Platinum Priority – Voiding Dysfunction

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Solifenacin Plus Tamsulosin Combination Treatment in Men With Lower Urinary Tract Symptoms and Bladder Outlet Obstruction: A Randomized Controlled Trial

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Tamsulosin

Abstract

Background: Alpha blockers are prescribed to manage lower urinary tract symptoms (LUTS) associated with benign prostatic hyperplasia (BPH). Antimuscarinics are prescribed to treat overactive bladder (OAB).

Objective: To investigate the safety of a combination of solifenacin (SOLI) and tamsulosin oral controlled absorption system (TOCAS) in men with LUTS and bladder outlet obstruction (BOO).

Design, setting, and participants: Randomized, double-blind, parallel-group, placebo-controlled study in men aged >45 yr with LUTS and BOO for ≥3 mo, total International Prostate Symptom Score (IPSS) ≥8, BOO index ≥20, maximum urinary flow rate (Qmax) ≤12 ml/s, and voided volume ≥120 ml.

Interventions: Once-daily coadministration of TOCAS 0.4 mg plus SOLI 6 mg, TOCAS 0.4 mg plus SOLI 9 mg, or placebo for 12 wk.

Outcome measurements and statistical analysis: Primary safety measurements: Qmax and detrusor pressure at Qmax (PdetQmax). Other safety assessments included postvoid residual (PVR) volume. Secondary end points included bladder contractile index (BCI) score and percent bladder voiding efficiency (BVE). An analysis of covariance model compared each TOCAS plus SOLI combination with placebo.

Results and limitations: Both active treatment groups were noninferior to placebo at end of treatment (EOT) for PdetQmax and Qmax. Mean change from baseline PVR was significantly higher at all time points for TOCAS 0.4 mg plus SOLI 6 mg, and at weeks 2, 12, and EOT for TOCAS 0.4 mg plus SOLI 9 mg versus placebo. Both treatment groups were similar to placebo for BCI and BVE. Urinary retention was seen in only one patient receiving TOCAS 0.4 mg plus SOLI 6 mg. Limitations of the study were that prostate size and prostate-specific antigen level were not measured.

Conclusions: TOCAS 0.4 mg plus SOLI 6 mg or 9 mg was noninferior to placebo at EOT for PdetQmax and Qmax in men with LUTS and BOO, and there was no clinical or statistical evidence of increased risk of urinary retention.

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1. **Introduction**

Lower urinary tract symptoms (LUTS) are prevalent in men aged >45 yr [1–3] and have a significant effect on health-related quality of life (HRQL) [3,4]. Alpha₁-blockers (α-blockers) are widely prescribed to manage LUTS associated with benign prostatic hyperplasia (BPH). However, bothersome storage symptoms, which may be related to coexisting detrusor overactivity or be secondary to bladder outlet obstruction (BOO), may persist in some men [5,6].

Tamsulosin is an α-blocker approved worldwide, at daily doses of 0.4 and 0.8 mg, for treatment of LUTS/BPH. Tamsulosin oral controlled absorption system (TOCAS) tablets are approved in Europe and elsewhere. Solifenacin (SOLI) is an antimuscarinic that is approved worldwide, at daily doses of 5 mg and 10 mg, for treatment of overactive bladder (OAB), and which effectively reduces detrusor overactivity and bothersome storage symptoms in LUTS. Although there have been historical concerns that men with BOO might experience urinary retention (UR), recent articles report effective use of antimuscarinics plus α-blockers for male LUTS, with no clinically significant effect on postvoid residual (PVR) volume or increased risk for acute urinary retention (AUR) [7–15]. Available data suggest that treatment with antimuscarinics plus α-blockers may be more effective in reducing LUTS associated with BPH than α-blockers alone.

The objective of this study was to investigate the safety of a combination of SOLI and TOCAS in men with LUTS and BOO.

2. **Patients and methods**

2.1. **Patients and study design**

This was a randomized, double-blind, parallel-group, placebo-controlled, multicenter study (ClinicalTrials.gov identifier: NCT00507455) in men aged >45 yr with LUTS and BOO for >3 mo, total International Prostate Symptom Score (IPSS) >8, maximum urinary flow rate (Qmax) <12 ml/s, BOO index >20, BOO index – detrusor pressure [Pdet] at Qmax [PdetQmax] – 2 Qmax, and voided volume 120 ml during free flow at baseline. All patients underwent screening for 1–3 wk (including a 2-wk washout, if required). At baseline, eligible patients were randomized to once-daily coadministration of TOCAS 0.4 mg plus SOLI 6 mg, TOCAS 0.4 mg plus SOLI 9 mg, or matching placebo for 12 wk. Among the patient exclusions were: history of UR in the preceding 12 mo, history or diagnosis of neurogenic bladder, chronic prostatitis or other causes of outflow tract obstruction, and/or pharmacologic treatment for BPH with α-adrenergic receptor antagonists and plant extracts or 5α-reductase inhibitors (Table 1).

Adverse events (AEs) were reported by the investigator. All procedures complied with the International Conference of Harmonization Guidelines for Good Clinical Practice and the Declaration of Helsinki and were approved by the institutional review board. All patients provided written informed consent.

2.2. **Assessments**

The primary objective was to evaluate the noninferiority of TOCAS 0.4 mg plus SOLI 6 mg or TOCAS 0.4 mg plus SOLI 9 mg versus placebo, on urodynamic variables as safety measures. Secondary objectives were to evaluate safety and tolerability of the combination treatment and to compare efficacy versus placebo. To address the concern that antimuscarinics might aggravate voiding difficulties or precipitate UR, PdetQmax, PVR volume, and UR incidence were evaluated. AUR was defined as those cases requiring emergency catheterization.

2.2.1. **Primary end points**

Changes from baseline to end of treatment (EOT) in PdetQmax and Qmax were assessed as primary urodynamic variables and based on readings taken during cystometry. Pdet was the force required to expel urine from the bladder during normal voiding. PdetQmax was assessed using simultaneous recording of voiding by a uroflowmeter during Pdet evaluation at screening and week 12. Qmax was collected during cystometry and free-flow uroflowmetry; however, the value obtained during the pressure-flow study was used for primary analysis to correlate Qmax and PdetQmax values. A Qmax reduction might indicate BOO or failure of the detrusor muscle to help expel urine.

2.2.2. **Secondary end points**

Although the study was powered for primary urodynamic variables, secondary urodynamic and efficacy variables were included to support the primary variables. Urodynamic end points included a bladder contractile index (BCI) and percent bladder voiding efficiency (BVE). The formula for determining BCI is PdetQmax plus 2Qmax. A BCI of 100–150 indicates normal and <100 indicates weak bladder contractility [10]. Percent BVE is a product of bladder contractility against urethral resistance and is measured according to the degree of bladder emptying. BCI and BVE were measured at screening and week 12.

Safety assessments included PVR measured at screening, baseline, and weeks 2, 4, 8, and 12.

Secondary efficacy assessments included IPSS; Patient Perception of Bladder Condition (PPBC) score; International Consultation on Incontinence Questionnaire–Male Lower Urinary Tract Symptoms (ICIQ-MaleLUTS) score; ICIQ-Lower Urinary Tract Symptoms Quality of Life (ICIQ-LUTSqol) score; volume voided per micturition; number of micturitions; urgency episodes; and incontinence episodes per 24 h. IPSS and PPBC were measured at screening, baseline, and weeks 2, 4, 8, and 12; ICIQ-MaleLUTS and ICIQ-LUTSqol were measured at baseline and weeks 4, 8, and 12. Patients completed a 3-d micturition diary before each visit.

2.3. **Statistical analysis**

Analysis of urodynamic measurements and efficacy variables was conducted using the full analysis set (FAS), that is, those patients receiving one or more doses of double-blind treatment with urodynamic measurements at baseline and postbaseline. Analysis of safety variables was conducted using the safety analysis set (ie, patients receiving one or more doses of treatment).

For the primary variables, an analysis of covariance (ANCOVA) model with site and treatment as factors and baseline value as covariate compared each combination of TOCAS plus SOLI with placebo. The noninferiority margins were 15 cm H₂O for PdetQmax and –3 ml/s for Qmax [16]. If the upper limit of the two-sided 95% confidence interval (CI) for the difference from placebo was <15 cm H₂O for PdetQmax and the lower limit of the two-sided 95% CI exceeded –3 ml/s for Qmax, the combination of TOCAS plus SOLI was noninferior to placebo. Each primary variable was tested at a one-sided significance level of 2.5%. Change from baseline to EOT in PVR and in urodynamic measurements including BCI and BVE were analyzed using a similar ANCOVA model. The last observation carried forward method was used for EOT results.

3. **Results**

A total of 222 patients were equally randomized to each group (safety set analysis) (Fig. 1). Of these, 192 (86.5%)...
Table 1 – Study inclusion and exclusion criteria at screening and baseline

<table>
<thead>
<tr>
<th>Inclusion criteria</th>
<th>Visit 1 Screening</th>
<th>Visit 2 Baseline</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>●</td>
<td>●</td>
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<tr>
<td>Age ≥45 yr</td>
<td>●</td>
<td>●</td>
</tr>
<tr>
<td>Willing and able to complete 3-d micturition</td>
<td>●</td>
<td>●</td>
</tr>
<tr>
<td>diary and questionnaires correctly</td>
<td>●</td>
<td>●</td>
</tr>
<tr>
<td>Voiding and storage LUTS ≥3 mo duration</td>
<td>●</td>
<td>●</td>
</tr>
<tr>
<td>IPSS score ≥8</td>
<td>●</td>
<td>●</td>
</tr>
<tr>
<td>BOOQ score ≥20</td>
<td>●</td>
<td>●</td>
</tr>
<tr>
<td>Maximum urinary flow rate ≤12 ml/s</td>
<td>●</td>
<td>●</td>
</tr>
<tr>
<td>Maximum voided volume ≥120 ml</td>
<td>●</td>
<td>●</td>
</tr>
<tr>
<td>IRB/IEC-approved written informed consent</td>
<td>●</td>
<td>●</td>
</tr>
<tr>
<td>HIPAA authorization</td>
<td>●</td>
<td>●</td>
</tr>
<tr>
<td>Biochemistry test results, normal range*</td>
<td>●</td>
<td>●</td>
</tr>
<tr>
<td>Hematology test results, normal range*</td>
<td>●</td>
<td>●</td>
</tr>
</tbody>
</table>

Exclusion criteria

- Indwelling urinary catheter
- History of urinary retention ≥12 mo
- Diagnosis/history of:
  - Carcinoma or pelvic radiation therapy
  - Neurogenic bladder
  - Chronic inflammation
  - Stone in bladder/ureter
  - Outflow tract obstruction, other ½
  - Uncontrolled narrow-angle glaucoma
  - Myasthenia gravis
  - Urinary/gastric retention
  - Diabetic neuropathy
  - Cardiovascular/cerebrovascular disease ½
  - Abnormal ECG ½
  - Other medical condition contraindicated for use of anticholinergics
  - Other medical condition unsuitable for trial ½
- Current UTI
- Recurrent UTI, >3 episodes within 12 mo
- Previous/planned prostate surgery:
  - TURP
  - TUMT
  - TUNA
  - Laser
- Previous bladder neck surgery
- Cataract surgery within 30 d of study end
- Other (minimally) invasive surgery within 12 mo
- Use of concomitant medication:
  - BPH drugs within 2 wk prior to visit ½
  - 5α-reductase inhibitors within 3 mo prior to visit ½
  - Study drug interacting, end prior to visit ½
  - Other medications ½
- Hypersensitivity to:
  - Solifenacin succinate or other anticholinergic
  - Tamsulosin hydrochloride or other α-AR-antagonist
  - Lactose or other inactive ingredient
- Nonpharmacologic therapy ½
- Participation in clinical trial within 30 d prior to visit ½
- Renal/hepatic impairment

LUTS = lower urinary tract symptoms; IPSS = International Prostate Symptom Score; BOO = bladder outlet obstruction index; IRB = institutional review board; IEC = independent ethics committee; HIPAA = Health Insurance Portability and Accountability Act; ECG = electrocardiogram; UTI = urinary tract infection; TURP = transurethral resection of the prostate; TUMT = transurethral microwave treatment; TUNA = transurethral needle ablation; BPH = benign prostatic hyperplasia; AR = adrenergic receptor. ½ Tests performed at visit 1. ½ Including chronic prostatitis. ½ Including bladder neck stenosis and urethral strictures. ½ Within 6 mo prior to visit 1; including myocardial infarction, uncontrolled angina, significant ventricular arrhythmias, sinus tachycardia, heart failure (NYHA class III-IV), orthostatic hypotension, and stroke.

* That would not allow the patient to qualify for the study, in the opinion of the study investigator.
* Including α-adrenergic receptor antagonists and plant extracts.
* Those drugs that affect the pharmacodynamics of solifenacin succinate or tamsulosin hydrochloride, including: combined α/β-adrenergic receptor antagonists, α-agonists, cholinergics or anticholinergics, and CYP3A4 inhibitors or inducers.
* Includes long-term therapy (>1 mo prior to randomization) with cholinergic or anticholinergic side effects, loop diuretics, calcium channel antagonists, phosphodiesterase-5 inhibitors, and beta blockers.
* For example, electrostimulation therapy or start of a bladder training program during the 2 wk prior to or during the study.

completed the study (TOCAS 0.4 mg plus SOLI 6 mg, n = 68; TOCAS 0.4 mg plus SOLI 9 mg, n = 62; placebo, n = 62). The FAS included 188 patients from 36 sites in Europe and the United States. Overall, all treatment groups in the safety analysis set had similar demographic and baseline characteristics (Table 2). For all treatment groups, at baseline, IPSS total score range was 17.5–18.2, number of micturitions per 24 h ranged from 10.5 to 10.7, and the volume voided per micturition range was 165–175 ml (Table 3).

3.1. Primary variables

Figures 2 and 3 depict primary data showing within-treatment group changes. Mean change in PdetQmax within the TOCAS 0.4 mg plus SOLI 6 mg group was significantly lower at week 12 and EOT versus baseline (p < 0.005) (Fig. 2). For Qmax, mean change within both active treatment groups was significantly higher at week 12 and EOT versus baseline (p < 0.0005) (Fig. 3).

Table 4 presents primary data comparing treatment groups. Both active treatment groups were noninferior to placebo at week 12 and EOT for PdetQmax and Qmax, given the respective noninferiority margins. Furthermore, both TOCAS plus SOLI groups showed statistically significant improvement from baseline in Qmax Versus placebo.

3.2. Safety assessments

Within treatment groups, mean change from baseline in PVR was significantly higher at all time points versus baseline for the TOCAS 0.4 mg plus SOLI 6 mg group, and at weeks 2, 12, and EOT for the TOCAS 0.4 mg plus SOLI 9 mg group (Fig. 4). At EOT, adjusted mean change was 24 ml for TOCAS 0.4 mg plus SOLI 6 mg, 20 ml for TOCAS 0.4 mg plus SOLI 9 mg (Table 5).

There were no notable differences in laboratory tests, electrocardiograms, and vital signs. Treatment-emergent AEs (TEAEs) were mild or moderate in intensity; those considered drug related occurred in 32.4%, 35.1%, and 20.3% of patients in the TOCAS 0.4 mg plus SOLI 6 mg, TOCAS 0.4 mg plus SOLI 9 mg, and placebo groups, respectively (Table 6). The most frequently occurring TEAE was dry
mouth. UR (two episodes) was seen in only one patient receiving TOCAS 0.4 mg plus SOLI 6 mg (0.5% of patients on active treatment); one episode was considered serious, requiring catheterization.

3.3. Secondary efficacy variables

When treatment groups were compared, significant improvements versus placebo were seen in number of micturitions per 24 h at week 2 and EOT; in voided volume per micturition at weeks 4, 8, 12, and EOT for both treatment groups; and in voided volume per micturition at week 2 for TOCAS 0.4 mg plus SOLI 6 mg (Fig. 5). Improvements were not statistically significant for adjusted mean change from baseline for IPSS total score, PPBC score, most ICIQ-MaleLUTS symptom scores, and number of urgency episodes and incontinence episodes per 24 h for either treatment group versus placebo (Table 5).

![Study flow diagram. BOOI = bladder outlet obstruction index; IPSS = International Prostate Symptom Score; TOCAS = tamsulosin oral controlled absorption system; SOLI = solifenacin; AE = adverse events.](https://example.com/study-flow-diagram.png)

Table 2 – Demographics and baseline characteristics: safety analysis population

<table>
<thead>
<tr>
<th></th>
<th>Placebo (n = 74)</th>
<th>TOCAS 0.4 mg + SOLI 6 mg (n = 74)</th>
<th>TOCAS 0.4 mg + SOLI 9 mg (n = 74)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Race, no. (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>71 (95.9)</td>
<td>74 (100)</td>
<td>69 (93.2)</td>
</tr>
<tr>
<td>Black/African American</td>
<td>2 (2.7)</td>
<td>0</td>
<td>2 (2.7)</td>
</tr>
<tr>
<td>Asian</td>
<td>1 (1.4)</td>
<td>0</td>
<td>1 (1.4)</td>
</tr>
<tr>
<td>Other</td>
<td>0</td>
<td>0</td>
<td>2 (2.7)</td>
</tr>
<tr>
<td>Age, mean ± SD, yr</td>
<td>64.3 ± 7.6</td>
<td>63.8 ± 8.4</td>
<td>65.6 ± 8.3</td>
</tr>
<tr>
<td>Age group, no. (%), yr</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>45–54</td>
<td>9 (12.2)</td>
<td>8 (10.8)</td>
<td>5 (6.8)</td>
</tr>
<tr>
<td>55–64</td>
<td>29 (39.2)</td>
<td>33 (44.6)</td>
<td>28 (37.8)</td>
</tr>
<tr>
<td>65–74</td>
<td>29 (39.2)</td>
<td>22 (29.7)</td>
<td>29 (39.2)</td>
</tr>
<tr>
<td>&gt;75</td>
<td>7 (9.5)</td>
<td>11 (14.9)</td>
<td>12 (16.2)</td>
</tr>
<tr>
<td>Weight, mean ± SD, kg</td>
<td>87.3 ± 14.7</td>
<td>92.1 ± 17.2</td>
<td>90.5 ± 13.8</td>
</tr>
<tr>
<td>BMI, mean ± SD, kg/m²</td>
<td>28.3 ± 4.5</td>
<td>29.7 ± 5.2</td>
<td>29.7 ± 4.3</td>
</tr>
</tbody>
</table>

TOCAS = tamsulosin oral controlled absorption system; SOLI = solifenacin; SD = standard deviation; BMI = body mass index.

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Table 3 – Primary, secondary, and safety variables at baseline

<table>
<thead>
<tr>
<th></th>
<th>Placebo  (n = 62)</th>
<th>TOCAS 0.4 mg + SOLI 6 mg  (n = 67)</th>
<th>TOCAS 0.4 mg + SOLI 9 mg  (n = 59)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary variables, mean ± SD</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$P_{detr}Q_{\max}$, cm H$_2$O</td>
<td>74.4 ± 29.7</td>
<td>73.9 ± 28.1</td>
<td>70.1 ± 27.8</td>
</tr>
<tr>
<td>$Q_{\max}$, ml/s</td>
<td>7.1 ± 3.0</td>
<td>8.2 ± 3.1</td>
<td>7.5 ± 2.8</td>
</tr>
<tr>
<td><strong>Secondary variables, mean ± SD</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BCI</td>
<td>109.9 ± 32.8</td>
<td>114.7 ± 31.4</td>
<td>107.6 ± 29.0</td>
</tr>
<tr>
<td>BVE</td>
<td>76.5 ± 21.6</td>
<td>82.4 ± 21.0</td>
<td>74.9 ± 25.0</td>
</tr>
<tr>
<td><strong>Efficacy assessments, mean ± SD</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IPSS total score</td>
<td>18.2 ± 6.4</td>
<td>17.5 ± 5.8</td>
<td>17.7 ± 5.8</td>
</tr>
<tr>
<td>IPSS storage score</td>
<td>7.9 ± 2.8</td>
<td>7.8 ± 2.6</td>
<td>7.8 ± 2.8</td>
</tr>
<tr>
<td>IPSS voiding score</td>
<td>10.3 ± 4.5</td>
<td>9.7 ± 4.6</td>
<td>9.8 ± 4.2</td>
</tr>
<tr>
<td>PPBC score</td>
<td>3.9 ± 1.2</td>
<td>4.0 ± 1.0</td>
<td>3.9 ± 0.9</td>
</tr>
<tr>
<td>ICQ–Male LUTS total symptom score</td>
<td>18.8 ± 6.8</td>
<td>19.0 ± 5.8</td>
<td>17.2 ± 5.5</td>
</tr>
<tr>
<td>ICQ–LUTS-qol symptom score</td>
<td>37.3 ± 12.5</td>
<td>36.5 ± 10.6</td>
<td>36.5 ± 11.4</td>
</tr>
<tr>
<td>Micturitions per 24 h, no.</td>
<td>10.5 ± 2.9</td>
<td>10.7 ± 2.9</td>
<td>10.7 ± 3.3</td>
</tr>
<tr>
<td>Urgency episodes per 24 h, no.</td>
<td>2.6 ± 3.4</td>
<td>2.9 ± 3.3</td>
<td>2.9 ± 4.2</td>
</tr>
<tr>
<td>Incontinence episodes per 24 h</td>
<td>1.6 ± 1.8</td>
<td>1.5 ± 1.4</td>
<td>2.2 ± 1.7</td>
</tr>
<tr>
<td>Volume voided per micturition, ml</td>
<td>165.5 ± 55.2</td>
<td>174.7 ± 62.5</td>
<td>173.0 ± 55.0</td>
</tr>
<tr>
<td>Safety variables, mean ± SD</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PVR, ml</td>
<td>47.0 ± 26.5</td>
<td>34.6 ± 20.4</td>
<td>39.2 ± 30.0</td>
</tr>
</tbody>
</table>

TOCAS = tamsulosin oral controlled absorption system; SOLI = solifenacin; SD = standard deviation; $P_{detr}Q_{\max}$ = detrusor pressure at maximum flow rate; $Q_{\max}$ = maximum flow rate; BCI = bladder contractility index; BVE = bladder voiding efficiency; IPSS = International Prostate Symptom Score; PPBC = patient perception of bladder condition; ICQ–Male LUTS = International Consultation on Incontinence Questionnaire-Male Lower Urinary Tract Symptoms; ICQ–LUTS-qol = International Consultation on Incontinence Questionnaire-Lower Urinary Tract Symptoms Quality of Life; PVR = postvoid residual.

* $n = 60$ for placebo, $n = 66$ for TOCAS 0.4 mg plus SOLI 6 mg, $n = 57$ for TOCAS 0.4 mg plus SOLI 9 mg.

** $n = 40$ for placebo, $n = 44$ for TOCAS 0.4 mg plus SOLI 6 mg, $n = 39$ for TOCAS 0.4 mg plus SOLI 9 mg.

† Number of micturitions per 24 h, urgency episodes per 24 h, incontinence episodes per 24 h, and volume voided per micturition are averages of the 3-d micturition diary.

‡ Scale >3.

§ Includes only those patients who had 3-d averaged incontinence episodes >0 at baseline ($n = 13$ for placebo, $n = 10$ for TOCAS 0.4 mg plus SOLI 6 mg, $n = 13$ for TOCAS 0.4 mg plus SOLI 9 mg).

4. Discussion

The combination of TOCAS plus SOLI at all doses studied was noninferior to placebo at EOT for $P_{detr}Q_{\max}$ and $Q_{\max}$ in men with LUTS and BOO. Both treatment groups were similar to placebo for BCI and BCE, indicating that this combination has no negative effect on bladder function during voiding in an obstructed population.

This is the first placebo-controlled study using an antimuscarinic plus an $\alpha$-blocker in men with BOO that demonstrated numerical improvements in $Q_{\max}$ versus placebo without statistical evidence of increased risk of AUR. In contrast, a 2006 meta-analysis of data from five randomized trials and 15 observational studies in men with LUTS suggestive of BPH found that antimuscarinics did not significantly alter $Q_{\max}$ [7], and a 2011 review of antimuscarinics for treatment of storage LUTS found no clinically significant $Q_{\max}$ Changes [11].

SOLI doses of 6 mg and 9 mg were selected based on doses in a dose-ranging study in patients with LUTS associated with BPH [17]. The TOCAS plus SOLI combination was well tolerated, which is in line with the individual variables.
Table 4 – Detrusor pressure at maximum flow rate (PdetQmax) and maximum flow rate (Qmax): adjusted mean change between treatment groups from baseline to week 12 and end of treatment in the full analysis set

<table>
<thead>
<tr>
<th></th>
<th>Placebo  (n = 62)</th>
<th>TOCAS 0.4 mg + SOLI 6 mg  (n = 67)</th>
<th>95% CI†</th>
<th>TOCAS 0.4 mg + SOLI 9 mg  (n = 59)</th>
<th>95% CI†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Change in PdetQmax, cmH2O, adjusted mean (SE)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Week 12</td>
<td>–1.2 (3.0)</td>
<td>–7.3 (2.8)</td>
<td>–6.1 (–14.2, 2.0)</td>
<td>–3.1 (3.1)</td>
<td>–1.9 (–10.4, 6.7)</td>
</tr>
<tr>
<td>EOT</td>
<td>–1.7 (3.2)</td>
<td>–7.8 (3.0)</td>
<td>–6.2 (–14.7, 2.4)</td>
<td>–6.7 (3.2)</td>
<td>–5.0 (–13.9, 3.8)</td>
</tr>
</tbody>
</table>
| Change in Qmax, ml/s, adjusted mean (SE)
| Week 12            | 0.1 (0.4)         | 1.7 (0.4)                         | 1.6 (0.4, 2.7)    | 2.2 (0.4)                         | 2.1 (0.9, 3.3)    |
| EOT                | 0.2 (0.4)         | 1.9 (0.4)                         | 1.7 (0.5, 2.9)    | 2.4 (0.4)                         | 2.2 (1.0, 3.47)   |

TOCAS = tamsulosin oral controlled absorption system; SOLI = solifenacin; CI = confidence interval; PdetQmax = detrusor pressure at maximum flow rate; SE = standard error; EOT = end of treatment; Qmax = maximum flow rate.

† For difference in change versus placebo, noninferiority is demonstrated by PdetQmax (upper limit <15) and Qmax (lower limit >–3), respectively.

Table 5 – Secondary and safety variables: adjusted mean change between treatment groups from baseline to end of treatment

<table>
<thead>
<tr>
<th></th>
<th>Placebo  (n = 62)</th>
<th>TOCAS 0.4 mg + SOLI 6 mg  (n = 67)</th>
<th>95% CI†</th>
<th>TOCAS 0.4 mg + SOLI 9 mg  (n = 59)</th>
<th>95% CI†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Change in secondary variables, adjusted mean (SE)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BCI</td>
<td>–1.6 (3.7)</td>
<td>1.8 (3.5)</td>
<td>3.5 (–6.6, 13.5)</td>
<td>3.9 (3.8)</td>
<td>5.5 (–4.9, 15.9)</td>
</tr>
<tr>
<td>BVE</td>
<td>–0.6 (2.8)</td>
<td>–1.4 (2.6)</td>
<td>–0.7 (–8.3, 6.8)</td>
<td>–3.8 (2.8)</td>
<td>–3.1 (–10.9, 4.6)</td>
</tr>
<tr>
<td>Change in efficacy assessments, adjusted mean (SE) *</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IPSS total score</td>
<td>–6.6 (0.7)</td>
<td>–8.0 (0.6)</td>
<td>–1.4 (–3.2, 0.4)</td>
<td>–6.9 (0.7)</td>
<td>–0.4 (–2.2, 1.5)</td>
</tr>
<tr>
<td>IPSS storage score</td>
<td>–2.7 (0.3)</td>
<td>–3.4 (0.3)</td>
<td>–0.7 (–1.5, 0.1)</td>
<td>–3.0 (0.3)</td>
<td>–0.3 (–1.1, 0.6)</td>
</tr>
<tr>
<td>IPSS voiding score</td>
<td>–3.9 (0.4)</td>
<td>–4.6 (0.4)</td>
<td>–0.7 (–1.9, 0.5)</td>
<td>–3.9 (0.5)</td>
<td>–0.0 (–1.3, 1.2)</td>
</tr>
<tr>
<td>PPBC score</td>
<td>–1.1 (0.1)</td>
<td>–0.9 (0.1)</td>
<td>0.1 (–0.2, 0.5)</td>
<td>–1.1 (0.1)</td>
<td>–0.0 (–0.4, 0.3)</td>
</tr>
</tbody>
</table>
| ICIQ-MaleLUTS total symptom score † | –5.2 (0.7) | –6.0 (0.7) | –0.8 (–2.7, 1.0) | –5.8 (0.7) | –0.7 (–2.6, 1.3)
| ICIQ-LUTSqol symptom score ‡ | –4.7 (1.1) | –5.3 (1.0) | –0.6 (–3.6, 2.3) | –7.3 (1.0) | –2.6 (–5.5, 0.3)
| No. of micatinations per 24 h ‡ | –1.0 (0.3) | –1.9 (0.3) | –1.0 (–1.9, –0.1) | –1.9 (0.3) | –0.9 (–1.9, –0.0)
| No. of incontinence episodes per 24 h ‡ | –1.4 (0.3) | –1.5 (0.2) | –0.0 (–0.7, 0.6) | –1.2 (0.3) | 0.2 (–0.5, 0.9)
| Volume voided per micatination, ml ‡ | 7.6 (5.7) | 36.3 (5.3) | 28.7 (13.3, 44.1) | 30.3 (5.7) | 22.8 (6.9, 38.6)
| Change in safety variables, adjusted mean (SE) |
| PVR, ml †† | –0.5 (6.3) | 23.6 (6.1) | 24.2 (6.9, 41.4) | 20.1 (6.2) | 20.6 (3, 37.8)

TOCAS = tamsulosin oral controlled absorption system; SOLI = solifenacin; CI = confidence interval; SE = standard error; BCI = bladder contractile index; BVE = bladder voiding efficiency; IPSS = International Prostate Symptom Score; PPBC = Patient Perception of Bladder Condition; ICIQ-MaleLUTS = International Consultation on Incontinence Questionnaire-Male Lower Urinary Tract Symptoms; ICIQ-LUTSqol = International Consultation on Incontinence Questionnaire-Lower Urinary Tract Symptoms Quality of Life; PVR = postvoid residual.

† 95% CI for the treatment difference versus placebo.

†† n = 60 for placebo, n = 67 for TOCAS 0.4 mg plus SOLI 6 mg, n = 58 for TOCAS 0.4 mg plus SOLI 9 mg.

‡ n = 60 for placebo, n = 66 for TOCAS 0.4 mg plus SOLI 6 mg, n = 57 for TOCAS 0.4 mg plus SOLI 9 mg.

§ n = 39 for placebo, n = 39 for TOCAS 0.4 mg plus SOLI 6 mg, n = 38 for TOCAS 0.4 mg plus SOLI 9 mg.

‖ n = 60 for placebo.

†† n = 13 for placebo, n = 10 for TOCAS 0.4 mg plus SOLI 6 mg, n = 11 for TOCAS 0.4 mg plus SOLI 9 mg.

§§ n = 73 for placebo, n = 74 for TOCAS 0.4 mg plus SOLI 6 mg, n = 72 for TOCAS 0.4 mg plus SOLI 9 mg.

* Scale ≥3.

Table 6 – Drug-related treatment-emergent adverse events occurring in >5% of patients in the safety analysis set

<table>
<thead>
<tr>
<th></th>
<th>Placebo  (n = 74)</th>
<th>TOCAS 0.4 mg + SOLI 6 mg  (n = 74)</th>
<th>TOCAS 0.4 mg + SOLI 9 mg  (n = 74)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with TEAEs, no. (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patients with drug-related AEs, no. (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Constipation</td>
<td>1 (1.4)</td>
<td>4 (5.4)</td>
<td>6 (8.1)</td>
</tr>
<tr>
<td>Dry mouth</td>
<td>3 (4.1)</td>
<td>9 (12.2)</td>
<td>14 (18.9)</td>
</tr>
<tr>
<td>Headache</td>
<td>5 (6.8)</td>
<td>3 (4.1)</td>
<td>1 (1.4)</td>
</tr>
<tr>
<td>Patients discontinuing study medication due to AEs, no. (%)</td>
<td>3 (4.1)</td>
<td>3 (4.1)</td>
<td>6 (8.1)</td>
</tr>
</tbody>
</table>

TOCAS = tamsulosin oral controlled absorption system; SOLI = solifenacin; TEAE = treatment-emergent adverse event; AE = adverse event.

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improvements at EOT versus placebo in mean voided volume and number of micturitions per 24 h, although the clinical significance remains to be determined. The SATURN (Solifenacin And Tamsulosin in males with lower URiNary tract symptoms associated with benign prostatic hyperplasia) study also found that TOCAS 0.4 mg plus SOLI 6 mg or 9 mg resulted in clinically and statistically significant improvement in storage symptoms versus TOCAS alone in a subset of men with LUTS/BPH who had clinically relevant levels of storage symptoms at baseline [21].

### 4.1. Study limitations
High prostate-specific antigen (PSA) levels or a larger prostate ($\geq$40 g) are associated with worsening LUTS and increased risk of AUR [22]. Although a digital rectal exam was performed and IPSS scores were measured, we cannot assess whether treatment response was influenced by prostate size, weight, or PSA level, as these were not measured. Other limitations were the short study duration, that results may have been influenced by factors such as not having a specific inclusion criteria for BOO-OAB patients, and that ANCOVA adjusted baseline measures of the response in the model, but did not adjust for filling volume. Although there is no uniformly accepted best parameter to assess voiding difficulties, $P_{\text{det}}$ was selected because it has been commonly used in previous studies using pharmacologic therapies for male LUTS and OAB.

This 12-wk study showed promising data, with only 0.5% of patients on active treatment experiencing UR. Further research is recommended to evaluate the longer term (>12 wk) safety and efficacy of treatment with TOCAS plus SOLI in this male population.

### 5. Conclusions
TOCAS plus SOLI at all doses studied was noninferior to placebo at EOT for the primary urodynamic variables, $P_{\text{det}}$ and $Q_{\text{max}}$ in men with LUTS and BOO. There was no statistical evidence of an increased risk of AUR, suggesting no negative effect on bladder function during voiding in those obstructed patients. This is the first placebo-controlled study using an antimuscarinic plus $\alpha$-blocker in men with BOO that demonstrates safety of the combination treatment and an increase in $Q_{\text{max}}$ versus placebo.

**Author contributions:** Steven A. Kaplan had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

**Study concept and design:** Kaplan, He, Koltun, Cummings, Schneider, Fakhoury.

**Acquisition of data:** Cummings, Koltun, Schneider, Fakhoury.

**Analysis and interpretation of data:** Kaplan, He, Koltun, Cummings, Schneider, Fakhoury.

**Drafting of the manuscript:** Kaplan, He, Koltun, Cummings, Schneider, Fakhoury.

**Critical revision of the manuscript for important intellectual content:** Kaplan, He, Koltun, Cummings, Schneider, Fakhoury.

**Statistical analysis:** He.

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Supervision: None.
Other (specify): None.

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References