report Synopsis: 16 December 2010