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A PILOT STUDY TO ASSESS THE EFFECT OF TREATMENT WITH AN NK-1 RECEPTOR ANTAGONIST ON URGE URINARY INCONTINENCE SYMPTOMS

Hypothesis / aims of study
Preclinical evidence suggests that upregulation of tachykinin-mediated bladder/spinal reflex signaling may have an effect on the micturitions reflex. The objective of this study was to test the hypothesis that aprepitant, a central nervous system penetrant neurokinin-1 (NK-1)–receptor antagonist, may be efficacious for treatment of urge urinary incontinence (UUI) or overactive bladder (OAB).

Study design, materials and methods
A double-blind, randomized, placebo-controlled, parallel-group pilot study was conducted in postmenopausal women with a history of UUI or mixed incontinence (with predominantly UUI). Patients were assigned to receive 160 mg aprepitant (n = 61) or placebo (n = 64) once daily for 8 weeks following a 1-week placebo run-in period. The primary end point was percentage change from baseline in average daily micturitions assessed by a voiding diary. Secondary end points included urgency episodes, total urinary incontinence (UI), and UUI episodes.

Results
Primary and secondary end points are summarized in Table 1. Average daily micturitions were significantly decreased for patients treated with aprepitant compared with the average for placebo at 8 weeks: the between-group treatment difference expressed as the percentage change from baseline and 95% confidence interval was –6.8, [95% –12.5, –1.1] (P = 0.019). Average daily urgency episodes were also significantly reduced compared with the average for placebo (P = 0.049); the average numbers of daily UUI and total UI episodes also were reduced, although differences were not statistically significant. Aprepitant was generally well tolerated.

Table 1. Average percent change and change from baseline in efficacy endpoints (sum of occurrences over a diary week divided by the number of days of diary completion) at 8 weeks of treatment

Daily Occurrences of End Points	Aprepitant	Placebo	Estimated Treatment Difference* Aprepitant – Placebo (95% CI)	*P*-Value
Micturitions				
Percent change from baseline	–10.2 ± 17.9	–3.3 ± 16.3	–6.8 (–12.5, –1.1)	0.019
Change from baseline	–1.3 ± 1.9	–0.4 ± 1.7	–0.9 (–1.5, –0.3)	0.003
Urge incontinence episodes				
Percent change from baseline	–50.4 ± 45.2	–35.6 ± 44.4	–14.5 (–30.2, 1.1)	0.070
Change from baseline	–1.5 ± 1.6	–1.1 ± 2.0	–0.4 (–1.0, 0.3)	0.234
Total incontinence episodes				
Percent change from baseline	–48.3 ± 45.9	–36.3 ± 43.7	–11.8 (–27.6, 4.1)	0.145
Change from baseline	–1.5 ± 1.7	–1.2 ± 2.1	–0.3 (–1.0, 0.3)	0.323
Urgency episodes				
Percent change from baseline	–23.2 ± 32.2	–9.3 ± 40.0	–13.2 (–26.3, –0.1)	0.049
Change from baseline	–1.8 ± 2.5	–0.5 ± 2.6	–1.2 (–2.1, –0.3)	0.007

*Computed from a statistical model adjusting for investigator sites
Data are shown as mean ± standard deviation

Interpretation of results
To our knowledge, this is the first clinical trial to demonstrate efficacy for an NK-1–receptor antagonist in UUI. The overall magnitude of treatment benefit (e.g., between-group difference of 6.8% for average daily micturitions) is similar to those reported for anticholinergics, the current standard of therapy in OAB/UUI. Aprepitant also significantly reduced the incidence of urge episodes over the 8 weeks of treatment. In addition, aprepitant was superior to placebo on patient-perceived improvement as well as bother of urinary symptoms. Taken together, the consistency of the data supports the efficacy of an NK-1 receptor antagonist in treatment of UUI.

Concluding message
The results of this study suggest that NK-1 receptor antagonism may represent a novel therapeutic approach to treating OAB/UUI.

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CLINICAL TRIAL REGISTRATION: **This clinical trial has not yet been registered in a public clinical trials registry.**

HUMAN SUBJECTS: **This study was approved by the IRB at each of 26 study sites and followed the Declaration of Helsinki Informed consent was obtained from the patients.**