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

European Association of Urology

Platinum Priority – Incontinence

Editorial by Giacomo Novara and Jean-Nicolas Cornu on pp. 306–308 of this issue

Randomized Double-blind, Active-controlled Phase 3 Study to Assess 12-Month Safety and Efficacy of Mirabegron, a β_3-Adrenoceptor Agonist, in Overactive Bladder

Christopher R. Chapple[a,*], *Steven A. Kaplan*[b], *David Mitcheson*[c], *Jiri Klecka*[d], *Jana Cummings*[e], *Ted Drogendijk*[f], *Caroline Dorrepaal*[f], *Nancy Martin*[e]

[a] *Royal Hallamshire Hospital, Sheffield, UK;* [b] *Weill Medical College of Cornell University, New York-Presbyterian Hospital/Weill Cornell Medical Center, New York, NY, USA;* [c] *St. Elizabeth's Medical Center, Brighton, MA, USA;* [d] *University Hospital Plzeň, Plzeň, Czech Republic;* [e] *Astellas Pharma Global Development, Northbrook, IL, USA;* [f] *Astellas Pharma Global Development, Leiderdorp, The Netherlands*

Article info

Article history:
Accepted October 28, 2012
Published online ahead of print on November 6, 2012

Keywords:
Mirabegron
Tolterodine
Overactive bladder

Abstract

Background: Despite several antimuscarinic treatment options for overactive bladder (OAB), there is still a need for distinct treatment approaches to manage this condition. Mirabegron, a β_3-adrenoceptor agonist, has demonstrated efficacy and tolerability for up to 12 wk in phase 3 trials.
Objective: To assess the 12-mo safety and efficacy of mirabegron.
Design, setting, and participants: Patients ≥18 yr of age with OAB symptoms for ≥3 mo.
Interventions: After a 2-wk single-blind placebo run-in, patients with eight or more micturitions per 24 h and three or more urgency episodes in a 3-d micturition diary were randomized 1:1:1 to once-daily mirabegron 50 mg, mirabegron 100 mg, or tolterodine extended release (ER) 4 mg for 12 mo.
Outcome measurements and statistical analysis: Primary variable: incidence and severity of treatment-emergent AEs (TEAEs). Secondary variables: change from baseline at months 1, 3, 6, 9, and 12 in key OAB symptoms.
Results and limitations: A total of 812, 820, and 812 patients received mirabegron 50 mg, mirabegron 100 mg, and tolterodine ER 4 mg, respectively. Baseline demographic and OAB characteristics were similar across groups. TEAEs were reported in 59.7%, 61.3%, and 62.6% of patients, respectively; most were mild or moderate. Serious TEAEs were reported in 5.2%, 6.2%, and 5.4% of patients, respectively. The most common TEAEs were similar across groups. Dry mouth was reported by 2.8%, 2.3%, and 8.6% of patients, respectively. Adjusted mean changes from baseline to final visit in morning systolic blood pressure were 0.2, 0.4, and −0.5 mm Hg for mirabegron 50 mg, 100 mg, and tolterodine ER 4 mg, respectively. Mirabegron and the active control, tolterodine, improved key OAB symptoms from the first measured time point of 4 wk, and efficacy was maintained throughout the 12-mo treatment period. The study was not placebo controlled, which was a limitation.
Conclusions: The safety and tolerability of mirabegron was established over 1 yr, with sustained efficacy observed over this treatment period.
Trial registration: ClinicalTrials.gov identifier: NCT00688688.
© 2012 European Association of Urology. Published by Elsevier B.V. All rights reserved.

* Corresponding author. Department of Urology, Royal Hallamshire Hospital, Glossop Road, Sheffield, S10 2JF, UK. Tel. +44 0114 2797841; Fax: +44 0114 2711901.
E-mail address: c.r.chapple@shef.ac.uk (C.R. Chapple).

0302-2838/$ – see back matter © 2012 European Association of Urology. Published by Elsevier B.V. All rights reserved.
http://dx.doi.org/10.1016/j.eururo.2012.10.048

1. Introduction

For several decades, oral antimuscarinic agents have represented the current mainstay of pharmacotherapy for improving overactive bladder (OAB) symptoms; however, they may elicit inadequate response in some patients, and/or their use may be associated with adverse events (AEs) (eg, dry mouth, constipation, and blurred vision) [1,2].

In the bladder, β_3-adrenoceptors are predominantly located in detrusor muscle and facilitate urine storage by inducing detrusor relaxation [3]. β_3-adrenoceptor agonists represent a new class of agents with a distinct mechanism of action [4–6]. Mirabegron is the first in class to have completed phase 3 registrational trials, and following approval in Japan and the United States, it represents a new oral agent for OAB treatment. Recent phase 3 trials have demonstrated the efficacy and safety of mirabegron for up to 12 wk of therapy (NCT00689104 and NCT00662909) [7,8]. The primary objective of the present study was to assess the safety and tolerability of 12-mo treatment with once-daily mirabegron (50 mg and 100 mg) in a randomized double-blind parallel group, active controlled trial. Secondary objectives were to assess the efficacy of 12-mo mirabegron treatment and the 12-mo safety and efficacy of mirabegron in parallel with tolterodine.

2. Methods

This study was conducted at 306 sites in Europe, the United States, Canada, South Africa, Australia, and New Zealand between April 2008 and May 2010, consisting of a 2-wk single-blind placebo run-in period followed by a 12-mo randomized treatment (Fig. 1). The study was conducted in accordance with ethical principles derived from the Declaration of Helsinki, Good Clinical Practice, and International Conference of Harmonization Guidelines. All patients provided written informed consent.

2.1. Patients and study design

Patients ≥18 yr of age with symptoms of OAB (urinary frequency and urgency with or without urgency incontinence) ≥3 mo were eligible for the placebo run-in. Approximately 2500 patients were planned for enrollment, based on estimates of numbers enrolling after completing studies NCT00689104 and NCT00662909. No formal sample size calculation was performed. Patients who had completed recent phase 3 mirabegron studies in Europe, the United States, Canada, and Australia had the option to enroll but required ≥30 d of drug washout. Antihypertensive drugs were permitted.

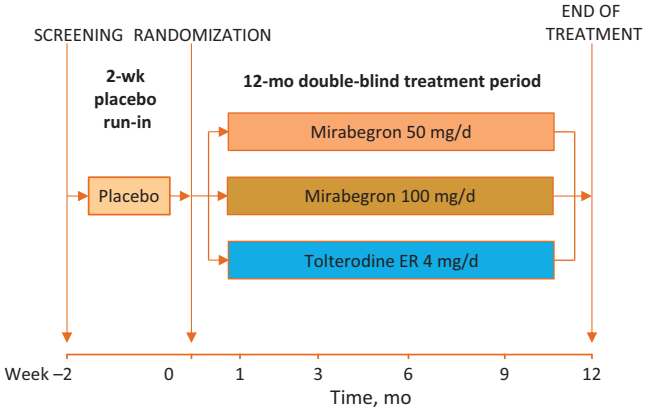

Fig. 1 – Study flow chart. ER = extended release.

During the placebo run-in, patients were eligible for randomization if they met the following criteria during the 3-d micturition diary period: average micturition frequency eight or more times per 24 h and three or more episodes of urgency (grade 3 or 4 using the Patient Perception of Intensity of Urgency Scale) with or without incontinence. Appendix 1 shows the inclusion and exclusion criteria.

Eligible patients were randomized 1:1:1 using a computer-generated randomization scheme, prepared by Pierrel Research Europe (Essen, Germany), to receive oral mirabegron 50 mg or 100 mg, or tolterodine extended release (ER) 4 mg once daily for 12 mo. The investigator, study site personnel, patients, and sponsor were blinded to treatment (including the medication received in prior trials). Demographics and other baseline characteristics were recorded at the start of the placebo run-in period. Patients completed a 3-d micturition diary just before the randomization visit and before visits at months 1, 3, 6, 9, and 12. In addition, patients recorded morning and afternoon blood pressure (BP) and pulse rate (PR) during the 5 d preceding randomization and at months 1, 3, 6, 9, and 12. Compliance was monitored by counting the medication dispensed to and returned by the patient at each visit. Patients were considered compliant if compliance was between 80% and 120% of the medication required to be taken in the interval since the previous visit.

2.2. Assessments and end points

2.2.1. Safety assessments

The primary safety variable was the incidence and severity of treatment-emergent adverse events (TEAEs). A TEAE was an AE starting or worsening in the period from the first double-blind study drug intake until 30 d after the last double-blind study drug intake. Safety was also assessed by evaluating vital signs (AM and PM sitting systolic and diastolic BP [SBP/DBP] and PR) and by laboratory tests (hematology, biochemistry, urinalysis), physical examination, and electrocardiographic (ECG) parameters (Appendix 2). An ambulatory blood pressure monitoring (ABPM) substudy conducted in a subset of patients at selected investigational sites in the United States measured SBP/DBP and heart rate every 15 min during a 24-h period at baseline and at months 6 and 12.

The protocol prespecified definition for recording a hypertension event was if the average SBP was ≥140 mm Hg and/or the average DBP was ≥90 mm Hg at two consecutive visits postbaseline in normotensive patients, average SBP increased ≥20 mm Hg and/or average DBP increased ≥10 mm Hg at two consecutive visits versus baseline in patients with hypertension at baseline, antihypertensive drugs were initiated, or if the dose of prior antihypertensive medication was increased due to BP increase. An independent data safety monitoring board (DSMB) reviewed safety data quarterly (or as needed).

2.2.2. Efficacy end points

Efficacy end points were secondary and included change from baseline at months 1, 3, 6, 9, and 12 in key OAB symptoms recorded in the 3-d micturition diary. Patient-reported outcomes were assessed using the overactive bladder questionnaire (OAB-q; at baseline and months 1, 3, 6, 9, and 12), Patient Perception of Bladder Condition (PPBC) scale (baseline and month 12), and the Treatment Satisfaction Visual Analog Scale (TS-VAS; baseline and month 12). In addition, two responder analyses based on incontinence episodes were performed at months 1, 3, 6, 9, and 12. Responders were defined as those with ≥50% decrease from baseline in the mean number of incontinence episodes per 24 h or those with zero incontinence episodes postbaseline at final visit (dry rate). The study was not designed to demonstrate a statistically significant difference in efficacy between treatment groups.

Download English Version:

https://daneshyari.com/en/article/3926378

Download Persian Version:

https://daneshyari.com/article/3926378

Daneshyari.com