Elderly trial
Wagg et al.

Efficacy, safety, and tolerability of mirabegron in patients aged ≥65yr with overactive bladder wet: a phase IV, double-blind, randomised, placebo-controlled study (PILLAR)

Wagg A, Staskin D, Engel E, Herschorn S, Kristy RM, Schermer CR. Eur Urol 2020;77(2):211-20.

INDICATIONS AND USAGE

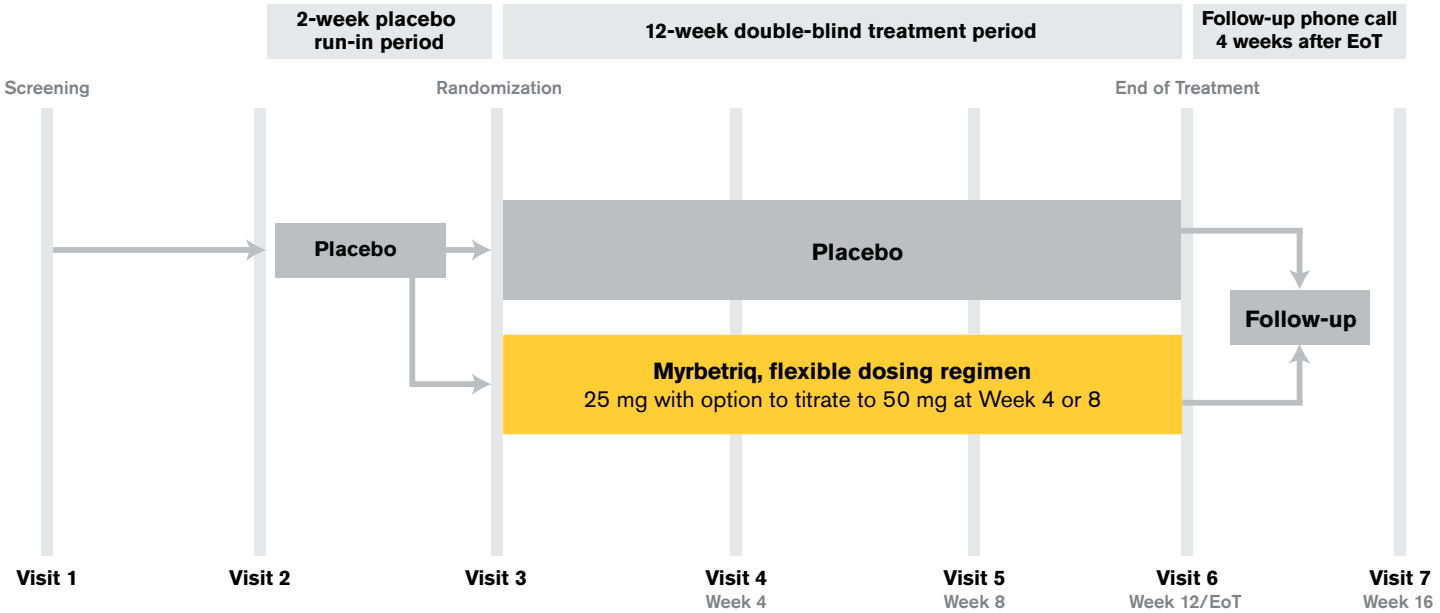
MYRBETRIQ® (mirabegron extended-release tablets) is indicated for the treatment of overactive bladder (OAB) in adult patients with symptoms of urge urinary incontinence, urgency, and urinary frequency.

OBJECTIVE[1]

The objective of this study was to assess the efficacy and safety of Myrbetriq in a flexible dosing regimen with placebo in the treatment of adults ≥65 years of age with OAB symptoms.

PILLAR STUDY DESIGN AND PATIENT POPULATION[1]

PILLAR was a double-blind, randomized, placebo-controlled, parallel-group, multicenter Phase IV study of community-dwelling patients ≥65 years of age who entered a 2-week placebo run-in period, during which time a 3-day micturition training diary was completed prior to being randomized to 1 of 2 treatment groups for 12 weeks. Entry criteria required that patients have symptoms of wet OAB for ≥3 months with ≥1 incontinence episode, ≥3 urgency episodes, and an average of ≥8 micturition episodes per day. Those who entered the 12-week treatment period were randomized 1:1 and stratified by age. Patients were randomized to Myrbetriq 25 mg or placebo and were given the option to increase to 50 mg at Week 4 or Week 8 based on individual efficacy, tolerability, and investigator discretion. Patients completed 3-day micturition diaries immediately before study visits at Week 4, 8, and 12.



EoT=End of Treatment.

This study was designed to detect a difference between placebo and total Myrbetriq groups and not for each individual Myrbetriq dosing group.

IMPORTANT SAFETY INFORMATION

MYRBETRIQ is contraindicated in patients with known hypersensitivity reactions to mirabegron or any inactive ingredients of the tablet.

MYRBETRIQ can increase blood pressure in adults. Periodic blood pressure determinations are recommended, especially in hypertensive patients. MYRBETRIQ is not recommended for use in severe uncontrolled hypertensive patients (defined as systolic blood pressure ≥ 180 mm Hg and/or diastolic blood pressure ≥ 110 mm Hg). Worsening of pre-existing hypertension was reported infrequently in patients taking MYRBETRIQ.

Please see Important Safety Information throughout.
Please click here for full Prescribing Information for Myrbetriq® (mirabegron extended-release tablets)

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25 mg, 50 mg

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SELECTED INCLUSION CRITERIA[1]

- Male and female community-dwelling patients ≥65 years of age with wet OAB symptoms (defined as urgency, urinary frequency, and urinary incontinence) with an average of ≥8 micturitions per 24 hours, ≥3 urgency episodes, and ≥1 urinary incontinence episode, based on a 3-day micturition diary

SELECTED EXCLUSION CRITERIA[1]

Patients were excluded from the study if they:

- Lived in a nursing home facility
- Had bladder outlet obstruction (BOO)
- Had predominant stress incontinence
- Had post-void residual volume (PVR) >150 mL
- Had neurogenic detrusor overactivity
- Had acute urinary tract infection
- Had recent initiation of conservative/invasive therapy for OAB
- Had permanent or intermittent catheterization
- Had severe renal or hepatic impairment or uncontrolled hypertension
- Had mental incapacity to complete the study or consent procedures

IMPORTANT SAFETY INFORMATION (cont'd)

In patients taking MYRBETRIQ, urinary retention has been reported in patients with bladder outlet obstruction (BOO) and in patients taking muscarinic antagonist medications for the treatment of OAB. A controlled clinical safety study in patients with BOO did not demonstrate increased urinary retention in patients treated with mirabegron; however, MYRBETRIQ should still be administered with caution to patients with clinically significant BOO. For example, monitor these patients for signs and symptoms of urinary retention. MYRBETRIQ should also be administered with caution to patients taking muscarinic antagonist medications for the treatment of OAB.

Angioedema of the face, lips, tongue, and/or larynx has been reported with MYRBETRIQ. In some cases, angioedema occurred after the first dose. Cases have been reported to occur hours after the first dose or after multiple doses. Angioedema, associated with upper airway swelling, may be life threatening. If involvement of the tongue, hypopharynx, or larynx occurs, promptly discontinue MYRBETRIQ and provide appropriate therapy and/or measures necessary to ensure a patent airway.

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CO-PRIMARY EFFICACY ENDPOINTS[1]

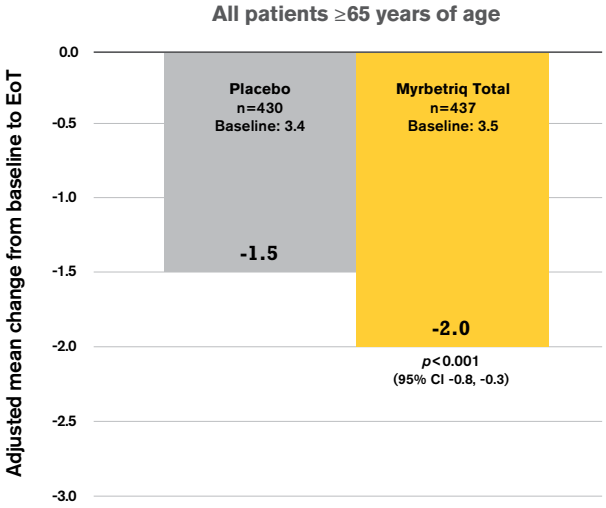
- Change from baseline to end of treatment (EoT, Week 12) in mean number of urinary incontinence episodes per 24 hours
- Change from baseline to EoT (Week 12) in mean number of micturitions per 24 hours

SECONDARY ENDPOINT[1]

- Change from baseline to EoT (Week 12) in mean volume voided per micturition

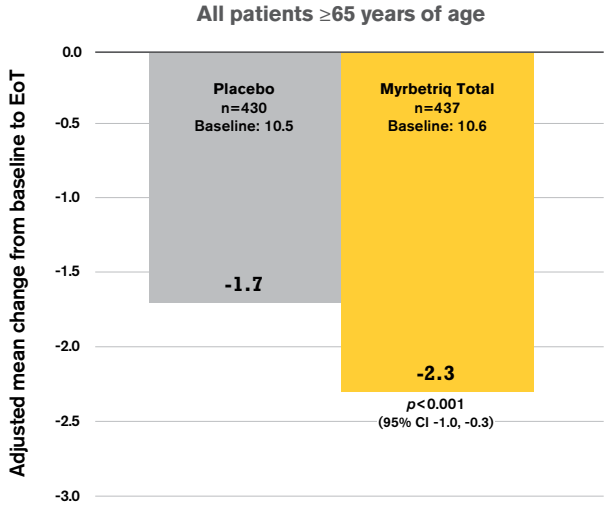
CO-PRIMARY ENDPOINT RESULTS[1]

Change from baseline to EoT (Week 12) in the mean number of incontinence episodes per 24 hours



- Myrbetriq significantly reduced the mean number of incontinence episodes per 24 hours

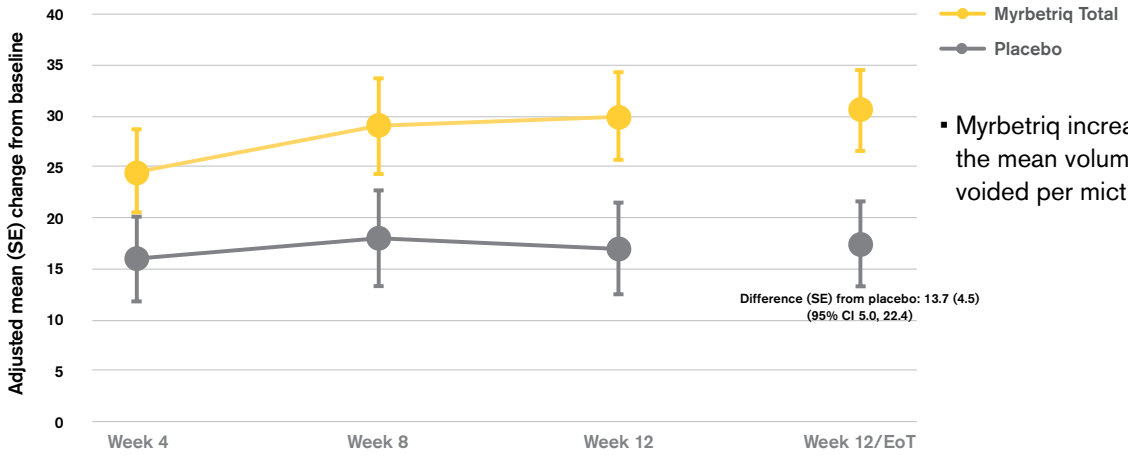
Change from baseline to EoT (Week 12) in the mean number of micturitions per 24 hours



- Myrbetriq significantly reduced the mean number of micturitions per 24 hours

SECONDARY ENDPOINT RESULTS

Mean volume voided per micturition at each visit



- Myrbetriq increased the mean volume voided per micturition

- 38% of elderly patients receiving Myrbetriq achieved zero incontinence (vs 30% in the placebo group) (OR 1.50; 95% CI 1.09, 2.06)

CI=confidence interval; OR=odds ratio; SE=standard error.

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SAFETY AND TOLERABILITY[1]

Percent of patients with treatment-emergent adverse events (TEAEs)* who received ≥1 dose of study medication

	Placebo (%)	Myrbetriq 25 mg (%)	Myrbetriq 50 mg (%)
Number of Patients	**442**	**226**	**219**
≥1 TEAE	39	44	50
Drug-related TEAEs[†]	13	21	17
Serious TEAEs	2.7	3.1	3.7
Serious drug-related TEAEs[†]	0.45	0	0
TEAEs leading to discontinuation	3.2	3.5	2.7
Drug-related TEAEs leading to discontinuation[†]	1.6	2.7	1.8
Cardiac disorders	1.1	0.88	3.2
Most frequent TEAEs[‡]			
Urinary tract infection[§]	7.0	7.1	4.1
Headache	2.7	6.6	3.7
Diarrhea	1.4	4.9	0.91
Fatigue	3.2	2.7	1.8
Upper respiratory tract infection	2.3	1.3	3.2
Nausea	1.4	3.1	0.46
Dizziness	1.6	0.44	2.3
Nasopharyngitis	2.3	1.3	0.91

*Treatment emergent adverse event (TEAE) is defined as an adverse event which started or worsened in the period from first double-blind medication intake until 30 days after the last double-blind medication intake.
[†]Possible or probable, as assessed by the investigator, or where relationship was missing.
[‡]Preferred term; affecting ≥2% of any treatment group.
[§]*Escherichia* urinary tract infection, streptococcal urinary tract infection, urinary tract infection, or urinary tract infection bacterial.

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IMPORTANT SAFETY INFORMATION (cont'd)

Since MYRBETRIQ is a moderate CYP2D6 inhibitor, the systemic exposure to CYP2D6 substrates is increased when co-administered with MYRBETRIQ. Therefore, appropriate monitoring and dose adjustment may be necessary, especially with narrow therapeutic index drugs metabolized by CYP2D6.

In clinical trials, the most commonly reported adverse reactions in adults (> 2% and > placebo) for MYRBETRIQ 25 mg and 50 mg versus placebo, respectively, were hypertension (11.3%, 7.5% vs 7.6%), nasopharyngitis (3.5%, 3.9% vs 2.5%), urinary tract infection (4.2%, 2.9% vs 1.8%), and headache (2.1%, 3.2% vs 3.0%).

In postmarketing experience, the following events have also occurred: atrial fibrillation, nausea, constipation, diarrhea, and dizziness.

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Reference: 1. Wagg A, Staskin D, Engel E, Herschorn S, Kristy RM, Schermer CR. Efficacy, safety, and tolerability of mirabegron in patients aged ≥65yr with overactive bladder wet: a phase IV, double-blind, randomised, placebo-controlled study (PILLAR). Eur Urol 2020;77(2):211-20.

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