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RANDOMISED, DOUBLE-BLIND, PLACEBO-CONTROLLED PHASE III STUDY TO ASSESS THE EFFICACY AND SAFETY OF MIRABEGRON 25 MG AND 50 MG ONCE-DAILY IN OVERACTIVE BLADDER (OAB)

Hypothesis / aims of study

Mirabegron, a potent and selective β_3-adrenoceptor agonist, is the first in a new class of agents developed for the treatment overactive bladder (OAB) [1], which mediates relaxation of the detrusor during the storage phase of the micturition cycle, improving bladder storage capacity without impeding bladder voiding. Two, large-scale, 12-week, Phase III studies have demonstrated the efficacy and tolerability of mirabegron at doses of 50 mg and 100 mg in patients with OAB in the US, Canada, Europe and Australia [2,3]. The study described herein was conducted to assess the efficacy of mirabegron 25 mg and 50 mg once-daily versus placebo in patients with OAB. One of the aims of this study was to confirm the efficacy of mirabegron 25 mg and to establish a potentially lowest effective dose.

Study design, materials and methods

This randomised, parallel-group, placebo-controlled, double-blind, multicentre, multinational study was conducted at 151 sites in Europe (56 sites) and North America (95 sites). Patients ≥18 years of age with symptoms of OAB for ≥3 months were enrolled in a 2-week, single-blind, placebo run-in. Over a 3-day micturition diary period, patients with an average ≥8 micturitions/24 h and ≥3 urgency episodes/72 h (with or without incontinence) were randomly assigned in a 1:1:1 ratio to receive once-daily treatment with mirabegron 25 mg, mirabegron 50 mg, or placebo for 12 weeks. Co-primary endpoints were changes from Baseline to Final Visit (End of Treatment) in the mean number of incontinence episodes/24 h and micturitions/24 h. Key secondary endpoints included, for example, changes from Baseline to Final Visit in mean volume voided/micturition and change from Baseline to Week 4 in mean number of incontinence episodes/24 h. Additional secondary endpoints included for example changes from Baseline to Final Visit in the Overactive Bladder Questionnaire (OAB-q) and Treatment Satisfaction-Visual Analog Scale (TS-VAS). Safety assessments included adverse event (AE) reporting, laboratory assessment, vital signs, ECG, and post-void residual (PVR) volume. The Safety Analysis Set (SAF) included all randomised patients who took ≥1 dose of study drug; the Full Analysis Set (FAS) included all SAF patients who had a micturition measurement in the Baseline diary and ≥1 micturition measurement post-Baseline. The FAS Incontinence (FAS-I) set included all FAS patients with ≥1 incontinence episode at Baseline. Assuming a dropout rate of about 28% during placebo run-in, 1821 patients were to be enrolled. The sample size of 437 patients was calculated based on an effect size of 0.7, a standard deviation of 2.7, a power of 90%, a two-sided confidence level of 0.025, and a drop-out rate after randomization of 15%.

Results

A total of 1306 patients were randomised to receive placebo (n=433), mirabegron 25 mg (n=433), and mirabegron 50 mg (n=440). Demographics and Baseline characteristics were consistent across treatment groups in the SAF. Overall, 68.7% of patients were female, mean age was 59.0 years, and 90.7% were Caucasians. OAB history characteristics were generally comparable across all treatment groups. Both mirabegron 25 and 50 mg groups demonstrated statistically significant improvements for the co-primary efficacy endpoints (Table). For secondary variables, the mirabegron 50 mg group demonstrated statistically significant improvements versus placebo in change from Baseline to Final Visit in mean volume voided/micturition and change from Baseline to Week 4 in mean number of incontinence episodes/24 h (Table). Both mirabegron groups also demonstrated statistically significant improvements versus placebo in mean number of micturitions/24 h at Week 8, mean number of incontinence episodes/24 h at Weeks 8 and 12, and mean number of urgency incontinence episodes/24 h at Weeks 4, 8, and 12. The mirabegron 50 mg group also demonstrated statistically significant improvements versus placebo at Weeks 8 and 12 in mean volume voided/micturition and mean level of urgency, and at Weeks 4 and 8 for urgency episodes (grades 3 or 4). For the TS-VAS, both mirabegron groups demonstrated statistically significant improvements from Baseline to Final Visit versus placebo. For the OAB-q, the mirabegron 50 mg group demonstrated statistically significant improvements from Baseline to Final Visit versus placebo in the Symptom Bother scale. Mirabegron was well tolerated and the incidence of treatment-emergent AEs (TEAEs) was similar between groups (50.1%, 48.6%, and 47.3% for the placebo, mirabegron 25 mg and mirabegron 50 mg groups, respectively). Common treatment-related TEAEs (occurring in ≥ 2% of patients in any treatment group) included hypertension (based on medDRA preferred term) in 5.3%, 6.9%, and 7.0%, and headache in 2.1%, 0.9% and 0.9%, in the placebo, mirabegron 25 mg and mirabegron 50 mg groups, respectively. There were no cases of urinary retention in mirabegron-treated patients and no patients had a significant increase in PVR that required intervention.

Interpretation of results

Both mirabegron 25 and 50 mg groups demonstrated statistically significant improvements in the co-primary efficacy variables versus placebo. Mirabegron 50 mg was effective at the first measured time post-dose (4 weeks), as measured by a significant reduction in incontinence episodes/24 h, and these effects were maintained throughout the duration of the study (12 weeks). These results provide evidence that mirabegron results in a clinically meaningful benefit to patients at both 25 mg and 50 mg dose, although greater efficacy was observed with mirabegron 50 mg.

Concluding message

In patients with OAB, mirabegron 25 mg and 50 mg were associated with significant improvements in efficacy measures of micturition frequency and incontinence episodes. Mirabegron 50 mg provides a more comprehensive efficacy benefit across the cardinal objective and subjective assessments that comprise the OAB syndrome. In this study, mirabegron was safe and well tolerated.

Table: Efficacy results in the FAS and FAS-I population

	mirabegron 25 mg			**mirabegron 50 mg**		
	Mean difference versus placebo	**SE**	***P*-value**	**Mean difference versus placebo**	**SE**	***P*-value**
Co-primary endpoints						
FAS population	N=410			N=426		
Change from Baseline to Final Visit in mean number of micturitions/24 h	–0.47	0.176	0.007	–0.42	0.174	0.015
FAS-I population	N=254			N=257		
Change from Baseline to Final Visit in mean number of incontinence episodes/24 h	–0.40	0.174	0.005	–0.42	0.173	0.001
Key secondary efficacy endpoints						
FAS population	N=410			N=426		
Change from Baseline to Final Visit in mean volume voided/micturition	4.6	3.16	0.15	12.4	3.13	<0.001
FAS-I population	N=254			N=255		
Change from Baseline to Week 4 in mean number of incontinence episodes/24 h	–0.34	0.172	0.039	–0.51	0.171	<0.001

References

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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

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