The Effect of Elective Sham Dose Escalation on the Placebo Response During an Antimuscarinic Trial for Overactive Bladder Symptoms

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Purpose: We analyzed the effects of baseline symptom severity and placebo response magnitude on the decision to dose escalate in a 12-week, randomized, double-blind, flexible dose antimuscarinic trial of subjects with overactive bladder symptoms.

Materials and Methods: Data from the placebo arm of the trial were used for this post hoc analysis. Subjects could elect dose escalation at week 2. Those in the placebo arm received sham escalation.

Results: Most placebo treated subjects who continued to week 2 elected dose escalation (75% or 325 of 435). Overactive bladder symptoms at baseline were similar between placebo escalators and nonescalators. Nonescalators showed a significantly larger placebo response than escalators, as measured by improvements in bladder diary end points and patient reported outcomes, and by the incidence rate of adverse events before and after sham escalation.

Conclusions: These findings suggest that the decision to dose escalate among placebo treated subjects is independent of baseline symptom severity but may be influenced by the placebo response magnitude for efficacy assessment and adverse events. Placebo nonescalators showed a rapid, large placebo response while placebo escalators showed a smaller placebo response even after sham escalation. These observations may have important implications for the design and interpretation of flexible dose trials using a placebo control.

Key Words: urinary bladder, overactive; fesoterodine; muscarinic antagonists; placebo effect; dose-response relationship, drug

Abbreviations and Acronyms

AE = adverse event
OAB = overactive bladder
PBO = placebo
PBO-E = placebo escalator group
PBO-NE = placebo nonescalator group
PPBC = Patient Perception of Bladder Condition
UPS = Urinary Perception Scale
USS = Urinary Sensation Scale
UUI = urgency urinary incontinence

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ANTIMUSCARINICS are first line pharmacological treatment for OAB.[1,2] Newer agents are available in 2 doses with flexible dosing recommendations.[3–5] For each of these agents PBO controlled, fixed dose trials have shown a substantial PBO response, which is typical of OAB trials of antimuscarinic treatment.[6,7] Fixed dose studies are fairly straightforward to interpret but may not reflect the clinical practice of flexible dose escalation.

PBO controlled, flexible dose trials, which use sham dose escalation in the PBO arm to maintain blinding, have also been done to assess the efficacy, safety and tolerability of antimuscarinic agents.[8–12] Flexible dose trials may be more representative of clinical practice but they may not be easy to interpret. For example, there may be differences in the proportion of patients on PBO and active treatment who request dose escalation and the

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factors motivating this decision. Also, little is known regarding potential differences in the PBO response between subjects who do vs do not request dose escalation. Identifying differences in the response between PBO-E and PBO-NE, and understanding the reasons for these differences are critical for accurately interpreting flexible dose trials.

We characterized the interaction between the PBO response and the decision to dose escalate by identifying differences between PBO-E and PBO-NE in baseline characteristics, and in efficacy, safety and tolerability before and after the decision to dose escalate using OAB treatment as an example.

MATERIALS AND METHODS

Study Design

This was a post hoc analysis of data from the PBO arm of a 12-week, randomized, double-blind, PBO controlled study of flexible dose fesoterodine in subjects with OAB (ClinicalTrials.gov NCT00536484). Full methodological details of the trial were described previously.[10] Briefly, subjects were randomized 1:1 to receive 4 mg fesoterodine or PBO ingested within 4 hours of bedtime. At week 2 after consultation with the investigator on efficacy and tolerability subjects could elect to maintain the 4 mg dose or escalate to an 8 mg dose. No additional dose adjustments were permitted. Sham escalation was used for PBO subjects who requested a dose increase. Only those randomized to PBO were included in this subset analysis.

The trial was approved by the appropriate institutional review boards and independent ethics committees, and was done in accordance with International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use good clinical practice guidelines. All subjects provided written informed consent before entering the trial. Participants were provided with information on antimuscarinic efficacy and safety (AEs), and informed that this was a randomized, PBO controlled trial.

Subjects

Men and women 18 years old or older were eligible to participate if they reported a 3-month or greater history of OAB symptoms before screening, recorded a mean of 8 or greater micturitions per 24 hours and 3 or greater urgency episodes per 24 hours in a 3-day bladder diary at baseline, and rated the bladder condition at baseline as causing at least some moderate problems using the validated PPBC.[13]

Assessments

Efficacy. Subjects completed 3-day bladder diaries, PPBC[13] and UPS[14] at baseline, and weeks 2, 6 and 12. Subjects recorded all micturitions, including incontinence episodes. They rated the sensation associated with each micturition using the validated 5-point USS, including 1—no feeling of urgency, 2—mild feeling of urgency, 3—moderate feeling of urgency, 4—severe feeling of urgency and 5—unable to hold and urine leak).[15] Diary end points were the numbers of micturitions, urgency episodes, severe urgency episodes and UUI episodes per 24 hours. Urgency episodes were defined as micturitions with a USS score of 3 or greater while severe urgency episodes were considered micturitions with a USS score of 4 or greater. For PPBC subjects rated bladder related problems on a scale of 1—no problems to 6—severe problems. On UPS subjects rated the urgency associated with typical urination as 1—usually not able to hold urine, 2—usually able to hold urine until reaching a toilet if I go immediately and 3—usually able to finish what I am doing before going to the toilet.

Safety. Treatment emergent AE reports were recorded throughout the study, as were the investigator opinion of whether each event was treatment related. Reasons for study discontinuations were also recorded.

Statistical Analysis

Post hoc efficacy analysis was done using data on subjects who received 1 or more dose of study drug, had 1 or more baseline or post-baseline efficacy assessment and continued to the week 2 visit. Post hoc safety and tolerability analyses were performed using data on subjects who received 1 or more dose of study drug and continued to the week 2 visit. Statistical comparisons between PBO-E and PBO-NE in diary variables and patient reported outcomes at baseline, and weeks 2, 6 and 12 were done using an ANCOVA model with terms for center, treatment, baseline covariate and baseline by treatment interaction (diary variables) or using the Cochran-Mantel-Haenszel test with ridit scoring and stratified by center (patient re-

Table 1. *PBO-NE and PBO-E baseline demographic and clinical characteristics*

	PBO-NE		PBO-E	
No. subjects	110		325	
No. gender (%):				
F	98	(89)	265	(81.5)
M	12	(11)	60	(18.5)
Mean ± SD age (range)	59.9 ± 12.9 (24–85)		60.3 ± 12.9 (22–88)	
No. race (%):				
White	94	(86)	289	(89)
Black	13	(12)	24	(7)
Asian	1	(1)	2	(1)
Other	2	(2)	10	(3)
No. UUI (%)	56	(51)	201	(62)
Mean No. bladder diary variables/24 hrs:				
Micturitions	12.9		13.0	
UUI episodes*	2.1		2.3	
Urgency episodes*	9.2		9.2	
Severe urgency episodes*	4.3		4.8	
No. UPS (%):				
Not able to hold urine	30	(25.6)	97	(29.9)
Able to hold urine if going to toilet immediately	83	(70.9)	214	(66.0)
Able to finish task before going to toilet	4	(3.4)	13	(4.0)
No. PPBC problems (%):†				
Some minor	1	(0.9)	0	
Some moderate	58	(50.0)	149	(46.0)
Severe	44	(37.9)	124	(38.3)
Many severe	13	(11.2)	51	(15.7)

* In subjects who reported this symptom at baseline.
† No subject had no or some very minor problems.