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POST HOC RESPONDER ANALYSES OF SUBJECTIVE AND OBJECTIVE OUTCOMES USING POOLED DATA FROM THREE RANDOMISED PHASE III TRIALS OF MIRABEGRON IN PATIENTS WITH OVERACTIVE BLADDER

Hypothesis / aims of study
In a pre-defined, pooled analysis of three large, randomised, double-blind, placebo-controlled, 12-week Phase III trials (NCT00689104, NCT00662909, NCT00912964) in patients with overactive bladder (OAB), the β_3-adrenoceptor agonist mirabegron, at a dose of 50 mg once-daily, resulted in statistically significant improvements vs placebo from baseline to Final Visit (End-of-Treatment) in objective outcome measures including number of incontinence episodes/24 hours as well as in subjective patient reported outcomes (PROs) including the patient perception of bladder condition (PPBC) and subsets of the overactive bladder questionnaire (OAB-q) measuring total health-related quality of life [HRQoL], and symptom bother. This post-hoc analysis assessed the proportion of patients who were simultaneously responders for incontinence episodes and various PROs at Final Visit in order to understand how improvements in objective measures correlate with the patient's experience as measured by validated and standard PRO instruments and to identify whether there is overall directional consistency in the responsiveness of PROs to treatment effect.

Study design, materials and methods
The Full Analysis Set (FAS) in each of the three studies comprised all randomised patients who took ≥1 dose of study drug and had micturition measurements in a 3-day micturition diary at baseline and at least one post-baseline diary; the FAS-Incontinence (FAS-I) also had ≥1 incontinence episode in the 3-day baseline diary. A responder for incontinence episodes was defined as a patient with a ≥50% reduction in incontinence episodes/24 hours from baseline to Final Visit; for PROs a responder was defined as a patient who achieved a change from baseline to Final Visit that exceeded the Minimally Important Difference (MID). MID has been defined as a 10-point change in the overall OAB-q and its subscores (HRQoL and symptom bother) and a 1-point change in PPBC. Data for the mirabegron 50 mg and placebo arms of the three Phase III studies were pooled and analysed to determine responder rates for incontinence frequency and PROs, individually and simultaneously (double and triple combinations; see Table). Assuming that at least 85% of the randomised patients were evaluable, approximately 430 patients were to be randomised to each treatment group within each study.

Results
The pooled placebo and mirabegron 50 mg groups consisted of 1328 and 1324 patients, respectively, in the FAS, and 878 and 862, respectively, in the FAS-I. Mirabegron 50 mg consistently demonstrated greater improvement than placebo for each of the responder analyses performed, whether assessing individual objective and subjective outcomes or combinations of these endpoints (Table). These improvements vs placebo were statistically significant for all double and triple responder analyses performed and for all single responder analyses except PPBC. The difference vs placebo in the responder rates for each of the double responder analyses was higher than the differences observed in the single responder analyses.

Interpretation of results
This post-hoc analysis demonstrates that improvement with mirabegron 50 mg once-daily in the objective outcome measure of incontinence episodes in patients with OAB translates into improvements in different subjective measures of patient well-being and quality of life. Because instruments that measure PROs measure different components of the response of patients, heterogeneity in the responsiveness of domains to treatment effect has been observed. However, the triple responder analyses conducted here, combining the objective outcome of incontinence episodes with two different PRO measures, suggest directional consistency in the effect of mirabegron on these PROs.

Concluding message
In this post-hoc analysis of pooled data from three large, randomised, Phase III trials, mirabegron 50 mg once-daily demonstrated that improvements on objective outcome measures are mirrored by improvements in clinically relevant PRO measurements, including OAB-q and PPBC using MID responder analyses.

Table: Single, double and triple responder analyses for the pooled mirabegron 50 mg group vs placebo, where a responder is defined as a patient who achieves the given improvement(s) between baseline and Final Visit

	Difference vs placebo, % (95% CIs)†	Odds ratio (95% CIs)‡	P-value‡
Single responder criterion			
≥50% reduction in incontinence episodes/24 h (FAS-I)	9.9% (5.5%, 14.4%)	1.54 (1.26, 1.89)	<0.001
MID in Symptom bother (FAS)	8.3% (4.5%, 12.1%)	1.43 (1.21, 1.70)	<0.001
MID in total HRQoL (FAS)	7.9% (4.0%, 11.8%)	1.46 (1.23, 1.74)	<0.001
MID in PPBC (FAS)	2.8% (-1.2%, 6.7%)	1.18 (0.99, 1.39)	0.059
Double responder criteria			
≥50% reduction in incontinence episodes/24	15.2% (10.4%, 20.0%)	1.87 (1.53, 2.29)	<0.001

h (FAS-I) *and* MID in Symptom bother (FAS)			
≥50% reduction in incontinence episodes/24 h (FAS-I) *and* MID in total HRQoL (FAS)	10.9% (6.1%, 15.7%)	1.60 (1.30, 1.97)	<0.001
≥50% reduction in incontinence episodes/24 h (FAS-I) *and* MID in PPBC (FAS)	6.8% (1.9%, 11.6%)	1.37 (1.11, 1.68)	0.003
Triple responder criteria			
≥50% reduction in incontinence episodes/24 h (FAS-I) *and* MID in Symptom bother (FAS) *and* MID in PPBC (FAS)	9.1% (4.2%, 13.9%)	1.55 (1.24, 1.93)	<0.001
≥50% reduction in incontinence episodes/24 h (FAS-I) *and* MID in total HRQoL (FAS) *and* MID in PPBC (FAS)	8.4% (3.6%, 13.2%)	1.51 (1.20, 1.90)	<0.001

CI, confidence interval
FAS, Full analysis set; all randomized patients who took at ≥1 dose of study drug and had micturition measurements in a 3-day micturition diary at baseline and ≥1 post-baseline diary
FAS-I, FAS-Incontinence; all FAS patients who also had ≥1 incontinence episode at baseline
HRQoL, health related quality of life
MID, minimally important difference (the smallest change in a PRO questionnaire score considered to be meaningful or important to a patient [≥10 points in HRQoL and Symptom Bother and ≥1 point in PPBC])
OAB-q, overactive bladder questionnaire
PPBC, patient perception of bladder condition
†95% 2-sided CIs for the differences of the proportions of responders are based on normal approximation
‡Odds ratios, corresponding 2-sided 95% CIs and P-values are derived from a logistic regression model including treatment group, gender, study and baseline value(s)

Disclosures
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