available at www.sciencedirect.com
journal homepage: www.europeanurology.com

European Association of Urology

Platinum Priority – Voiding Dysfunction

Editorial by Christian Gratzke and Karl-Erik Andersson on pp. 166–167 of this issue

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

Steven A. Kaplan [a,*], *Weizhong He* [b], *William D. Koltun* [c], *Jana Cummings* [b], *Tim Schneider* [d], *Allam Fakhoury* [b]

[a] *Weill Medical College of Cornell University, New York-Presbyterian Hospital/Weill Cornell Medical Center, New York, NY, USA;* [b] *Astellas Pharma Global Development, Northbrook, IL, USA;* [c] *Medical Center for Clinical Research, San Diego, CA, USA;* [d] *PUR/R Praxisklinik Urologie Rhein-Ruhr, Mülheim, Germany*

Article info

Article history:
Accepted July 6, 2012
Published online ahead of print on July 17, 2012

Keywords:
Bladder outlet obstruction
Lower urinary tract symptoms
Solifenacin
Tamsulosin

EU ✱ ACME
www.eu-acme.org/europeanurology

Please visit www.eu-acme.org/europeanurology to read and answer questions on-line. The EU-ACME credits will then be attributed automatically.

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 (Q_{max}) ≤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: Q_{max} and detrusor pressure at Q_{max} ($P_{det}Q_{max}$). 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 $P_{det}Q_{max}$ and Q_{max}. 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 $P_{det}Q_{max}$ and Q_{max} in men with LUTS and BOO, and there was no clinical or statistical evidence of increased risk of urinary retention.

* Corresponding author. Weill Medical College of Cornell University, New York-Presbyterian Hospital/Weill Cornell Medical Center, 425 East 61st St., New York, NY 10065-4805, USA.
Tel. +1 212 746 4811; Fax: +1 212 746 0780.
E-mail address: kaplans@med.cornell.edu (S.A. Kaplan).

0302-2838/$ – see back matter
http://dx.doi.org/10.1016/j.eururo.2012.07.003

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]. Alpha$_1$-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 (Q_{max}) ≤12 ml/s, BOO index ≥20 (BOO index = detrusor pressure [P_{det}] at Q_{max} [$P_{det}Q_{max}$] − 2 Q_{max}), 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 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, $P_{det}Q_{max}$, 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 $P_{det}Q_{max}$ and Q_{max} were assessed as primary urodynamic variables and based on readings taken during cystometry. P_{det} is the force required to expel urine from the bladder during normal voiding. $P_{det}Q_{max}$ was assessed using simultaneous recording of voiding by a uroflowmeter during P_{det} evaluation at screening and week 12. Q_{max} was collected during cystometry and free-flow uroflowmetry; however, the value obtained during the pressure-flow study was used for primary analysis to correlate Q_{max} and $P_{det}Q_{max}$ values. A Q_{max} 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 $P_{det}Q_{max}$ plus $5Q_{max}$. 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 H_2O for $P_{det}Q_{max}$ and −3 ml/s for Q_{max} [16]. If the upper limit of the two-sided 95% confidence interval (CI) for the difference from placebo was <15 cm H_2O for $P_{det}Q_{max}$ and the lower limit of the two-sided 95% CI exceeded −3 ml/s for Q_{max}, 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%)