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Long-term Safety and Efficacy of Mirabegron and Solifenacin in Combination Compared with Monotherapy in Patients with Overactive Bladder: A Randomised, Multicentre Phase 3 Study (SYNERGY II)

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Abstract

Background: The long-term potential of solifenacin and mirabegron combination treatment for patients with overactive bladder (OAB) has not been previously assessed.
Objectives: To evaluate the safety and efficacy of solifenacin succinate 5 mg plus mirabegron 50 mg tablets (combination treatment) versus solifenacin or mirabegron monotherapy in patients with OAB over 12 mo.
Design, setting, and participants: Randomised, double-blind, multicentre, phase 3 trial (SYNERGY II) of patients with "wet" OAB symptoms (urinary frequency and urgency with incontinence) for ≥3 mo. The study was conducted from March 2014 to September 2016; with 1829 patients randomised. The full analysis set was comprised of 1794 patients.
Outcome measurements and statistical analysis: The primary objective was safety, measured as treatment-emergent adverse events (TEAEs). Efficacy was measured as the change from baseline to the end of treatment in the mean number of incontinence episodes/24 h and micturitions/24 h.
Results and limitations: The median age was 60 yr (range 19–86 yr) and 1434 patients (80%) were female. Overall, 856 patients (47%) experienced ≥1 TEAE. TEAE frequency was slightly higher in the combination group (596 patients, 49%; mirabegron 126 patients, 41%; solifenacin 134 patients, 44%). Serious TEAEs were reported by 67 patients (3.7%); one was considered possibly treatment-related (mirabegron group, atrial fibrillation). Dry mouth was the most common TEAE (combination 74 patients, 6.1%; solifenacin 18 patients, 5.9%; mirabegron 12 patients, 3.9%). Combination therapy was statistically superior to mirabegron and solifenacin for the number of incontinence episodes (vs mirabegron: adjusted mean difference [AMD] −0.5, 95% confidence interval [CI] −0.7 to −0.2, $p < 0.001$; vs solifenacin: AMD −0.1, 95% CI −0.4 to 0.1, $p = 0.002$) and micturitions (vs mirabegron: AMD −0.5, 95% CI −0.8 to −0.2, $p < 0.001$; vs solifenacin: AMD −0.4, 95% CI −0.7 to −0.1, $p = 0.004$).
Conclusions: Mirabegron and solifenacin combination treatment for OAB symptoms was well tolerated over 12 mo and led to efficacy improvements over each monotherapy. This innovative combination is a treatment option that could become widely used in the clinic.
Patient summary: This study looked at the safety and efficacy of a combination of solifenacin succinate 5 mg plus mirabegron 50 mg tablets over 12 mo in patients with the overactive bladder (OAB) symptoms of increased urination frequency, heightened urgency to urinate, and unintentional passing of urine. We compared this treatment with solifenacin succinate 5 mg or mirabegron 50 mg alone, and found that the combination treatment was well tolerated by patients and led to greater improvements in symptoms. This novel combination could be an improved treatment option in the clinical setting for patients with OAB.
This study is registered at ClinicalTrials.gov as NCT02045862.

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1. Introduction

Individuals are diagnosed with overactive bladder (OAB) if they experience urinary urgency, usually with increased daytime frequency and nocturia, that is not caused by a proven infection or other obvious pathology [1]. Pharmacotherapy options principally include antimuscarinics, including solifenacin, and the β_3-adrenoreceptor agonist mirabegron.

Mirabegron and solifenacin have different mechanisms of action [2,3] and co-administration appears to have no noticeable effect on their pharmacokinetics [4]. Studies have demonstrated that combination treatment for 12 wk leads to improved efficacy without a substantial impact on the safety profile when compared with monotherapy [5–7].

In the 12-wk phase 3 SYNERGY study, clinically relevant improvements in incontinence episodes and micturitions were apparent with solifenacin 5 mg in combination with mirabegron 25 or 50 mg when compared with the individual monotherapies in the general OAB population with urinary incontinence [8]. The overall safety profile was acceptable, with a slightly higher frequency of treatment-emergent adverse events (TEAEs) for the combination groups versus the monotherapies.

To address our hypothesis that the positive results from SYNERGY would be maintained in the longer term, we evaluated the safety and efficacy of combination treatment with solifenacin 5 mg and mirabegron 50 mg in comparison with each monotherapy over 12 mo in patients with OAB (SYNERGY II).

2. Patients and methods

2.1. Study design

This was a multinational, randomised, double-blind, parallel-group, active-controlled, multicentre phase 3 study in men and women with symptoms of "wet" OAB (urinary frequency and urgency with incontinence) for ≥3 mo. The study was conducted from March 2014 to September 2016 at 251 sites in 32 countries. The majority of patients were recruited from the SYNERGY [8] or BESIDE [6] studies. Demographic data were collected at screening; the inclusion and exclusion criteria are presented in Supplementary Table 1.

SYNERGY II comprised a single-blind, 2-wk placebo run-in (to washout prior OAB treatment); a randomised, double-blind, active-controlled, 12-mo treatment period; and a 2-wk follow-up during which no OAB treatments were permitted (Fig. 1). Eligible patients were randomised 4:1:1 into the treatment period and received solifenacin succinate 5 mg plus mirabegron 50 mg (combination 5 + 50 mg), solifenacin succinate 5 mg, or mirabegron 50 mg. Patients took two tablets orally per day; placebo and the corresponding active tablets were indistinguishable in appearance and shape.

This study was conducted in accordance with the Declaration of Helsinki, Good Clinical Practice, and International Council for Harmonisation guidelines. An independent ethics committee or institutional review board reviewed the ethical, scientific, and medical appropriateness of the study at each site. Signed informed consent forms were obtained before any study-related procedures were performed.

2.2. Safety assessments

Evaluation of safety was the primary study objective. The frequency of TEAEs was assessed throughout the study, including TEAEs of special interest. Site-based vital sign, laboratory, electrocardiogram, and postvoid residual (PVR) volume assessments were also conducted. Deaths and serious potential cardiovascular events were categorised as major adverse cardiovascular events (MACEs), non-MACEs, or non-cardiovascular events by an independent cardiovascular adjudication committee.

2.3. Efficacy assessments

Before each visit, patients completed a micturition eDiary using a validated electronic handheld device for 7 consecutive days (3 d for volume voided). The primary efficacy variables were change from baseline to the end of treatment (EOT) in mean number of incontinence episodes/24 h and micturitions/24 h.

Secondary efficacy variables were change from baseline to EOT in mean volume voided (MVV) per micturition, overactive bladder questionnaire (OAB-q) health-related quality of life (HRQoL) total and symptom bother score, and treatment satisfaction-visual analogue scale (TS-VAS) score. Changes over time were analysed for all of the primary and secondary variables at 1, 3, 6, 9, and 12 mo, with the exception of MVV per micturition, which was assessed at 3, 6, and 12 mo only.

Responder variables included the percentage of patients with zero incontinence episodes/24 h at EOT, micturition frequency normalisation at EOT (≥8 micturitions/24 h at baseline and <8 micturitions/24 h post-baseline), and ≥10-point improvement from baseline in OAB-q HRQoL total and symptom bother scores at EOT.

2.4. Statistical analyses

All statistical analyses were performed using SAS version 9.3 or higher (SAS, Cary, NC, USA). Using a randomisation ratio of 4:1:1 and assuming that 1200 and 300 patients were enrolled in the combination and monotherapy groups, respectively, and that 23–25% of the patients

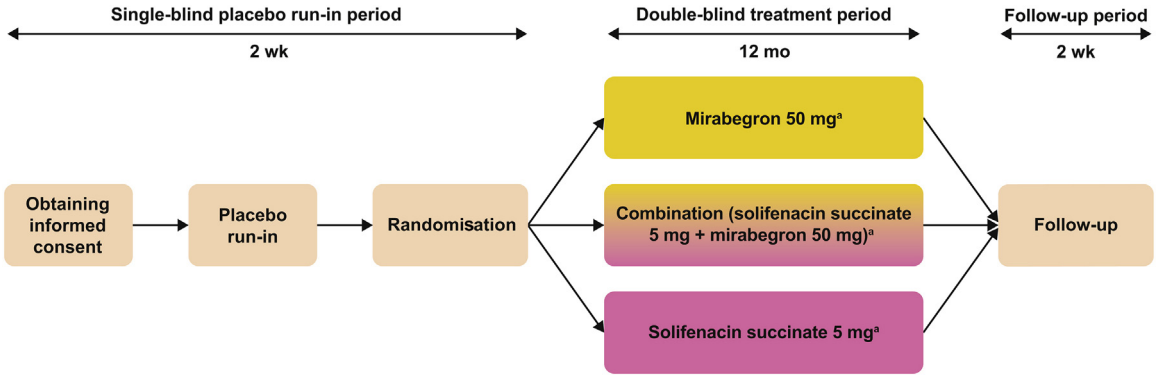

Fig. 1 – Study design. [a] Once daily.

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