68

Nitti V[1], Herschorn S[2], Auerbach S[3], Khullar V[4], Amarenco G[5], Blauwet M B[6], Boerrigter P[7], Hakimi Z[8], Siddiqui E[9], Martin N[10]

1. *NYU Langone Medical Center, Department of Urology, New York, NY, USA,* ***2.*** *University of Toronto, Division of Urology, Toronto, Canada,* ***3.*** *Hoag Memorial Presbyterian Hospital, Newport Beach, CA, USA,* ***4.*** *St Mary's Hospital, Imperial College, Urogynaecology Department, London, UK,* ***5.*** *Department of Neurologic Rehabilitation, Urodynamic and Neurophysiology Laboratory, Hôpital Rothschild, Assistance Publique-Hôpitaux de Paris, Paris, France,* ***6.*** *Astellas Pharma Global Development, Inc., Biostatistics, Deerfield, IL, USA,* ***7.*** *Astellas Pharma Global Development EU, Leiderdorp, The Netherlands,* ***8.*** *Astellas Pharma Europe, Leiderdorp, The Netherlands,* ***9.*** *Astellas Pharma Europe Ltd, Staines, Middlesex, UK,* ***10.*** *Astellas Scientific and Medical Affairs, Inc. Deerfield, IL, USA*

THE POTENT AND SELECTIVE B3-ADRENOCEPTOR AGONIST MIRABEGRON IMPROVES PATIENT-REPORTED OUTCOMES IN OVERACTIVE BLADDER–RESULTS FROM TWO PHASE III STUDIES

Hypothesis / aims of study

Oral antimuscarinic agents are currently the mainstay of pharmacotherapy for the treatment of overactive bladder (OAB). However, in some patients these agents elicit a suboptimal response or are associated with adverse events, such as dry mouth and constipation [1]. In the absence of another therapeutic class for the treatment of OAB symptoms, these patients either persist with an unsatisfactory treatment or discontinue pharmacotherapy. Mirabegron is a potent and selective β_3-adrenoceptor agonist developed for the treatment of OAB. Patient-reported outcomes (PROs) of symptom bother, health-related quality of life (HRQoL), treatment satisfaction and disease perception are becoming increasingly important in the assessment of treatments for OAB. Herein the findings on PROs related to symptom bother, health-related quality of life (HRQoL) and treatment satisfaction from two Phase III studies of mirabegron in North America (Study A; NCT00662909) [2] and Europe/Australia (Study B; NCT00689104) are reported [3].

Study design, materials and methods

Both studies were 12-week, multicentre, randomised, double-blind, parallel-group, placebo-controlled studies; although Study B also included an additional active-controlled group (tolterodine sustained release [SR] 4 mg). Patients with ≥3 months of OAB symptoms were enrolled into a 2-week, single-blind, placebo run-in period. Based on 3-day micturition diaries, patients with ≥8 micturitions/24 h and ≥3 urgency episodes/72 h (with or without incontinence) were randomised to receive placebo or mirabegron 50 mg or 100 mg once-daily, or, in Study B only, tolterodine SR 4 mg once-daily. Co-primary endpoints were changes from Baseline to Final Visit (end of treatment at 12 weeks) in the mean number of incontinence episodes/24 h and mean number of micturitions/24 h. Secondary endpoints included PROs, as assessed by the Overactive Bladder Questionnaire (OAB-q), Patient Perception of Bladder Condition (PPBC) and Treatment Satisfaction-Visual Analog Scale (TS-VAS). The required sample size was calculated to be 430 randomised patients in each treatment group assuming ≥85% of the randomised patients were evaluable and a dropout rate of 20% during the placebo run-in period.

Results

In Study A, 1328 patients were randomised and received study drug (placebo: n=453; mirabegron 50 mg: n=442; mirabegron 100 mg: n=433). Mean age was 60.1 years, 74.3% were female, 29.7% had urgency incontinence, 38.1% had mixed stress/urgency incontinence (urgency predominant) and 32.2% had frequency without incontinence. In Study B, 1978 patients were randomised and received study drug (placebo: n=494; mirabegron 50 mg: n=493; mirabegron 100 mg: n=496; tolterodine SR 4 mg: n=495). Mean age was 59.1 years, 72.2% were female, 39.5% had urgency incontinence, 22.7% had mixed stress/urgency incontinence with urgency predominant and 37.8% had frequency without incontinence. At 12 weeks (or Final Visit), the 50 mg and 100 mg mirabegron doses demonstrated significant improvements in the co-primary efficacy endpoints and PROs (OAB-q, PPBC, and TS-VAS) compared with placebo in both studies (Table); improvements in PRO endpoints were similar to tolterodine in Study B (data not shown) which supports the validity of the study design.

Interpretation of results

In these two large Phase III studies in OAB patients, significant improvements in OAB symptoms with mirabegron 50 mg and 100 mg once-daily were associated with significant improvements in PROs compared with placebo over 12 weeks of treatment. Patients receiving mirabegron at 50 and 100mg doses experienced greater improvements in treatment satisfaction, HRQoL total and symptom bother, and patients' perception of bladder condition compared with placebo. The improvement in PROs with both 50 mg and 100 mg doses of mirabegron can be attributed to its efficacy and safety profile and reflects clinically meaningful improvements in patients with OAB.

Concluding message

In patients with OAB, mirabegron 50 mg and 100 mg was associated with significant improvements in efficacy, measured objectively and using PROs for patients' perception of disease, treatment satisfaction, symptom bother and HRQoL compared with placebo. These results demonstrate that the symptom improvement measured objectively in these OAB patients also translated into an improvement in Patient Reported Outcomes and HRQoL and overall is reflective of a clinically meaningful improvement with mirabegron treatment.

Adjusted mean* (standard error) change from Baseline to Final Visit		
Endpoints	**Study A (North America; n=1328)**	**Study B (Europe/Australia; n=1978)**

	Placebo	**mirabegron**		**Placebo**	**mirabegron**	
		50 mg	**100 mg**		**50 mg**	**100 mg**
Co-primary endpoints						
Mean number of incontinence episodes/24 h[§]	–1.13 (0.112)	–1.47[†] (0.114)	–1.63[†] (0.117)	–1.17 (0.113)	–1.57[†] (0.113)	–1.46[†] (0.115)
Mean number of micturitions/24 h[§]	–1.05 (0.132)	–1.66[†] (0.133)	–1.75[†] (0.135)	–1.34 (0.110)	–1.93[†] (0.111)	–1.77[†] (0.110)
PRO secondary endpoints						
Treatment satisfaction (TS-VAS)[‖]	0.70 (0.155)	1.55[†Ψ] (0.156)	2.09[†Ψ] (0.159)	1.89 (0.146)	2.55[†Ψ] (0.149)	2.66[†Ψ] (0.146)
Symptom bother (OAB-q)[§]	–11.0 (0.97)	–17.0[†Ψ] (0.98)	–20.0[†Ψ] (0.99)	–14.9 (0.84)	–19.6[†Ψ] (0.85)	–19.9[†‡] (0.84)
HRQoL total score (OAB-q)[‖]	10.7 (0.89)	14.8[†‡] (0.90)	17.3[†‡] (0.90)	13.7 (0.76)	16.1[†Ψ] (0.77)	17.0[†Ψ] (0.77)
PPBC[§]	–0.5 (0.05)	–0.7[†Ψ] (0.05)	–0.8[†Ψ] (0.05)	–0.8 (0.05)	–1.0[†‡] (0.06)	–1.1[†‡] (0.05)
*Least squares mean adjusted for Baseline, gender and geographical region; [†]p<0.05 versus placebo with[Ψ] or without[‡] multiplicity adjustment; [§]Negative change indicates improvement; [‖]Positive change indicates improvement						

References

1. Chapple CR, et al. Eur Urol 2008; 54:543-62
2. Nitti V, et al. Neurourol Urodyn 2011; 30: 927–929 Abstract 92
3. Khullar V, et al. Presented at the 41st Annual Meeting of the International Continence Society, Glasgow, UK, August–September 2011. Abstract 328

Disclosures

Funding: This study was funded by Astellas Pharma Europe B.V.and Astellas Pharma Global Development, Inc. **Clinical Trial:** Yes **Public Registry:** Yes **Registration Number:** NCT00662909, NCT00689104 **RCT:** Yes **Subjects:** HUMAN **Ethics Committee:** The protocol was reviewed by an Independent Ethics Committee or Institutional Review Board for each study site. In the EU and North America, approval for the protocol was obtained from the relevant competent authorities prior to study initiation. **Helsinki:** Yes **Informed Consent:** Yes