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SAFETY OF SOLIFENACIN COMBINED WITH TAMSULOSIN HYDROCHLORIDE ORAL CONTROLLED ABSORPTION SYSTEM IN MEN WITH LOWER URINARY TRACT SYMPTOMS AND BLADDER OUTLET OBSTRUCTION: A URODYNAMIC STUDY

Hypothesis / aims of study

Lower urinary tract symptoms (LUTS) are common in men >45 years of age. Storage symptoms in such men may be related to co-existing detrusor overactivity or may be secondary to bladder outflow obstruction (BOO). Given the possible safety concerns of an antimuscarinic in obstructed patients, this safety study investigated the effect of a combination of the antimuscarinic, solifenacin succinate (SOLI) and tamsulosin hydrochloride oral controlled absorption system (TOCAS) on bladder function in men with LUTS and BOO. The primary objective of this study was to evaluate the non-inferiority of TOCAS 0.4 mg + SOLI 6 mg or TOCAS 0.4 mg + SOLI 9 mg, vs placebo via urodynamic variables. Secondary objectives included tolerability and safety of TOCAS + SOLI, and efficacy of the combination treatment vs placebo.

Study design, materials and methods

This was a double-blind, parallel-group, placebo-controlled study in men >45 years with voiding and storage LUTS for ≥3 months, total International Prostate Symptom Score (IPSS) ≥8, BOO index ≥20, maximum urinary flow rate (Qmax) ≤12 mL/sec, and voided volume of ≥120 mL during free flow. At baseline, eligible patients were randomized to once-daily treatment with either TOCAS 0.4 mg + SOLI 6 mg, TOCAS 0.4 mg + SOLI 9 mg, or matching placebos for 12 weeks. Change from baseline to Week 12 was assessed for primary urodynamic variables detrusor pressure at maximum flow rate (PdetQmax) and Qmax. Secondary urodynamic variables included Bladder Contractile Index (BCI) and Percent Bladder Voiding Efficiency (BVE). Safety assessments included Post-Void Residual volumes (PVR). Efficacy assessments were IPSS, Patient Perception of Bladder Condition (PPBC) scores, 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). Patients also completed a 3-day micturition diary.

Results

A total of 222 patients were equally randomized (n=74) to each group, and 192 (86.5%) patients completed the study (TOCAS 0.4 mg + SOLI 6 mg, n=68; TOCAS 0.4 mg + SOLI 9 mg, n=62; placebo, n=62). The Full Analysis Set included 188 patients. Mean change from baseline in PdetQmax within the TOCAS 0.4 mg + SOLI 6 mg group was significantly lower at Week 12 and at end of treatment (EOT).

Table 1. PdetQmax and Qmax: within treatment group change from baseline to Week 12 and EOT in the Full Analysis Set

	TOCAS 0.4 mg + SOLI 6 mg (n=67)	***P*-value[a]**	**TOCAS 0.4 mg + SOLI 9 mg (n=59)**	***P*-value[a]**	**Placebo (n=62)**	***P*-value[a]**
PdetQmax, mean change from baseline						
Week 12	-7.62	0.0044	-2.13	0.5439	-1.34	0.6833
EOT	-7.92	0.0021	-5.31	0.2189	-2.32	0.4858
Qmax, mean change from baseline						
Week 12	1.44	0.0003	2.14	0.0004	0.29	0.4111
EOT	1.59	0.0001	2.27	0.0003	0.38	0.3043

[a] *Based on t-test for change from baseline within treatment; EOT=end of treatment.*

Data comparing treatment groups are shown in Table 2. Both active treatment groups were non-inferior to placebo at Week 12 and EOT for PdetQmax and Qmax. Furthermore, both TOCAS + SOLI groups showed statistically significant improvement from baseline in Qmax vs placebo.

Table 2. PdetQmax and Qmax: between treatment group change from baseline to Week 12 and EOT in the Full Analysis Set

	TOCAS 0.4 mg+SOLI 6 mg (n=67)	**95% CI[a]**	**TOCAS 0.4 mg+SOLI 9 mg (n=59)**	**95% CI[a]**	**Placebo (n=62)**
PdetQmax, adjusted mean change from baseline (SE)					
Week 12	-7.31 (2.80)	-6.09 (-14.20, 2.02)	-3.08 (3.10)	-1.87 (-10.42, 6.69)	-1.22 (2.98)
EOT	-7.84 (2.95)	-6.15 (-14.67, 2.37)	-6.69 (3.20)	-5.00 (-13.85, 3.84)	-1.69 (3.15)
Qmax, adjusted mean change from baseline (SE)					
Week 12	1.71 (0.39)	1.57 (0.43, 2.72)	2.22 (0.43)	2.09 (0.90, 3.27)	0.13 (0.42)
EOT	1.85 (0.41)	1.67 (0.50, 2.85)	2.35 (0.43)	2.18 (0.98, 3.37)	0.17 (0.43)

[a] *For difference in change vs placebo non-inferiority is demonstrated by PdetQmax (upper limit <15) and Qmax (lower limit >–3), respectively; EOT=end of treatment; SE=standard error.*

Mean change from baseline in PVR was significantly higher at all time points for the TOCAS 0.4 mg + SOLI 6 mg group, and at Weeks 2, 12, and EOT for the TOCAS 0.4 mg + SOLI 9 mg group; this was significantly lower for the placebo group at Weeks 2 and 8. When treatment groups were compared, adjusted mean change from baseline was significantly higher for PVR at all time points for both treatment groups vs placebo (adjusted mean change at EOT: 25.63 mL and 19.07 mL, respectively). There were no clinically significant differences in laboratory tests, ECG and vital signs. Treatment-emergent adverse events (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 + SOLI 6 mg, TOCAS 0.4 mg + SOLI 9 mg, and placebo groups, respectively. The most frequently occurring TEAE was dry mouth. Urinary retention (2 episodes) was seen in only 1 patient receiving TOCAS 0.4 mg + SOLI 6 mg; 1 episode was considered serious. No significant differences were seen in mean change from baseline at any time point for IPSS Total Score, PPBC score, most ICIQ-MaleLUTS Symptom Scores, and 3-day average number of urgency episodes and incontinence episodes/24 hours vs placebo for both TOCAS + SOLI groups. A significant improvement vs placebo was seen in the 3-day average voided volume/micturition at Weeks 4, 8, 12 and EOT in both treatment groups, and at Week 2 in the TOCAS 0.4 mg + SOLI 6 mg group.

Interpretation of results

Both TOCAS 0.4 mg + SOLI 6 mg and TOCAS 0.4 mg + SOLI 9 mg were non-inferior to placebo for the primary urodynamic variables, given the non-inferiority upper limit of <15 and lower limit of >–3 for PdetQmax and Qmax, respectively. We believe this is the first placebo-controlled study using an antimuscarinic in men that demonstrates improvements in Qmax vs placebo. Although the study was not powered for secondary endpoints, both treatment groups were similar to placebo for BCI and BCE, indicating that this combination does not have a negative effect on bladder function during voiding in an obstructed population. There was an increase in the adjusted mean change from baseline for PVR vs placebo for both treatment groups, which was not clinically significant. Both treatments were well tolerated. Adverse events were in line with the known safety profiles of SOL+TOCAS.

Concluding message

The combination of TOCAS + SOLI was non-inferior to placebo at Week 12 and EOT for PdetQmax and Qmax in men with LUTS and BOO, suggesting no negative effect on bladder function during voiding in these obstructed patients. In addition TOCAS + SOLI improved urinary flow rate compared with baseline, and showed no significant increase in PVRs. Improvements in secondary efficacy endpoints were also seen with SOL+TOCAS treatment; however, these were not significantly different to placebo. The combination of SOL+TOCAS was well tolerated, in line with the safety profiles of the individual components. There was no evidence of increased urinary retention.

Specify source of funding or grant	**This study was undertaken with a research grant from Astellas EU and Astellas Pharma US, Inc.**
Is this a clinical trial?	**Yes**
Is this study registered in a public clinical trials registry?	**Yes**
Specify Name of Public Registry, Registration Number	**Registry: Clinicaltrials.gov** **Registration number: NCT00507455**
Is this a Randomised Controlled Trial (RCT)?	**Yes**
What were the subjects in the study?	**HUMAN**
Was this study approved by an ethics committee?	**Yes**
Specify Name of Ethics Committee	**Mid Lands Institutional Review Board**
Was the Declaration of Helsinki followed?	**Yes**
Was informed consent obtained from the patients?	**Yes**