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EFFICACY OF MIRABEGRON IN PATIENTS WITH OVERACTIVE BLADDER (OAB): PRE-SPECIFIED ANALYSIS OF THREE RANDOMISED, DOUBLE-BLIND, PLACEBO-CONTROLLED, PHASE III STUDIES

Hypothesis / aims of study

Current pharmacological approaches to treating overactive bladder (OAB) mainly depend on the use of oral antimuscarinic agents. In some patients these agents are associated with suboptimal efficacy or adverse events, such as dry mouth and constipation [1]. The lack of an alternative therapeutic class means that these patients either have to persist with an unsatisfactory treatment or discontinue therapy. Mirabegron is a potent and selective β_3-adrenoceptor agonist that has been approved in Japan for the treatment of OAB and may provide a new therapeutic option in such patients. A recent post hoc analysis from a phase III study supports the improved efficacy of mirabegron in patients who discontinued prior antimuscarinic agents due to inadequate efficacy or poor tolerability [2]. The objective of this analysis was to examine the efficacy of mirabegron across three phase III OAB studies (NCT00689104, NCT00662909 and NCT00912964) including antimuscarinic-naïve patients, as well as patients who discontinued prior antimuscarinics due to insufficient efficacy or poor tolerability.

Study design, materials and methods

This is a pre-specified pooled analysis of three randomised, double-blind, placebo-controlled studies in which the efficacy of mirabegron (50 or 100 mg) was compared with placebo for the co-primary endpoints: change from Baseline to Final Visit in mean number of micturitions per 24 h and in the mean number of incontinence episodes/24 h. The Full Analysis Set (FAS) population included randomised patients who took at least one dose of study drug and who had a Baseline micturition measurement and at least 1 post-Baseline micturition measurement, and was used to evaluate the change from Baseline to Final Visit in the mean number of micturitions/24 h. The FAS-incontinence population (FAS-I) included FAS patients who also had at least one incontinence episode at Baseline and was used to evaluate change from Baseline to Final Visit in the mean number of incontinence episodes/24 h. Key secondary endpoints included change from Baseline to Final Visit in mean volume voided/micturition, change from Baseline to Week 4 for the co-primary endpoints, and change from Baseline to Final Visit for the mean number of urgency incontinence episodes/24 h, urgency episodes (Patient's Perception of Intensity and Urgency Scale [PPIUS] grade 3 or 4)/24 h and level of urgency (based on PPIUS). The adjusted mean difference versus placebo for change from Baseline and corresponding 95% CI were generated from an ANCOVA model with treatment group, gender and study as fixed factors and Baseline as a covariate. In addition for incontinence episode endpoints, hypothesis testing was performed using a stratified rank ANCOVA. Assuming that at least 85% of the randomised patients were evaluable, approximately 430 patients were to be randomised to each treatment group in each study, assuming a dropout rate of approximately 20% during the placebo run-in period.

Results

Overall there were 3542 patients included in the FAS population (placebo n=1328; mirabegron 50 mg n=1324; and mirabegron 100 mg n=890) and 2317 in the FAS-I population (placebo n=878; mirabegron 50 mg n=862; mirabegron 100 mg n=577). Patients in the FAS population were predominantly female (~72%), mean age ~59 years. Approximately 52% of patients in each treatment group in the FAS had taken previous OAB drugs before enrolling in the present studies. Among patients with previous OAB medication, reason for discontinuation (insufficient efficacy or poor tolerability) of previous OAB medication was similar across all treatment groups. Each mirabegron group demonstrated a statistically significant reduction from Baseline to Final Visit in the co-primary endpoints (Table). In addition both doses of mirabegron significantly improved the co-primary endpoints at Week4, and improved mean volume voided/24 h, mean level of urgency, mean number of urgency incontinence episodes/24 h, and urgency episodes (grade 3 or 4) compared with placebo (Table).

Interpretation of results

This pooled analysis of data from three phase III trials demonstrated similar statistically significant and clinically meaningful improvements for mirabegron 50 mg and 100 mg compared with placebo for the co-primary efficacy endpoints of change from Baseline to Final Visit in mean number of incontinence episodes/24 hours and mean number of micturitions/24 h. In addition both doses of mirabegron significantly improved secondary endpoints, showing reductions in mean number of incontinence episodes/24 h and micturitions/24 h as early as Week 4 and improving measures of urgency and mean volume voided compared with placebo.

Concluding message

In this large pool of OAB patients, mirabegron 50 mg and 100 mg demonstrated significant improvement in OAB symptoms compared with placebo.

Table: Overview of co-primary and key secondary efficacy endpoints: adjusted mean* (standard error) change from Baseline*			
	Placebo	**mirabegron 50 mg**	**mirabegron 100 mg**
Co-primary efficacy endpoints at Final Visit			
Number of Incontinence Episodes/24 h (FAS-I)	N=878 -1.10 (0.07)	N=862 -1.49 (0.07)†	N=577 -1.50 (0.08)†
Number of Micturitions/24 h (FAS)	N=1328 -1.20 (0.07)	N=1324 -1.75 (0.07)†	N=890 -1.74 (0.09)†
Key Secondary efficacy endpoints			
FAS population	*N=1328*	*N=1324*	*N=890*
Volume Voided per Micturition at Final Visit	9.4 (1.29)	21.4 (1.30)†	21.7 (1.64)†
Number of Micturitions/24 h at Week 4	-0.77 (0.07)	-1.17 (0.07)†	-1.33 (0.08)†
Level of Urgency at Final Visit	-0.15 (0.02)	-0.26 (0.02)†	-0.26 (0.02)†
Number of Urgency Episodes (Grade 3 or 4)/24 h at Final Visit	-1.29 (0.09)	-1.93 (0.09)†	-1.89 (0.12)†
FAS-I population	*N=878*	*N=862*	*N=577*
Number of Incontinence Episodes/24 h at Week 4	-0.67 (0.07)	-1.12 (0.07)†	-1.09 (0.09)†
Number of Urgency Incontinence Episodes/24 h at Final Visit	-0.98 (0.07)	-1.38 (0.06)†	-1.38 (0.08)†
* Estimates are based on an analysis of covariance (ANCOVA) model, which included treatment group, gender and study as fixed factors and baseline as a covariate.; †p<0.001 versus placebo with multiplicity adjustment. P values for incontinence episode endpoints are from a stratified rank ANCOVA model and p-values for other efficacy endpoints are from the ANCOVA model			

References

1. Chapple CR et al. Eur Urol 2008; 54:543-62
2. Khullar V et al. Presented at the 27th Annual Meeting of the European Association of Urology, Paris, France, February 2012

Disclosures

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