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Benign Prostatic Enlargement

Combination Therapy with Solifenacin and Tamsulosin Oral Controlled Absorption System in a Single Tablet for Lower Urinary Tract Symptoms in Men: Efficacy and Safety Results from the Randomised Controlled NEPTUNE Trial

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Abstract

Background: Storage symptoms are particularly bothersome in men with lower urinary tract symptoms (LUTS) but may not be adequately treated by α-blocker monotherapy.
Objective: To assess the efficacy and safety of a fixed-dose combination (FDC) of solifenacin and an oral controlled absorption system (OCAS) formulation of tamsulosin compared with placebo and compared with tamsulosin OCAS (TOCAS) monotherapy in men with moderate to severe storage symptoms and voiding symptoms.
Design, setting, and participants: A double-blind 12-wk phase 3 study in 1334 men with storage and voiding LUTS: total International Prostate Symptom Score (IPSS) ≥13, maximum urinary flow rate (Q_{max}) 4.0–12.0 ml/s, two or more urgency episodes per 24 h of Patient Perception of Intensity of Urgency Scale grade 3 or 4, and eight or more micturitions per 24 h.
Intervention: Patients were randomised to placebo, TOCAS 0.4 mg, FDC solifenacin 6 mg plus TOCAS 0.4 mg, or FDC solifenacin 9 mg plus TOCAS 0.4 mg.
Outcome measurements and statistical analysis: Primary efficacy end points were (1) total IPSS and (2) Total Urgency and Frequency Score (TUFS). An FDC met the success criteria if it demonstrated superiority compared with placebo and noninferiority compared with TOCAS for total IPSS, as well as superiority compared with TOCAS for TUFS.
Results and limitations: Reductions in total IPSS and TUFS were observed with both solifenacin 6 mg plus TOCAS (−7.0 and −8.1, respectively) and solifenacin 9 mg plus TOCAS (−6.5 and −7.6, respectively) compared with TOCAS (−6.2 and −6.7, respectively) and placebo (−5.4 and −4.4, respectively). Solifenacin 6 mg plus TOCAS met all prespecified success criteria for both primary end points, while solifenacin 9 mg plus TOCAS met success criteria compared with placebo but not compared with TOCAS. Both FDCs improved quality of life (QoL) measures and were well tolerated, with low incidences of acute urinary retention.
Conclusions: The FDC of solifenacin 6 mg plus TOCAS significantly improved storage and voiding symptoms, as well as QoL parameters, compared with placebo. This FDC also improved storage symptoms and QoL compared with TOCAS alone in men with moderate to severe storage symptoms and voiding symptoms, and it was well tolerated.
Trial registration: ClinicalTrials.gov Identifier: NCT01018511.

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1. Introduction

Lower urinary tract symptoms (LUTS) can be divided into three groups: storage symptoms (eg, frequency, urgency, nocturia), voiding symptoms (eg, slow stream, hesitancy, intermittency, terminal dribble), and postmicturition symptoms (eg, incomplete bladder emptying, postmicturition dribbling) [1,2]. Historically, the presence of male LUTS was associated with benign prostatic hyperplasia (BPH), although current guidelines suggest that *benign prostatic obstruction* or *bladder outlet obstruction (BOO)* may be more appropriate terminology in the absence of a histologic diagnosis [2]. BPH is a progressive disease and can lead to benign prostatic enlargement (BPE) and then obstruction, all of which are associated with LUTS [3,4].

A number of pharmacologic options are available for the treatment of LUTS. Antimuscarinics are first-line therapy for overactive bladder (OAB) symptoms but are used less often in men owing to a perceived association with urinary retention. α-Blockers are used primarily for the treatment of symptoms relating to BPE and BPH, while 5-α-reductase inhibitors, alone or in combination with an α-blocker, are recommended for use in men with enlarged prostates (>40 ml) [2]. However, while these agents are effective in alleviating voiding symptoms, they have limited efficacy for storage symptoms, which patients find the most bothersome [5–9]. Current European guidelines suggest that antimuscarinics can be used in combination with an α-blocker when symptom relief is insufficient with either drug alone [2], and a number of studies support combination use (reviewed by Athanasopoulos et al.) [10].

A once-daily fixed-dose combination (FDC) tablet containing solifenacin and an oral controlled absorption system (OCAS) formulation of tamsulosin has been developed to address both storage and voiding symptoms in men with LUTS. This combination showed greater improvements in storage symptoms than tamsulosin OCAS (TOCAS) monotherapy in the phase 2 SATURN trial in the subset of men with both storage and voiding symptoms (two or more urgency episodes per 24 h of Patient Perception of Intensity of Urgency Scale [PPIUS] grades 3 or 4, eight or more micturitions per 24 h, total International Prostate Symptom Score [IPSS] ≥13, and maximum urinary flow rate [Q_{max}] 4.0–15.0 ml/s) at baseline) [11]. FDC therapy was well tolerated, and adverse event (AE) profiles were consistent with those of solifenacin and tamsulosin alone.

We report the results of the phase 3 NEPTUNE trial, which evaluated the efficacy and safety of two solifenacin plus TOCAS FDCs compared with placebo and compared with TOCAS monotherapy in men with storage and voiding LUTS. Solifenacin doses of 6 mg and 9 mg were chosen, based on the results of the phase 2 SATURN study.

2. Materials and methods

2.1. Study design and objectives

NEPTUNE was a randomised double-blind parallel-group placebo-controlled multicentre phase 3 trial conducted between January 2010 and March 2011, across 112 centres in 13 countries. The trial assessed the efficacy of solifenacin plus TOCAS FDCs compared with both TOCAS monotherapy and placebo in men with storage and voiding LUTS. The trial was approved by independent ethics committees and was conducted in accordance with the Declaration of Helsinki and other applicable guidelines, laws, and regulations.

2.2. Patients

Men aged ≥45 yr with storage and voiding symptoms and diagnosed as having LUTS for ≥3 mo were eligible for enrolment. Patients were required to have a total IPSS ≥13 and a Q_{max} of 4.0–12.0 ml/s, with a voided volume ≥120 ml during free flow, two or more urgency episodes per 24 h (PPIUS grade 3 or 4), and eight or more micturitions per 24 h before randomisation. Exclusion criteria included ultrasound-estimated prostate weight ≥75 g; evidence of symptomatic urinary tract infection or a known history or diagnosis of any other relevant medical condition, including specific urinary conditions; and postvoid residual (PVR) volume >150 ml.

After a 2-wk placebo run-in period, eligible patients were randomised (1:1:1:1) using an interactive response technology to 12 wk of double-blind treatment with placebo, TOCAS 0.4 mg, solifenacin 6 mg plus TOCAS 0.4 mg, or solifenacin 9 mg plus TOCAS 0.4 mg. Dose selection was based on the SATURN study, in which three solifenacin doses, coadministered with tamsulosin, were tested to allow for a dose-response evaluation in male LUTS patients, in accordance with International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use guidelines. All treatments were identical in appearance. Patients visited the clinic at screening, at the end of the run-in period (baseline), and after 4, 8, and 12 wk of double-blind treatment. Patients could then enter a 40-wk open-label flexible-dose extension study (NEPTUNE II; ClinicalTrials.gov Identifier: NCT01021332). Results for the NEPTUNE study are presented in this paper.

2.3. Efficacy assessments

2.3.1. Primary efficacy end points

NEPTUNE evaluated changes from baseline to end of treatment in two primary efficacy variables: total IPSS and Total Urgency and Frequency Score (TUFS). TUFS, previously reported as Total Urgency Score [12], is a measure capturing the two important storage symptoms, urgency and frequency, in a single parameter, and it has been validated in both OAB and LUTS. TUFS was derived from 3-d patient micturition diaries, in which subjects graded the level of urgency at each void according to the PPIUS scale (0–4). TUFS is calculated by adding the PPIUS scores of every void in a patient's voiding diary and dividing by the number of days recorded in the diary.

2.3.2. Secondary efficacy end points

Secondary efficacy end points were change from baseline to end of treatment in IPSS storage and voiding subscores, micturition diary variables, and quality of life (QoL) parameters. Micturition diary variables included maximum and mean volume voided per micturition, micturition frequency, urgency episodes, urgency incontinence episodes, incontinence episodes, nocturia, and pads used (all per 24 h). QoL was assessed using the IPSS QoL, the OAB questionnaire (OAB-q; health-related QoL [HRQoL] total score, subscores, and symptom bother score), the Patient Global Impression (PGI) Scale, and the Clinician Global Impression (CGI) Scale.

2.4. Safety assessments

Safety variables included AEs, PVR volume, Q_{max}, vital signs, electrocardiogram (ECG) parameters, physical examination, and standard laboratory measurements.