SYNOPSIS

Name of Sponsor/Company: Astellas Pharma Global Development, Inc. (formerly Astellas Pharma US, Inc.)		
Name of Finished Product: VESIcare® (solifenacin succinate) and Tamsulosin Hydrochloride Oral Control Absorption System (TOCAS)		
Name of Active Ingredient: solifenacin succinate		
Title of Study: A Phase 2, Randomized, Double-Blind, Parallel Group, Placebo Controlled, Multi-Center Study to Evaluate the Safety of the Co-Administration of Solifenacin Succinate with 0.4 mg Tamsulosin Hydrochloride OCAS (TOCAS) Using Urodynamics in Male Subjects with Lower Urinary Tract Symptoms (LUTS) and Bladder Outlet Obstruction (BOO)		
Responsible Medical Officer/Investigators: [redacted], MD, MPH. [redacted].		
Study Center(s): This study was conducted at 40 centers in the US and Europe.		
Publication (reference): There are no publications based on this study as of the date of this report.		
Study Period: Screening Period: 1 to 3 weeks (may include a 2-week washout period); Treatment Period: 12 weeks **Date of first enrollment:** 25 June 2007 **Date of last evaluation:** 18 Aug 2008	**Phase of Development:** 2	

Objectives:

The primary objective of this study was:

- to evaluate the urodynamic variables in male patients with Lower Urinary Tract Symptoms (LUTS) and Bladder Outlet Obstruction (BOO) treated with co-administration of 6 mg solifenacin succinate with TOCAS or 9 mg solifenacin succinate with TOCAS versus placebo.

The secondary objectives were:

- to evaluate the tolerability and safety of co-administration of 6 mg solifenacin succinate with TOCAS or 9 mg solifenacin succinate with TOCAS in male subjects with LUTS and BOO
- to compare the efficacy of co-administration of 6 mg solifenacin succinate with TOCAS or 9 mg solifenacin succinate with TOCAS versus placebo in signs and symptoms of benign prostatic hyperplasia (BPH) in male subjects with LUTS and BOO.

Methodology: This was a randomized, double-blind, parallel group, placebo-controlled, multicenter study. Patients were randomized (1:1:1) to receive once daily co-administration of either 6 mg solifenacin succinate with 0.4 mg TOCAS (6 mg solifenacin succinate with TOCAS), 9 mg solifenacin succinate with 0.4 mg TOCAS (9 mg solifenacin succinate with TOCAS) or matching placebos for 12 weeks.

Patients visited the clinic at screening (Visit 1), the end of the screening period (Visit 2) and after 2, 4, 8 and 12 weeks of double-blind treatment (Visits 3, 4, 5 and 6, respectively).

At the screening visit (Visit 1), laboratory results, International Prostate Symptom Score (IPSS), cystometry, uroflowmetry and electrocardiogram (ECG) results were checked against the inclusion and exclusion criteria for subject eligibility. At Visit 2 (baseline), eligible patients were randomized to 12 weeks of double-blind treatment with co-administration of solifenacin succinate and TOCAS or matching placebos.

Patients completed a 3-day micturition diary during the 3 days preceding each of Visits 2 through 6.

Safety assessments, including vital signs, laboratory tests and post-void residual (PVR) volumes were collected at Visits 1 through 6, and adverse events were recorded on Visits 2 through 6. Cystometry, uroflowmetry, physical examination and ECG evaluations were conducted during Visits 1 and 6.

Efficacy assessments including International Prostate Symptom Score (IPSS) and Patient Perception of Bladder Condition (PPBC) scores were collected at Visit 1 through 6. International Consultation on Incontinence Questionnaire-Male Lower Urinary Tract Symptoms (ICIQ MaleLUTS) and International Consultation on Incontinence Questionnaire-Lower Urinary Tract Symptoms Quality of Life (ICIQ-LUTSqol) questionnaires were completed by the patient at Visits 2, 4, 5 and 6.

Number of Patients (enrolled and analyzed): A total of 222 patients were randomly assigned to study drug and received at lease one dose of double-blind study drug, and was the population used for all safety analyses. A total of 192 (86.5%) patients completed the study (placebo - 62 patients; 6 mg solifenacin succinate with TOCAS - 68 patients; 9 mg solifenacin succinate with TOCAS - 62 patients) and 30 (13.5%) patients were withdrawn from the study (placebo - 12 patients; 6 mg solifenacin succinate with TOCAS - 6 patients; 9 mg solifenacin succinate with TOCAS - 12 patients).

Diagnosis and Main Criteria for Inclusion: Male patients >45 years of age with voiding and storage LUTS for at least 3 months, a total IPSS score ≥8, a BOO indicated by a Bladder Outlet Obstruction Index (BOOI) ≥20, and a maximum urinary flow rate of ≤12 mL/sec, with a voided volume of ≥120 mL during free flow in a representative assessment of uroflowmetry.

Test Product, Dose and Mode of Administration, Batch Numbers: See Synopsis Table 1.

Duration of Treatment (or Duration of Study, if applicable): Twelve weeks of once daily co-administration of either 6 mg solifenacin succinate with 0.4 mg TOCAS, 9 mg solifenacin succinate with 0.4 mg TOCAS, or matching placebos.

Reference Product, Dose and Mode of Administration, Batch Numbers: See Synopsis Table 1.

Criteria for Evaluation:

Primary Urodynamic Evaluation:

PdetQmax (detrusor pressure at maximum flow rate) was evaluated using simultaneous recording of urinary voiding by a uroflowmeter during detrusor pressure evaluation by cystometry at Visits 1 and 6.

Qmax (maximum flow rate) was obtained from freeflow uroflow readings which were obtained in order to determine the eligibility criteria, which was required to be less than or equal to 12 mL per second. For the primary endpoint, Qmax was obtained from uroflowmetry postcystometry.

Secondary Urodynamic and Efficacy Evaluation:

Secondary urodynamic and efficacy evaluations included assessment Bladder Contractile Index (BCI) and Percent Bladder Voiding Efficiency (BVE).

Safety Evaluation:

Safety assessments included treatment-emergent adverse events (TEAEs), serious adverse events (SAEs), vital signs, physical examinations, electrocardiogram (ECG), laboratory assessments and PVR (ultrasound).

Statistical Methods:

Efficacy:

The efficacy variables including change from baseline to end of treatment in IPSS (mean of total/voiding/storage symptom scores), PPBC, micturition frequency per 24 hours, number of urgency episodes per 24 hours, number of incontinence episodes per 24 hours, voided volume per micturition, ICIQ MaleLUTS, and ICIQ LUTSqol scores were analyzed using analysis of covariance (ANCOVA) with the site and treatment group as the factors and the baseline value as the covariate to compare the co-administration of solifenacin succinate with TOCAS to the placebo. Statistical comparisons were 2-sided with alpha = 0.05, and no adjustment to the significance level was made.

All efficacy assessments and changes from baseline at each visit were summarized by treatment group.

Safety:

The primary variables were the change from baseline to end of treatment in PdetQmax and Qmax. The ANCOVA with the site and treatment as the factors and the baseline value as the covariate was used to compare each co-administration of solifenacin succinate with TOCAS to the placebos.

Summary

Demographics: Demographics are summarized in the Synopsis Table 2.

Drug Administration: This study was conducted at 40 sites in the United States and Europe. All analysis populations, except the Full Analysis Set (FAS) population, included patients from the 40 sites; the FAS population included patients from 36 of the 40 sites. A total of 222 patients were equally randomized (n = 74) to each group to receive either placebo, 6 mg solifenacin succinate with TOCAS, or 9 mg solifenacin succinate with TOCAS, and was considered the safety analysis set (SAF) population. The SAF population was defined as patients who received at lease one dose of double-blind study drug, and was the population used for all safety analyses. A total of 192 (86.5%) patients completed the study (placebo - 62 patients; 6 mg solifenacin succinate with TOCAS - 68 patients; 9 mg solifenacin succinate with TOCAS - 62 patients) and 30 (13.5%) patients were withdrawn from the study (placebo - 12 patients; 6 mg solifenacin succinate with TOCAS - 6 patients; 9 mg solifenacin succinate with TOCAS - 12 patients). A total of 188 patients were in the FAS population (62 placebo patients; 67 patients with 6 mg solifenacin succinate with TOCAS; and 59 patients with 9 mg solifenacin succinate with TOCAS). The FAS population was defined as patients who received at least 1 dose of double-blind study drug and had urodynamic measurements at baseline and post-baseline on treatment visits.

Efficacy Results:

Primary Urodynamic Results

Detrusor Pressure at Maximum Flow Rate (PdetQmax)

The mean change from baseline within the 6 mg solifenacin succinate with TOCAS group in PdetQmax was significantly lower at Week 12 (-7.62 cmH_2O; P = 0.0044) and at end of treatment (-7.92 cmH_2O; P = 0.0021) as compared to placebo in the FAS population. No significant differences were observed in the mean change from baseline at Week 12 and end of treatment within the placebo and 9 mg solifenacin succinate with TOCAS

treatment groups; although there were reductions at both time points.

When treatment groups were compared, the mean change from baseline at Week 12 was -7.31 cmH_2O in the 6 mg solifenacin succinate with TOCAS group and -3.08 cmH_2O in the 9 mg solifenacin succinate with TOCAS group compared with -1.22 cmH_2O in the placebo group. Both active treatment groups were considered non-inferior based on the difference in change compared with placebo (6 mg solifenacin succinate with TOCAS; treatment difference -6.09, 95% CI = [-14.20, 2.02]; 9 mg solifenacin succinate with TOCAS; treatment difference = -1.87, 95% CI = [-10.42, 6.69]), given the non-inferiority upper limit of <15. Additionally, the 9 mg solifenacin succinate with TOCAS group was considered non-inferior to the 6 mg solifenacin succinate with TOCAS group; 95% CI 4.22 (-3.99, 12.43).

No significant differences were observed compared between placebo at Week 12 in the 6 mg solifenacin succinate with TOCAS and in the 9 mg solifenacin succinate with TOCAS treatment groups in PdetQmax based on the 95% CIs for the differences in the adjusted mean changes from baseline. Results were consistent when site [redacted] was excluded from data analysis.

Results at the end of treatment were similar when treatment groups were compared; the mean change from baseline was -7.84 cmH_2O in the 6 mg solifenacin succinate with TOCAS group and -6.69 cmH_2O in the 9 mg solifenacin succinate with TOCAS group compared with -1.69 cmH_2O in the placebo group. Both treatment groups were considered non-inferior based on the difference in change compared with placebo given the non-inferiority upper limit of <15 (versus 6 mg solifenacin succinate with TOCAS, treatment difference = -6.15, 95% CI = [-14.67, 2.37]; and versus 9 mg solifenacin succinate with TOCAS, treatment difference = -5.00, 95% CI = [-13.85, 3.84]). Additionally, the 9 mg solifenacin succinate with TOCAS group was considered non-inferior to the 6 mg solifenacin succinate with TOCAS group, the treatment difference was 1.15 with a 95% CI of -7.42, 9.71.

No significant differences were observed compared with placebo at the end of treatment in the 6 mg solifenacin succinate with TOCAS and 9 mg solifenacin succinate with TOCAS treatment groups in PdetQmax based on the 95% CIs for the differences in the adjusted mean changes from baseline.

Maximum Flow Rate (Qmax)

The mean change from baseline for the 6 mg solifenacin succinate with TOCAS group and for the 9 mg solifenacin succinate with TOCAS group for Qmax was significantly higher at Week 12 (1.44 mL/sec; P = 0.0003 and 2.14 mL/sec; P = 0.0004, respectively) and at end of treatment (1.59 mL/sec; P = 0.0001 and 2.27 mL/sec; P = 0.0003, respectively). No significant differences were observed in the mean change from baseline at Week 12 and end of treatment within the placebo group; although there were slight increases at both timepoints.

When treatment groups were compared, the mean change from baseline at Week 12 was 1.71 mL/sec in the 6 mg solifenacin succinate with TOCAS group and 2.22 mL/sec in the 9 mg solifenacin succinate with TOCAS group compared with 0.13 mL/sec in the placebo group. Both active treatment groups were considered non-inferior based on the differences in the change compared to placebo (1.57 [95% CI = 0.43, 2.72] for 6 mg solifenacin succinate with TOCAS and 2.09 [95% CI = 0.90, 3.27] for 9 mg solifenacin succinate with TOCAS) given the non-inferiority lower limit of >-3. When the active treatment groups were compared, the 9 mg solifenacin succinate with TOCAS group was non-inferior to the 6 mg solifenacin succinate with TOCAS group; treatment difference = 0.51 and 95% CI = -0.63, 1.66.

Compared with placebo, both 6 mg solifenacin succinate with TOCAS and 9 mg solifenacin succinate with TOCAS showed superior improvements in maximum flow rate at Week 12 based on the 95% CIs for the differences in the adjusted mean changes from baseline in Qmax; 6 mg solifenacin succinate with TOCAS (95% CI = 0.43, 2.72) and 9 mg solifenacin succinate with TOCAS (95% CI = 0.90, 3.27).

Results at the end of treatment were similar; the mean change from baseline was 1.85 mL/sec in the 6 mg solifenacin succinate with TOCAS group and 2.35 mL/sec in the 9 mg solifenacin succinate with TOCAS group compared with 0.17 mL/sec in the placebo group. Both treatment groups were considered non-inferior based on the difference in change compared with placebo given the non-inferiority lower limit of >-3 (6 mg solifenacin succinate with TOCAS: treatment difference = 1.67, 95% CI = [0.50, 2.85]; and 9 mg solifenacin succinate with TOCAS: treatment difference = 2.18 and 95% CI = [0.98, 3.37]). Additionally, the 9 mg solifenacin succinate with TOCAS group was non-inferior to the 6 mg solifenacin succinate with TOCAS group: treatment difference = 0.50 and 95% CI = [-0.67, 1.67]).

Compared with placebo, 6 mg solifenacin succinate with TOCAS and 9 mg solifenacin succinate with TOCAS treatment groups showed superior improvements at the end of treatment in Qmax based on the 95% CIs for the differences in the adjusted mean changes from baseline; 6 mg solifenacin succinate with TOCAS (95% CI: 0.50, 2.85) and 9 mg solifenacin succinate with TOCAS (95% CI: 0.98, 3.37).

Secondary Efficacy Results

Bladder Contractile Index (BCI)

Mean values for BCI at baseline were within normal limits for the placebo group, 6 mg solifenacin succinate with TOCAS group, and the 9 mg solifenacin succinate with TOCAS group (109.85, 114.71 and 107.58 BCI, respectively). No significant differences were observed for the within- or between-groups comparisons in the mean change from baseline to Week 12 or end of treatment.

Bladder Voiding Efficiency (BVE)

Mean values for BVE at baseline in the placebo, 6 mg solifenacin succinate with TOCAS, and 9 mg solifenacin succinate with TOCAS groups were 76.46, 82.42 and 74.91 BE, respectively. No significant differences were observed within or between treatment groups in the mean change from baseline at Week 12 and end of treatment.

International Prostate Symptom Score (IPSS)

Overall, mean values compared with baseline for the IPSS Total Score were significantly ($P < 0.0001$) lower within all treatment groups at Weeks 2, 4, 8, 12 and end of treatment.

When treatment groups were compared, no significant differences were observed in the mean change from baseline at all time points, although reductions in the total score were observed at all time points in all treatment groups. Results were similar in the FAS population when site [redacted] was excluded from the analysis.

IPSS Voiding and Storage Scores indicated larger values for worse conditions. Results were consistent for the IPSS Voiding Score and the IPSS Storage Score compared with the IPSS Total Score; mean values were significantly ($P < 0.0001$) lower compared with baseline within all treatment groups at Weeks 2, 4, 8, 12 and end of treatment.

When treatment groups were compared with placebo, no significant difference was observed in the mean

change from baseline at all time points, although reductions in the voiding score and storage score were observed at all timepoints in all treatment groups.

IPSS Individual Score and QOL Scores

Overall, mean values for the IPSS Individual Score for all 7 questions and the QOL Score were significantly lower compared with baseline within all treatment groups at Weeks 2, 4, 8, 12 and end of treatment.

No significant differences were observed in the mean change from baseline among treatment groups in QOL scores at all time points.

Patient Perception of Bladder Condition (PPBC)

Overall, the mean change in baseline for the PPBC assessment were significantly lower within all treatment groups at Weeks 2, 4, 8, 12 and end of treatment; however, no significant differences were observed at all time points when treatment groups were compared.

3-Day Averaged Number of Micturitions per 24 Hours

Overall, the mean change from baseline was significantly lower within the 6 mg solifenacin succinate with TOCAS and the 9 mg solifenacin succinate with TOCAS treatment groups at all time points, and at Weeks 4 and 8 in the placebo treatment group.

No significant differences were observed in the mean change from baseline at Weeks 4, 8 and 12 when treatment groups were compared. The mean change from baseline was significantly lower in the 6 mg solifenacin succinate with TOCAS and 9 mg solifenacin succinate with TOCAS groups at Week 2 ($P = 0.0246$ and $P = 0.0430$, respectively) and end of treatment ($P = 0.0331$ and $P = 0.0464$, respectively) compared with placebo. When site [redacted] was excluded from data analysis, the mean change from baseline was significantly lower at Week 2 ($P = 0.0275$), Week 12 ($P = 0.0472$), and end of treatment ($P = 0.0342$) in the 6 mg solifenacin succinate with TOCAS compared with placebo; no significant differences were observed in the 9 mg solifenacin succinate with TOCAS group compared with placebo at any timepoints.

3-Day Averaged Voided Volume per Micturition

The mean change from baseline for the 3-day averaged voided volume per micturitions were significantly higher within the 6 mg solifenacin succinate with TOCAS and the 9 mg solifenacin succinate with TOCAS treatment groups at all timepoints and at most timepoints in the placebo treatment group.

When treatment groups were compared, the mean change from baseline in the 6 mg solifenacin succinate with TOCAS was significantly higher compared with placebo at Weeks 2, 4, 8, 12 and end of treatment and at the same time points, with the exception of Week 2, in the 9 mg solifenacin succinate with TOCAS group.

3-Day Averaged Number of Urgency Episodes (Scale ≥3) per 24 Hours

Overall, mean change from baseline for the 3-day average number urgency episodes (scale ≥3) per 24 hours were significantly lower within the 6 mg solifenacin succinate with TOCAS and the 9 mg solifenacin succinate with TOCAS treatment groups at all time points, and at most time points in the placebo treatment group.

No significant differences were observed in the mean change from baseline when all treatment groups were compared, although there were reductions in urgency episodes per 24 hours at all time points for all treatment groups.

3-Day Averaged Number of Incontinence Episodes per 24 Hours

The mean change from baseline for the 3-day average number of incontinence episodes per 24 hours were significantly lower within the 6 mg solifenacin succinate with TOCAS at all time points (Weeks 2, 4, 8, 12, and end of treatment), at Weeks 2 and 4 in the 9 mg solifenacin succinate with TOCAS group, and at Weeks 8, 12 and end of treatment in the placebo treatment group.

No significant differences were observed in the mean change from baseline when treatment groups were compared, although there were reductions in incontinence episodes per 24 hours at all time points for all treatment groups.

Summary of ICIQ-MaleLUTS Scores

MaleLUTS Total Symptom Score and the Total Symptom Bother Score results were consistent; the mean change from baseline was significantly lower within all treatment groups at all time points, Weeks 4, 8, 12, and end of treatment. When treatment groups were compared, no significant differences in the mean change from baseline were observed at all time points in the Total Symptom Scores and Total Symptom Bother Score, although all treatment groups had reductions in scores at all time points. Results were consistent when site [redacted] was excluded from data analysis.

Voiding Score and the Voiding Bother Score results were consistent; the mean change from baseline was significantly lower within all treatment groups at all time points (Weeks 4, 8, 12, and end of treatment). When treatment groups were compared, no significant differences in the mean change from baseline was observed in the Voiding Score among all treatment groups at all time points, although there were reductions in each group. Results were consistent when site [redacted] was excluded from data analysis. No significant differences were observed in the mean change from baseline in the Voiding Bother Score in the 6 mg solifenacin succinate with TOCAS and 9 mg solifenacin succinate with TOCAS groups compared with placebo at all time points; the mean change from baseline was significantly (P = 0.0382) lower at Week 4 in the 9 mg solifenacin succinate with TOCAS treatment group (-7.2) compared with the 6 mg solifenacin succinate with TOCAS group (-3.2). When site [redacted] was excluded from data analysis, no significant differences in mean change from baseline were observed when treatment groups in the Voiding Bother Score across all treatment groups at all timepoints.

Incontinence Score and the Incontinence Bother Score results were consistent; the mean change from baseline was significantly lower within all treatment groups at Weeks 4, 8, 12 and end of treatment. When treatment groups were compared, no significant differences in the mean change from baseline were observed at all timepoints in the Incontinence Score and Incontinence Bother Score, although all treatment groups had reductions.

Frequency Score and the Frequency Bother Score results were consistent; the mean change from baseline was significantly lower within all treatment groups at Weeks 4, 8, 12 and end of treatment. When treatment groups were compared, no significant differences were observed in the mean change from baseline at all time points for the Frequency Bother Score; however, in the Frequency Score the mean change from baseline was significantly lower compared with placebo at Week 4 in the 6 mg solifenacin succinate with TOCAS group (P = 0.0504), at Week 12 in the 6 mg solifenacin succinate with TOCAS and the 9 mg solifenacin succinate with TOCAS groups (P = 0.0342 and P = 0.0111, respectively), and end of treatment in the 6 mg solifenacin succinate with TOCAS and the 9 mg solifenacin succinate with TOCAS groups (P = 0.0551 and 0.0318, respectively).

MaleLUTS Nocturia Score and the Nocturia Bother Score results were consistent within all treatment groups;

the mean change from baseline was significantly lower at Weeks 4, 8, 12 and end of treatment. When treatment groups were compared, no significant differences in the mean change from baseline were observed at all time points in the Nocturia Score, and in the Nocturia Bother Score in the 6 mg solifenacin succinate with TOCAS and 9 mg solifenacin succinate with TOCAS treatment groups compared with placebo. The mean change from baseline at Week 4 was significantly (P = 0.0301) lower in the 9 mg solifenacin succinate with TOCAS group (-2.2) compared with the 6 mg solifenacin succinate with TOCAS group (-1.3).

ICIQ-LUTSqol Symptom Score mean change from baseline results was significantly lower within all treatment groups at Weeks 4, 8, 12 and end of treatment. When treatment groups were compared, no significant differences were observed in the mean change from baseline in the 6 mg solifenacin succinate with TOCAS compared with placebo at all time points; however, mean changes from baseline were significantly (P = 0.0312 and P = 0.0300, respectively) lower at Week 8 and Week 12 in the 9 mg solifenacin succinate with TOCAS group compared with placebo. The mean change from baseline at Week 4 in the 9 mg solifenacin succinate with TOCAS group was significantly (P = 0.0373) lower compared with the 6 mg solifenacin succinate with TOCAS group.

ICIQ-LUTSqol Overall Symptom Interference of Life Score mean change from baseline results was significantly lower within all treatment groups at Weeks 4, 8, 12 and end of treatment. When treatment groups were compared, no significant differences in the mean change from baseline were observed at all time points, although all treatment groups had reductions in scores.

Safety Results:.

Most TEAEs were mild or moderate in intensity across all treatment groups. TEAEs occurred in 39.2% of patients in the placebo group, 51.4% of patients in the 6 mg solifenacin succinate with TOCAS group and 50.0% of patients in the 9 mg solifenacin succinate with TOCAS group. The most frequently occurring TEAE among all treatment groups was dry mouth (placebo: 4.1%; 6 mg solifenacin succinate with TOCAS: 12.2% and 9 mg solifenacin succinate with TOCAS: 18.9%); this AE occurred more frequently in the active treatment groups compared with the placebo group. More patients in the 6 mg solifenacin succinate with TOCAS and 9 mg solifenacin succinate with TOCAS treatment groups compared with the placebo group experienced TEAEs that were considered by the investigator to be drug-related; 32.4% and 35.1%, respectively, versus 20.3% for placebo. The most frequently occurring treatment-emergent AE that was drug-related was dry mouth; this AE occurred more frequently in the 6 mg solifenacin succinate with TOCAS (12.2%) and 9 mg solifenacin succinate with TOCAS (18.9%) treatment groups than in the placebo group (4.1%). There was 1 patient who experienced 2 episodes of urinary retention in the 6 mg solifenacin succinate with TOCAS group, of which 1 was considered serious.

Five patients reported a total of 7 SAEs that occurred across all treatment groups; 2 SAEs in the placebo group, 3 SAEs in the 6 mg solifenacin succinate with TOCAS group, and 2 in the 9 mg solifenacin succinate with TOCAS group.

No deaths occurred during the study.

One patient in the placebo group experienced 2 SAEs (prostatitis and urethritis), 2 patients in the 6 mg solifenacin succinate with TOCAS experienced 3 SAEs (myocardial infarction, constipation, and urinary retention), and 2 patients in the 9 mg solifenacin succinate with TOCAS group experienced 2 SAEs (colon cancer and accidental overdose). All SAEs were mild or moderate in severity, and 4 of the 7 SAEs were

considered possibly or probably related to study drug. All but 1 patient in 9 mg solifenacin succinate with TOCAS group recovered from the SAEs; this patient had colon cancer that was moderate in severity and was unresolved during the study. The investigator considered the colon cancer to be not related to study drug.

Results for PVR within treatment groups based on the SAF population indicated that the mean change from baseline in the placebo group was significantly lower at Week 2 (-12.46 mL; P = 0.0347) and Week 8 (-15.67 mL; P = 0.0108), with non-significant reductions at Week 4, 12, and end of treatment. The mean change from baseline in PVR values within the 6 mg solifenacin succinate with TOCAS group was significantly higher at all time points; Week 2 (21.34 mL; P = 0.0039), Week 4 (17.34 mL; P = 0.0029), Week 8 (13.55 mL; P = 0.0488), Week 12 (27.27 mL; P = 0.0008), and end of treatment (25.91 mL; P = 0.0004). The mean change from baseline in PVR values within the 9 mg solifenacin succinate with TOCAS group was significantly higher at Week 2 (13.74 mL; P = 0.0365), Week 12 (21.02 mL; P = 0.0026), and end of treatment (21.58 mL; P = 0.0007).

When treatment groups were compared based on the SAF population, the mean change from baseline was significantly higher in the 6 mg solifenacin succinate with TOCAS and 9 mg solifenacin succinate with TOCAS treatment groups compared with placebo at all time points; Week 2 (17.68 mL; P = 0.0014 and 11.52 mL; P = 0.0118, respectively), Week 4 (14.66 mL; P = 0.0069 and 9.49 mL; P = 0.0380), Week 8 (9.23 mL; P = 0.0058 and 6.46 mL; P = 0.0152), Week 12 (25.41 mL; P = 0.0176 and 21.16 mL; P = 0.0531), and end of treatment (23.62 mL; P = 0.0063 and 20.05 mL; P = 0.0193). No significant differences were observed in the mean change from baseline in the 9 mg solifenacin succinate with TOCAS group compared with the 6 mg solifenacin succinate with TOCAS group at all time points.

CONCLUSIONS:

Urodynamic

The primary urodynamic variables included detrusor pressure at maximum flow rate (PdetQmax) and maximum flow rate (Qmax). The following conclusions can be made:

- The PdetQmax (detrusor pressure at maximum flow rate) and Qmax (maximum flow rate) results at Week 12 and end of treatment for the 6 mg solifenacin succinate with TOCAS and the 9 mg solifenacin succinate with TOCAS groups were considered non-inferior compared with placebo; however, the 6 mg solifenacin succinate with TOCAS and 9 mg solifenacin succinate with TOCAS groups showed superior improvements in Qmax compared with placebo.
- The secondary variables were urodynamic variables including Bladder Contractile Index (BCI), Bladder Voiding Efficiency (BVE) and efficacy variables including International Prostate Symptom Score (IPSS) (mean total score, voiding score, and storage score), IPSS Individual Score and QOL Score, Patient Perception of Bladder Condition (PPBC), ICIQ MaleLUTS and ICIQ-LUTSqol. Assessments based on the Subject Micturition Diary included the 3-day averaged number of micturitions per 24 hours, 3-day averaged voided volume per micturition, 3-day averaged number of urgency episodes per 24 hours, and 3-day averaged number of incontinence episodes per 24 hours.
- No significant differences in the mean change from baseline for IPSS Total Score were observed compared with placebo at all time points (Weeks 2, 4, 8, 12, and end of treatment). Results were consistent for the IPSS Voiding Score and the IPSS Storage Score compared with the IPSS Total score.

- No significant differences were observed in the mean change from baseline for the IPSS Individual Score (part of the IPSS Score) compared with placebo in most questions (sensation of incomplete emptying, frequency of urinating, intermittency, urgency, and nocturia) at all time points (Weeks 2, 4, 8, 12, and end of treatment). The mean change from baseline in weak stream was significantly lower in the 6 mg solifenacin succinate with TOCAS and 9 mg solifenacin succinate with TOCAS groups compared with placebo at various weeks, and in straining at Week 2 in the 6 mg solifenacin succinate with TOCAS group. No significant differences were observed in the mean change from baseline compared with placebo in QOL scores at all time points.
- No significant differences was observed in the mean change from baseline in PPBC scores compared with placebo at all time points (Weeks 2, 4, 8, 12, and end of treatment).
- Information collected from the Subject Micturition Diary indicated there was no significant difference in the 3-day averaged number of micturitions per 24 hours compared with placebo at Weeks 4, 8 and 12; however, the averaged number of micturitions per 24 hours were significantly lower indicating improvement in the 6 mg solifenacin succinate with TOCAS and 9 mg solifenacin succinate with TOCAS groups at Week 2 (P = 0.0246, P = 0.0430, respectively) and end of treatment (P = 0.0331, P = 0.0464) compared with placebo. When site [redacted] was excluded from data analysis, significant improvement in the averaged number of micturitions per 24 hours was observed in the 6 mg solifenacin succinate with TOCAS with significantly lower mean values at Week 2 (P = 0.0275), Week 12 (P = 0.0472), and end of treatment (P = 0.0342); no significant difference was observed in the 9 mg solifenacin succinate with TOCAS group compared with placebo at all time points.
- Significant improvement compared with placebo was observed in the 3-day averaged voided volume per micturition at Weeks 4, 8, 12, and end of treatment in the 9 mg solifenacin succinate with TOCAS group and at Weeks 2, 4, 8, 12, and end of treatment in the 6 mg solifenacin succinate with TOCAS group. No significant differences were observed in the mean change from baseline in the active treatment groups compared with placebo in the 3-day averaged number of urgency episodes per 24 hours and 3-day averaged number of incontinence episodes per 24 hours at all time points (Weeks 2, 4, 8, 12, and end of treatment).
- No significant difference was observed in the mean change from baseline compared with placebo among treatment groups in most ICIQ-MaleLUTS Symptom scores at all time points (Weeks 4, 8, 12, and end of treatment). Significantly lower values were observed in the mean change from baseline compared with placebo in the ICIQ-MaleLUTS Frequency Score at Week 12 and end of treatment in the 6 mg solifenacin succinate with TOCAS and 9 mg solifenacin succinate with TOCAS groups.
- The mean change from baseline for the ICIQ-LUTSqol Symptom Score was significantly (P = 0.0312 and P = 0.0300, respectively) lower at Week 8 and Week 12 compared with placebo in the 9 mg solifenacin succinate with TOCAS group; however, no significant difference was observed in the mean change from baseline in the 6 mg solifenacin succinate with TOCAS group compared with placebo at all time points (Weeks 4, 8, 12, and end of treatment). Results were consistent when site [redacted] was excluded from data analysis.
- No significant differences were observed in the mean change from baseline at all time points (Weeks 4, 8, 12, and end of treatment) for ICIQ-LUTSqol Overall Symptom Interference of Life Score, although

all treatment groups had reductions in the mean change from baseline for ICIQ-LUTSqol Overall Symptom Interference of Life Score at all time points.

Safety

Treatment with 6 mg solifenacin succinate and 9 mg solifenacin succinate administered concomitantly with 0.4 mg TOCAS was generally well tolerated.

No deaths occurred during the study. Overall, there was a greater number of TEAEs in the 6 mg solifenacin succinate with TOCAS and in the 9 mg solifenacin succinate with TOCAS treatment groups versus placebo. The most frequently occurring TEAE was dry mouth. Constipation occurred more frequently in the 6 mg solifenacin succinate with TOCAS group and in the 9 mg solifenacin succinate with TOCAS group than in the placebo group. All SAEs that occurred during the study were mild or moderate in severity; 4 of the 7 SAEs were considered possibly or probably related to study drug. All but one patient recovered from the SAEs; the SAE in this patient was considered to be not related to study drug.

For laboratory evaluations, there were no clinically significant differences observed among treatment groups in hematology parameters. The majority of patients had chemistry values that were within normal limits at baseline and throughout the study; however, a small percentage of patients had values that were below or above normal limits. Chemistry values that were elevated in at least 10% of patients at post-baseline among treatment groups were blood urea nitrogen, gamma-GT, glucose and serum creatinine.

No clinically significant differences were observed in vital signs at Weeks 2 through Week 12 compared with baseline and in ECG results at screening, Week 12 and end of treatment in all treatment groups.

Date of Report: 31 Aug 2009

Synopsis Table 1: Identity of Study Drug

Study Drug	Product Dosage/ Strength	Study Dose	Mode of Administration	Manufacturer	Drug Production Lot #
Tamsulosin Hydrochloride (OCAS)	0.4 mg tablet	0.4 mg of tamsulosin hydrochloride corresponded to 0.367 mg free base	Oral	[redacted], Japan	[redacted]
Solifenacin succinate	6 mg or 9 mg tablet	6 mg or 9 mg of solifenacin succinate corresponded to 4.53 mg or 6.79 mg of solifenacin free base	Oral	[redacted] US	[redacted] (6 mg) [redacted] (9mg)
Placebo Tamsulosin Hydrochloride OCAS Tablets	NA	NA	Oral	[redacted], Japan	[redacted]
Placebo Solifenacin Succinate Tablets	NA	NA	Oral	[redacted] US	[redacted]

NA: not applicable.

Synopsis Table 2: Demographic Characteristics

Parameter	Placebo n = 74	6 mg solifenacin succinate with 0.4 mg TOCAS n = 74	9 mg solifenacin succinate with 0.4 mg TOCAS n = 74	Total N = 222
Sex, n (%)				
Male (%)	74 (100)	74 (100)	74 (100)	222 (100)
Race, n (%)				
White	71 (95.9)	74 (100)	69 (93.2)	214 (96.4)
Black or African-American	2 (2.7)	0	2 (2.7)	4 (1.8)
Asian	1 (1.4)	0	1 (1.4)	2 (0.9)
Other	0	0	2 (2.7)	2 (0.9)
Ethnicity, n (%)				
Non-Hispanic or Latino	72 (97.3)	71 (95.9)	69 (93.2)	212 (95.5)
Hispanic or Latino	2 (2.7)	3 (4.1)	5 (6.8)	10 (4.5)
Age Group (yrs), n (%)				
45-54	9 (12.2)	8 (10.8)	5 (6.8)	22 (9.9)
55-64	29 (39.2)	33 (44.6)	28 (37.8)	90 (40.5)
65-74	29 (39.2)	22 (29.7)	29 (39.2)	80 (36.0)
75 and above	7 (9.5)	11 (14.9)	12 (16.2)	30 (13.5)
Age (yrs)				
Mean ± SD	64.3 ± 7.60	63.8 ± 8.43	65.6 ± 8.26	64.6 ± 8.11
Median	64.0	63.0	65.0	64.0
Range	49, 81	48,81	50, 85	48, 85
Weight (kg)				
Mean ± SD	87.3 ± 14.67	92.1 ± 17.15	90.5 ± 13.81	90.0 ± 15.34
Median	86.5	91.0	90.7	89.5
Range	57, 130	57, 140	65, 127	57, 140
Height (cm)				
Mean ± SD	175.7 ± 6.94	176.2 ± 6.42	174.7 ± 6.10	175.5 ± 6.50
Median	175.3	176.0	174.5	175.3
Range	160, 194	158, 190	160, 190	158, 194
BMI (kg/m^2)				
Mean ± SD	28.3 ± 4.46	29.7 ± 5.22	29.7 ± 4.33	29.2 ± 4.71
Median	27.7	29.3	29.5	28.4
Range	20, 38	19, 45	22, 39	19, 45

Population base: the Safety Analysis Set (SAF) population consisted of patients who received at least 1 dose of double-blind treatment.
BMI: body mass index; SD: standard deviation; TOCAS: Tamsulosin hydrochloride Oral Control Absorption System.
Source: Table 12.1.3.1.

Synopsis Table 3: Treatment-Emergent Adverse Events Occurring in at Least 5% of Patients

MedDRA (v.9.1) System Organ Class† Preferred Term	Placebo n = 74 n (%)	6 mg solifenacin succinate with 0.4 mg TOCAS n = 74 n (%)	9 mg solifenacin succinate with 0.4 mg TOCAS n = 74 n (%)
All Systems, Any AE	29 (39.2)	38 (51.4)	37 (50.0)
Eye Disorders			
Vision blurred	1 (1.4)	1 (1.4)	4 (5.4)
Gastrointestinal Disorders			
Constipation	1 (1.4)	4 (5.4)	6 (8.1)
Dry mouth	3 (4.1)	9 (12.2)	14 (18.9)
General Disorders and Administration Site Conditions			
Fatigue	2 (2.7)	4 (5.4)	0
Nervous System Disorders			
Dizziness	3 (4.1)	1 (1.4)	4 (5.4)
Headache	6 (8.1)	3 (4.1)	2 (2.7)

Population base: the Safety Analysis Set (SAF) population consisted of patients who received at least 1 dose of double-blind treatment.
AE: adverse event; TOCAS: Tamsulosin hydrochloride Oral Control Absorption System.
† Patients may have reported more than 1 type of AE within a system organ class.
Notes: Treatment-emergent adverse events were AEs that occurred from the first dose to within 14 days after the last dose of double-blind study medication.
Source: Table 12.6.1.1, Appendix 13.2.7.1.

Synopsis Table 4: Drug-Related Adverse Events Occurring in at Least 5% of Patients

MedDRA (v.9.1) System Organ Class† Preferred Term	Placebo n = 74 n (%)	6 mg solifenacin succinate with 0.4 mg TOCAS n = 74 n (%)	9 mg solifenacin succinate with 0.4 mg TOCAS n = 74 n (%)
All Systems, Any AE	15 (20.3)	24 (32.4)	26 (35.1)
Gastrointestinal Disorders			
Constipation	1 (1.4)	4 (5.4)	6 (8.1)
Dry mouth	3 (4.1)	9 (12.2)	14 (18.9)
Nervous System Disorders			
Headache	5 (6.8)	3 (4.1)	1 (1.4)

Population base: the Safety Analysis Set (SAF) population consisted of patients who received at least 1 dose of double-blind treatment.
AE: adverse event; TOCAS: Tamsulosin hydrochloride Oral Control Absorption System.
† Patients may have reported more than 1 type of AE within a system organ class.
Notes: Treatment-emergent adverse events were defined as AEs that occurred from the first dose to within 14 days after last dose of double-blind study medication. Drug-related was defined as possibly or probably related.
Source: Table 12.6.1.2.