Results of a Randomized Phase III Trial of Mirabegron in Patients with Overactive Bladder

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Abbreviations and Acronyms

APTC = Antiplatelet Trialists' Collaboration
BP = blood pressure
DBP = diastolic blood pressure
FAS = full analysis set
FAS-I = FAS-Incontinence
HRQOL = health related quality of life
MACE = Major Adverse Cardiovascular Events
OAB = overactive bladder
OAB-q = OAB questionnaire
PPBC = Patient Perception of Bladder Condition
PVR = post-void residual
SBP = systolic blood pressure
TEAE = treatment emergent adverse event
TS-VAS = treatment satisfaction visual analog scale

Purpose: Many patientswith overactive bladder discontinue pharmacotherapy due to suboptimal efficacy or side effects. Mirabegron, a β_3-adrenoceptor agonist, may offer an effective and well tolerated alternative treatment for overactive bladder.

Materials and Methods: A randomized, double-blind, placebo controlled trial was conducted in the United States and Canada. After a 2-week placebo run-in period, adults with overactive bladder symptoms for 3 or more months were randomized 1:1:1 to receive placebo, 50 or 100 mg mirabegron once daily for 12 weeks. Efficacy data were collected via patient completed diaries and quality of life assessments. Co-primary efficacy end points were changes from baseline to final visit in mean number of incontinence episodes per 24 hours and micturitions per 24 hours. Key secondary micturition and incontinence end points were also evaluated. Safety assessments included treatment emergent adverse events, laboratory assessments, vital signs, electrocardiograms and post-void residual volume.

Results: Compared to placebo, 50 and 100 mg mirabegron groups demonstrated statistically significantly greater mean decreases (95% CI) from baseline for incontinence episodes (−1.13 [−1.35, −0.91], −1.47 [−1.69, −1.25] and −1.63 [−1.86, −1.40]) and micturitions (−1.05 [−1.31, −0.79], −1.66 [−1.92, −1.40] and −1.75 [−2.01, −1.48]) per 24 hours ($p < 0.05$). Significant improvements in all key secondary end points were observed for both mirabegron doses vs placebo. The incidence of frequently reported treatment emergent adverse events (hypertension, urinary tract infection, headache, nasopharyngitis) was similar in the mirabegron and placebo groups. Dry mouth was reported for 1.5%, 0.5% and 2.1% of patients in the placebo, 50 and 100 mg mirabegron groups, respectively.

Conclusions: Once daily mirabegron in a 50 or 100 mg dose is an effective treatment for overactive bladder symptoms with a low occurrence of side effects.

Key Words: 2-(2-aminothiazol-4-yl)-4′-(2-((2-hydroxy-2-phenylethyl)amino) ethyl)acetanilide; urinary bladder, overactive; adrenergic beta-agonists

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Study received institutional review board/independent ethics committee approval.

Clinical Trial Registration NCT00662909 (www.clinicaltrials.gov).

The complete list of investigators and site information for this trial are available at http://www.mirabegron-posters.com/documents/Investigator_and_Site_Information_047.pdf.

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ANTIMUSCARINIC agents are the current pharmacological mainstay for OAB.[1,2] However, some patients have a suboptimal response to antimuscarinic therapy, or experience side effects such as dry mouth or constipation.[3,4] A high proportion of patients discontinue therapy with less than 25% remaining on therapy at 1 year.[5,6] Therefore, a need exists for effective and well tolerated treatment options with mechanisms of action distinct from those of current therapies.

While stimulation of muscarinic receptors in the bladder facilitates urine voiding, activation of β-adrenergic receptors facilitates urine storage through flattening and lengthening of the bladder base.[7] A role for β_3-adrenergic receptors in promoting urine storage has been proposed.[8,9] β_3-agonists relax the detrusor smooth muscle during the storage phase of the bladder fill-void cycle, which increases bladder capacity.[10] In addition, they have the potential to reduce the occurrence of side effects such as dry mouth.

Mirabegron, a β_3-adrenoceptor agonist,[11] is a first in class drug for the treatment of OAB. Mirabegron demonstrated significant dose dependent improvements in key OAB symptoms in a phase II study,[12] and in this phase III study we further evaluated the safety and efficacy of mirabegron in patients with OAB.

METHODS

A phase III, randomized, parallel group, double-blind, placebo controlled, multicenter study was conducted at 132

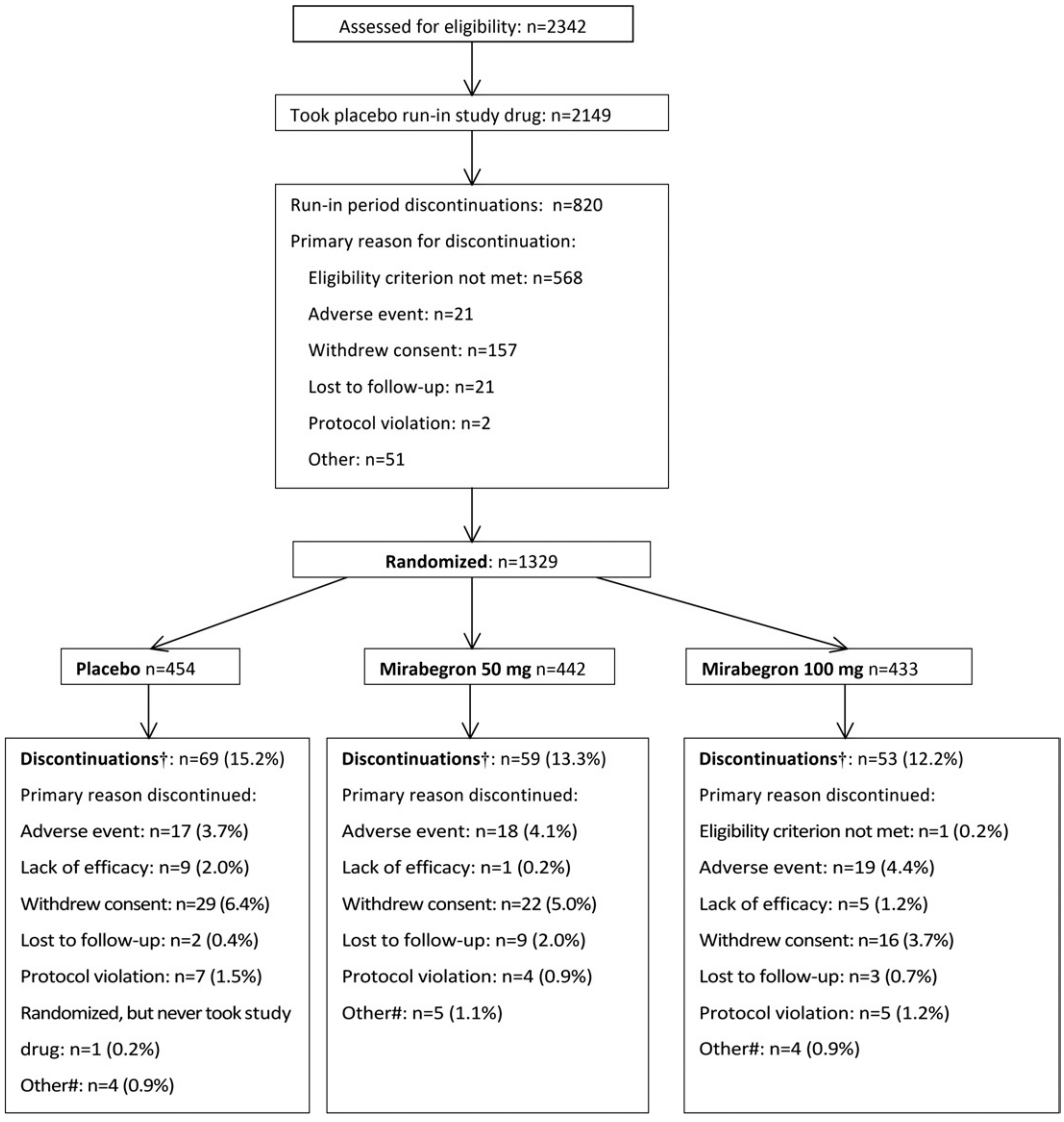

Figure 1. Patient disposition. Dagger indicates discontinuations reported for all randomized patients. Number sign indicates other reasons for discontinuation included noncompliance with diary completion, study visits or study drug; error by study site personnel; investigator decision to withdraw patient; and average urinary output exceeded baseline exclusion criterion.