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Efficacy and Safety of Solifenacin Plus Tamsulosin OCAS in Men with Voiding and Storage Lower Urinary Tract Symptoms: Results from a Phase 2, Dose-finding Study (SATURN)

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Abstract

Background: Storage symptoms are often undertreated in men with lower urinary tract symptoms (LUTS).
Objective: To evaluate the combination of an antimuscarinic (solifenacin) with an α-blocker (tamsulosin) versus tamsulosin alone in the treatment of men with LUTS.
Design, setting, and participants: A double-blind, 12-wk, phase 2 study in 937 men with LUTS (≥3 mo, total International Prostate Symptom Score [IPSS] ≥13, and maximum urinary flow rate 4.0–15.0 ml/s).
Intervention: Eight treatment groups: tamsulosin oral controlled absorption system (OCAS) 0.4 mg; solifenacin 3, 6, or 9 mg; solifenacin 3, 6 or 9 mg plus tamsulosin OCAS 0.4 mg; or placebo.
Outcome measurements and statistical analysis: The primary efficacy end point was change from baseline in total IPSS. Secondary end points included micturition diary and quality-of-life (QoL) parameters. Post hoc subgroup analyses were performed by severity of baseline storage symptoms, with statistical comparisons presented only for tamsulosin OCAS alone versus combination therapy, due to the small sample size of the solifenacin monotherapy and placebo subgroups.
Results and limitations: Combination therapy was associated with significant improvements in micturition frequency and voided volume versus tamsulosin OCAS alone in the total study population; improvements in total IPSS were not significant. Statistically significant improvements in urgency episodes, micturition frequency, total urgency score, voided volume, IPSS storage subscore, IPSS-QoL index, and Patient Perception of Bladder Condition were observed in a subpopulation of men with two or more urgency episodes per 24 h (Patient Perception of Intensity of Urgency Scale grade 3 or 4) and eight or more micturitions per 24 h at baseline (storage symptoms subgroup) with combination therapy versus tamsulosin OCAS alone ($p \leq 0.05$ for the dose–response slope, all variables). Combination therapy was well tolerated, and adverse events were consistent with the safety profiles of both compounds.
Conclusions: Solifenacin plus tamsulosin OCAS did not significantly improve IPSS in the total study population but offered significant efficacy and QoL benefits over tamsulosin OCAS monotherapy in men with both voiding and storage symptoms at baseline. Combination therapy was well tolerated.
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1. Introduction

Lower urinary tract symptoms (LUTS) include voiding, storage, and postmicturition symptoms. In men, these are conventionally associated with benign prostatic hyperplasia (BPH) or benign prostatic obstruction; however, they often cannot be attributed to physiologic changes to the prostate, thus treatment guidelines focus on symptom management [1].

Despite a high prevalence of storage symptoms in studies in men with LUTS, the symptoms are commonly undertreated [2,3]. Moreover, under- or inappropriate treatment for storage LUTS is more common in men than in women: In an analysis of claims data from >7.2 million US patients aged >45 yr with overactive bladder (OAB), pharmacologic therapy was prescribed to 17.1% of men versus 28.6% of women ($p < 0.001$) [4].

α-Blocker monotherapy (eg, tamsulosin) is usually considered the first-line therapy for moderate to severe male LUTS [1]. However, symptom control with these agents may be variable, especially in men with predominant storage symptoms. Current European Association of Urology treatment guidelines suggest that antimuscarinics (eg, solifenacin) can be added to α-blockers to manage storage symptoms that persist after α-blocker monotherapy [1], and a number of studies support the benefit of α-blocker plus antimuscarinic combination treatment [5].

We report the results of a phase 2 study, Solifenacin and Tamsulosin in Males with Lower Urinary Tract Symptoms Associated with Benign Prostatic Hyperplasia (SATURN), that evaluated the efficacy and safety of different doses of an antimuscarinic (solifenacin) in combination with an α-blocker (tamsulosin in an oral controlled absorption system [OCAS] formulation) in men with LUTS. The results of this study were expected to establish the most useful clinical dose of combination therapy for further evaluation in the phase 3 Study of Solifenacin Succinate and Tamsulosin Hydrochloride OCAS in males with moderate to severe storage lower urinary tract symptoms (NEPTUNE).

2. Patients and methods

SATURN was a double-blind, parallel-group, placebo-controlled, multicentre, dose-ranging study. The study included a single-blind, 2-wk, placebo run-in period followed by a randomised, double-blind, placebo-controlled, 12-wk treatment period. The study was conducted at 102 centres in 17 European countries, in accordance with the International Conference on Harmonisation–Good Clinical Practice guidelines and the principles of the Declaration of Helsinki. All study materials were reviewed and approved by local independent ethics committees, and all patients provided written informed consent before screening.

2.1. Patients

The study enrolled men aged ≥45 yr who were diagnosed with LUTS with both voiding and storage symptoms. Inclusion criteria included total International Prostate Symptom Score (IPSS) ≥13, a maximum urinary flow rate (Q_{max}) of 4.0–15.0 ml/s, with a volume voided during free flow ≥120 ml. Presence of storage symptoms was determined by the investigator, but there were no specific inclusion criteria regarding the level of storage symptoms. All patients underwent ultrasound evaluation of prostate size (transrectal preferred), although no minimum or maximum prostate size was specified for inclusion in the study. Patients were excluded if they had a postvoid residual (PVR) volume >200 ml, evidence of a symptomatic urinary tract infection, a known history or diagnosis of specific urinary conditions (including urinary retention), previous surgery of the bladder neck or prostate, or any other relevant medical history as determined by the investigator.

2.2. Treatments

After a 2-wk placebo run-in period, patients were randomised to placebo, tamsulosin OCAS 0.4 mg monotherapy, solifenacin 3, 6, or 9 mg plus tamsulosin OCAS 0.4 mg, or dose-matched solifenacin monotherapy (2:4:4:4:4:1:1:1 randomisation ratio) (Fig. 1). As it was expected that the optimal dose of solifenacin in men with LUTS would be lower than in OAB, the 3- and 6-mg doses were selected from a safety perspective. The 9-mg dose was included to provide information about the dose–response curve at the higher end of the dose range. The approved dose of tamsulosin OCAS for LUTS was used.

2.3. End points

The primary end point was change in total IPSS from baseline to end of treatment. Secondary end points included change from baseline to end of treatment in IPSS voiding and storage subscores, micturition diary variables (micturition frequency, urgency episodes of Patient Perception of Intensity of Urgency Scale [PPIUS] grade 3 or 4, urgency incontinence episodes, and mean volume voided per micturition), and quality-of-life (QoL) assessments (IPSS-QoL index and Patient Perception of Bladder Condition [PPBC]). Micturition diaries were completed by patients 3 d prior to the baseline and assessment visits. The PPIUS is a 5-point, validated questionnaire used for the judgement of urgency preceding every void, with episodes being rated from 0 to 4 (0, no urgency; 1, mild urgency; 2, moderate urgency; 3, severe urgency; 4, urge incontinence) [6]. The PPBC is a 6-point validated instrument used to judge the general bladder condition, with patients being asked to rate their symptoms from 1 (“does not cause me any problems”) to 6 (“causes me many severe problems”) [7]. Safety parameters included patient-reported adverse events and PVR volume determined by ultrasound.

As solifenacin is expected to treat storage symptoms specifically, the total urgency and frequency score (TUFS) was evaluated as a post hoc secondary end point to assess improvements in both frequency and urgency using a single parameter, calculated as the mean of daily totals for all recorded PPIUS urgency grading (0–4) for each diary day. The TUFS (previously known as total urgency score) has been validated in patients with OAB and LUTS [8,9].

2.4. Statistics

Efficacy analyses were carried out in the full analysis set, defined as all patients who received at least one dose of study medication and who had a total IPSS at baseline and at least one postrandomisation total IPSS value. Baseline characteristics and safety analyses were reported for the safety set, defined as all patients who received at least one dose of study medication and for whom any data were reported after the first dose of study drug.

The primary efficacy analysis was based on a general linear model, including solifenacin dose and baseline total IPSS as covariates and country as a fixed factor. The dose–response relationship was tested by using parametric statistical modelling to calculate the slope resulting from the addition of increasing solifenacin doses to tamsulosin OCAS. The slope represents the expected increase in change from baseline for each increase of 1 mg in the dose of solifenacin (given in combination