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RESULTS OF A PHASE 1B MULTICENTER STUDY EVALUATING THE SAFETY AND POTENTIAL ACTIVITY OF TWO ESCALATING DOSES OF HMAXI-K GENE TRANSFER BY DIRECT INJECTION INTO THE BLADDER WALL IN FEMALE PARTICIPANTS WITH IDIOPATHIC (NON-NEUROGENIC) OVERACTIVE BLADDER SYNDROME AND DETRUSOR OVERACTIVITY: DOUBLE BLIND, IMBALANCED PLACEBO CONTROLLED DESIGN WITHIN 2 SEQUENTIAL ACTIVE TREATMENT GROUPS

Hypothesis / aims of study

hMaxi-K is currently the only gene therapy approach to treat benign urologic conditions with FDA approved IND's. hMaxi-K is a plasmid vector expressing the gene for Maxi-K, a potassium channel involved in regulation of smooth muscle tone which has been demonstrated to play a key role in normal bladder physiology in animal studies. This is the first study to evaluate the safety and effectiveness of direct bladder wall injections of this plasmid to treat the symptoms of overactive bladder and urinary incontinence in women.

Study design, materials and methods:

Primary Objective: To evaluate occurrence of adverse events and their relationship to hMaxi-K treatment following multiple intramuscular (IM) injections into the bladder wall of two dose levels (16000 µg and 24000 µg) in women with moderate OAB/DO of ≥ six months duration.

Secondary Objective: To evaluate the following additional safety parameters (changes from baseline compared to placebo): Clinical laboratory tests, Electrocardiogram changes and Physical Examination.

To evaluate efficacy parameters (change from baseline compared to placebo) that include: number of micturitions per day, volume per micturition, urgency episodes, incontinence episodes, pad weight, number of uninhibited contractions during cystometrogram (CMG) and other general and bladder-specific quality of life assessments.

Methodology: This was a double blind, imbalanced placebo controlled sequential dose trial.

Participants were healthy women of 18 years of age or older, of non-childbearing potential, with moderate OAB/DO of ≥ six months duration with at least one of the following: frequent micturition ≥ 8 times per day, symptoms of urinary urgency or nocturia (the complaint of waking at night two or more times to void), urge urinary incontinence (five or more incontinence episodes per week), and detrusor overactivity with ≥ 1 uncontrolled phasic contraction(s) of the detrusor of at least 5 cm/ H₂O pressure documented on CMG. All of the participants had failed prior treatment with anticholinergics. Four had failed onabotulinumtoxinA therapy.

Participants were randomly assigned to either hMaxi-K at one of two doses (16,000 mcg, or 24,000 mcg, or placebo. Treatment was administered as 20-30 IM injections into the bladder wall during cystoscopy. Participants were seen 8 times within a 24-week period with a study follow-up of 18 months. All reported adverse events occurring after study drug dosing were recorded. Complex CMG's were done at screening visit 1A (week – 1) and at week 4 (visit 5) and week 24 (visit 8) post-injection. Post void residual volume (PVR) was measured at every visit with a Bladderscan®.

The data to assess efficacy were evaluated using summary descriptive statistics by treatment group (combined placebo vs 2 active treatment groups and combined placebo vs combined treatment groups). Linear mixed effect models were used to estimate difference of changes from baseline between placebo and active treatment and to test whether there was dose-response for different outcomes. Generalized estimating equation (GEE) models were to be used to estimate effects for the binary endpoints.

Results

There were 6 participants who received 16000 mcg, 3 participants who received 24000 mcg and 4 participants who received placebo. In both active treatment groups, the majority of adverse events (AEs) were mild in severity and all were considered unrelated to study drug. Two women had mild unrelated UTIs post-treatment with hMaxi-K: one receiving 24000 mcg at month after dosing and the other receiving 16000 mcg at 6 months after dosing. There was one unrelated serious AE reported in the 16000 mcg group; exacerbation of pre-existing asthma due to the cold weather which required an ER visit and resolved after asthma treatment was given. No subject was discontinued due to an AE and all enrolled subjects completed the 6 month trial. In addition, during the 18 month long-term post study safety follow-up, no issues were reported in the subjects followed to date (9 of 13 completed 18 month follow-ups; 13 of 13 completed the 12 month follow-ups).

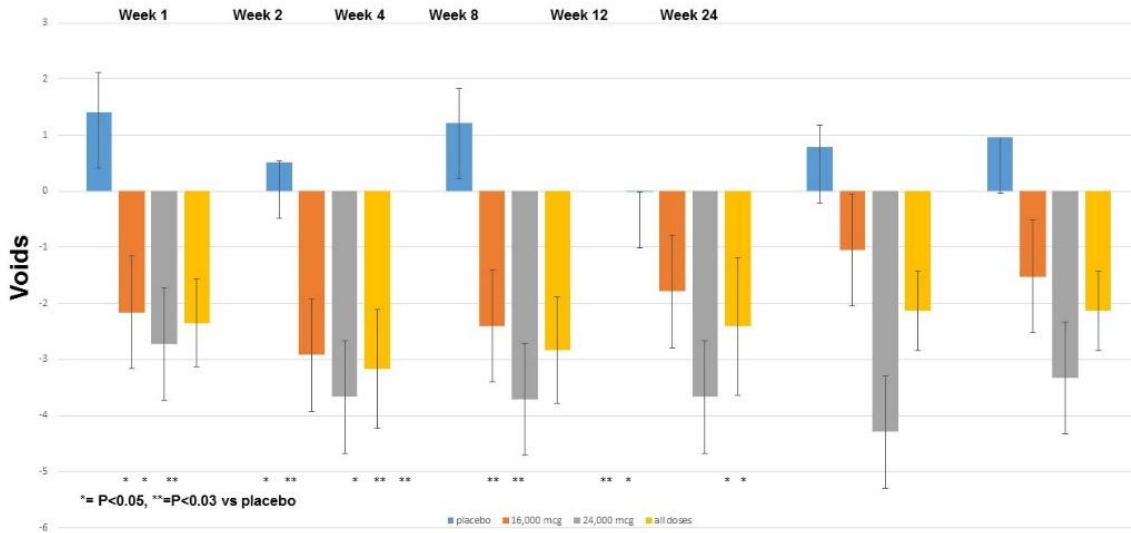
The average of diary data collected for 7 days prior to each visit revealed statistically significant ($p < 0.05$) improvements vs placebo and baseline with durable reduction in mean number of voids per day and mean number of urgency episodes per day over the 6 months of the trial. The changes displayed in the two tables below are mean changes (+/- SE) from baseline compared to placebo. Quality of life parameters (King Health Questionnaire) showed statistically significant sustained mean changes for the individual active treatments and for the combined active treatment groups (all doses) vs placebo and vs baseline in the domains of Impact on Life, Role Limitations, Physical Limitations, Social Limitations and Sleep Energy.

Interpretation of results

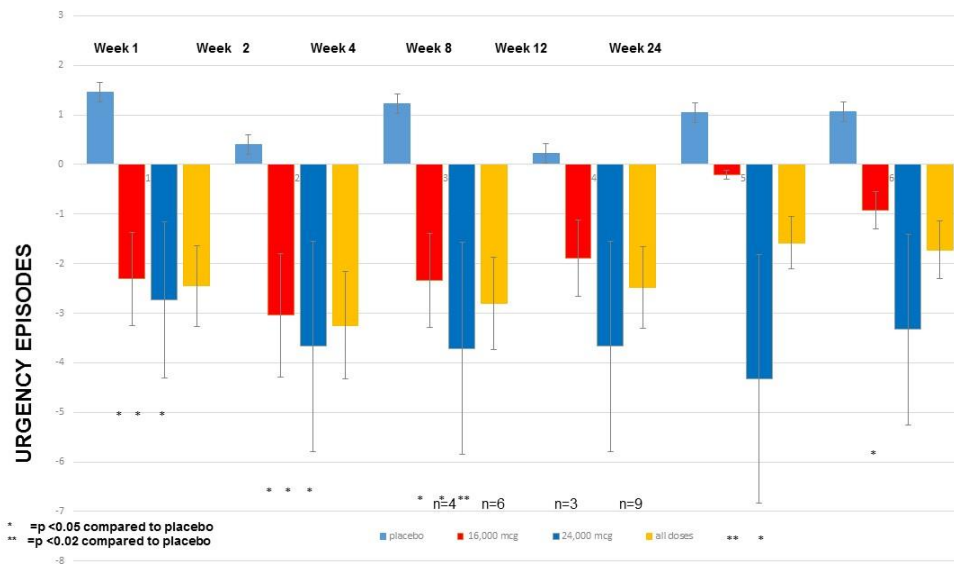
This phase IB clinical trial extends and substantiates prior pre-clinical reports that the instillation into the rat bladder of a plasmid containing the gene that expresses the human Maxi-K channel can safely reduce untoward effects of detrusor instability. (1-3) The measured significant reduction of the number of voiding and urgency episodes after a single administration of hMaxi-K lasted

for the 6 month duration of the trial. Those results were observed in the absence of a change in PVR and treatment-related serious adverse events.

CHANGE FROM BASELINE IN MEAN VOIDS



CHANGE FROM BASELINE IN MEAN URGENCY EPISODES



Concluding message

The results of this novel clinical trial show for the first time that a single intradetrusor administration of human Maxi-K gene was safe. Though the number of participants was small, there was a durable, positive effect. These findings justify further study of this approach for treatment of OAB/DO.

References

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Disclosures

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