EUROPEAN UROLOGY 67 (2015) 577–588

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

European Association of Urology

Voiding Dysfunction

Combination Treatment with Mirabegron and Solifenacin in Patients with Overactive Bladder: Efficacy and Safety Results from a Randomised, Double-blind, Dose-ranging, Phase 2 Study (Symphony)

Paul Abrams[a,*], *Con Kelleher*[b], *David Staskin*[c], *Tomasz Rechberger*[d], *Richard Kay*[e], *Reynaldo Martina*[f], *Donald Newgreen*[f], *Asha Paireddy*[f], *Rob van Maanen*[f], *Arwin Ridder*[f]

[a] Bristol Urological Institute, Southmead Hospital, Bristol, UK; [b] Guys and St Thomas' Hospitals, London, UK; [c] Tufts University School of Medicine, Boston, MA, USA; [d] II Department of Gynaecology, Medical University, Lublin, Poland; [e] RK Statistics Ltd., Bakewell, UK; [f] Astellas Pharma BV, Leiden, The Netherlands

Article info

Article history:
Accepted February 7, 2014

Keywords:
Combination therapy
Mirabegron
Overactive bladder
Solifenacin

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: Combining the β3-adrenoceptor agonist mirabegron and the antimuscarinic (AM) agent solifenacin may improve efficacy in the treatment of overactive bladder (OAB) while reducing the AM side effects.

Objective: The primary objective was to evaluate the efficacy of combinations of solifenacin/mirabegron compared with solifenacin 5 mg monotherapy. The secondary objective was to explore the dose–response relationship and the safety/tolerability compared with placebo and monotherapy.

Design, setting, and participants: A phase 2, factorial design, randomised, double-blind, parallel-group, placebo- and monotherapy-controlled trial, conducted at 141 sites in 20 European countries. Male and female patients were aged ≥18 yr with symptoms of OAB for ≥3 mo.

Intervention: A total of 1306 patients (66.4% female) were randomised to 12 wk of treatment in 1 of 12 groups: 6 combination groups (solifenacin 2.5, 5, or 10 mg plus mirabegron 25 or 50 mg), 5 monotherapy groups (solifenacin 2.5, 5, or 10 mg, or mirabegron 25 or 50 mg), or placebo.

Outcome measurements and statistical analysis: Change from baseline to end of treatment in mean volume voided per micturition (MVV) (primary end point) and mean numbers of micturitions per 24 h, incontinence episodes per 24 h, and urgency episodes per 24 h were analysed using an analysis of covariance model. Safety assessments included treatment-emergent adverse events (TEAEs), blood pressure, pulse rate, post-void residual (PVR) volume, and laboratory and electrocardiography (ECG) parameters.

Results and limitations: Compared with solifenacin 5 mg monotherapy, all combinations with solifenacin 5 or 10 mg significantly improved MVV, with adjusted differences ranging from 18.0 ml (95% confidence interval [CI], 5.4–30.0) to 26.3 ml (95% CI, 12.0–41.0). Three combination groups significantly reduced micturition frequency compared with solifenacin 5 mg, ranging from −0.80 (95% CI, −1.39 to −0.22) to −0.98 (95% CI, −1.68 to −0.27). Five of six combinations significantly reduced urgency episodes compared with solifenacin 5 mg, ranging from −0.98 (95% CI, −1.78, to −0.18) to −1.37 (95% CI, −2.03 to −0.70). No dose-related trends in TEAEs, blood pressure, pulse

* Corresponding author. Bristol Urological Institute, Southmead Hospital, Bristol, BS10 5NB, UK.
Tel. +44 0117 9595690; Fax: +44 0117 9502229.
E-mail address: paul.abrams@bui.ac.uk (P. Abrams).

http://dx.doi.org/10.1016/j.eururo.2014.02.012

rate, PVR volume, or laboratory or ECG parameters were observed between combination and monotherapy groups, although the incidence of constipation was slightly increased with combination therapy.
Conclusions: Combination therapy with solifenacin/mirabegron significantly improved MVV, micturition frequency, and urgency compared with solifenacin 5 mg monotherapy. All combinations were well tolerated, with no important additional safety findings compared with monotherapy or placebo.
Patient summary: To improve treatment of overactive bladder (OAB), mirabegron/solifenacin in combination was compared with each drug alone and placebo. Combination therapy improved OAB symptoms and had similar safety and acceptability.
Trial registration: Clinical trials.gov: NCT01340027.

1. Introduction

Antimuscarinic (AM) agents are the mainstay of oral pharmacotherapy for overactive bladder (OAB), but persistence with treatment is limited by insufficient efficacy and AM-associated adverse events (AEs) [1]. The approval of the β3-adrenoceptor agonist mirabegron has added a new class of pharmacotherapy for OAB. In 12-wk trials, mirabegron (25, 50, and 100 mg) demonstrated significant reductions compared with placebo in micturition and incontinence episode frequency, with an incidence of AM-associated AEs similar to placebo [2–4].

As these agents have different mechanisms of action, combining a β3-adrenoceptor agonist with an AM agent may improve efficacy in OAB treatment; combinations with reduced doses may deliver an improved tolerability profile compared with monotherapy, without compromising efficacy. The potential for modulation of bladder function with combination therapy has been demonstrated in preclinical models [5]. In view of the minimal cardiovascular effects observed with both agents, a key element in understanding the safety of the combination will be to evaluate cardiovascular parameters.

The primary objective of the current study was to evaluate the efficacy of combinations of solifenacin (2.5 and 5 mg) plus mirabegron (25 and 50 mg) compared with solifenacin 5 mg monotherapy (the recommended daily starting dose of solifenacin and the most widely used dose in clinical practice). Secondary objectives included evaluation of the dose–response relationship of combinations of solifenacin (2.5, 5, and 10 mg) and mirabegron (25 and 50 mg) and comparison of the safety/tolerability between combination therapy and placebo and the corresponding monotherapies.

2. Methods

2.1. *Study design and patient population*

This phase 2, factorial design, multicentre, randomised, double-blind, parallel-group, placebo- and monotherapy-controlled trial enrolled male and female patients aged ≥18 yr with symptoms of OAB (urgency, urinary frequency, and/or urgency incontinence) for ≥3 mo.

Following a 2-wk, single-blind placebo run-in period and washout of existing OAB medications (prior use of solifenacin or mirabegron was not excluded) and prohibited medications, patients with eight or more micturitions per 24 h and one urgency episode or more per 24 h (with or without incontinence), based on a 3-d electronic patient micturition diary, were randomised to 12 wk of treatment in 1 of 12 groups (6 combination groups, 5 active-control groups, and 1 placebo arm) in a 2:1 ratio for primary compared with secondary treatment groups (Fig. 1). Using a double-blind, double-dummy technique, all patients received three tablets daily throughout the treatment phase: solifenacin (2.5, 5, or 10 mg) or placebo, mirabegron 25 mg or placebo, and mirabegron 50 mg or placebo.

The study protocol was approved by an institutional review board/independent ethics committee at each site. All subjects gave written informed consent.

2.2. *Efficacy assessments*

The primary efficacy variable was change from baseline to end of treatment (EOT) in mean volume voided per micturition (MVV). Changes from baseline to EOT were also assessed for mean number of micturitions per 24 h and mean number of incontinence episodes per 24 h (key secondary efficacy variables), as well as mean number of urgency episodes per 24 h (grade 3 or 4, according to the Patient Perception of Intensity of Urgency Scale) [6], an additional secondary efficacy variable.

2.3. *Safety assessment*

Safety parameters assessed at screening and at each study visit included laboratory assessments, vital signs (blood pressure [BP] and pulse rate), electrocardiography (ECG) parameters, postvoid residual (PVR) volume (determined by bladder scan or ultrasound), and the frequency of treatment-emergent AEs (TEAEs). Using a standard office device, BP and pulse rate were measured in triplicate (each reading approximately 2 min apart) by the investigator and the average calculated using two readings, as well as by patients (results provided in the Supplement and Supplemental Table 2) using an automated device for 5 d consecutively. Standard office device measurements are reported herein.

2.4. *Statistical analyses*

A sample size of 140 patients in the five primary treatment groups provided 80% power to detect a significant difference of ≥17.3 ml in MVV (based on treatment differences from previous studies [2,3,7,8]) between a combination group and solifenacin 5 mg monotherapy, based on a two-sided t test with $\alpha = 0.05$ and a standard deviation of 50 ml; a sample size of 70 patients in the remaining treatment arms provided a power of ≥80% to detect a difference of ≥24 ml compared with placebo. The study was not powered to detect differences in the key secondary efficacy variables. Assuming postrandomisation dropout rates of 10%, 1326 patients were to be randomised.