PHASE II SAFETY AND EFFICACY STUDY OF SINGLE DOSE OF INTRAVESICAL RESINIFERATOXIN (RTX) IN PATIENTS WITH INTERSTITIAL CYSTITIS

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Hypothesis / aims of study
Interstitial cystitis (IC) is a painful bladder condition of unknown etiology and poorly understood pathophysiology. There is no uniformly successful treatment. Interest in using vanilloid receptor (VR1) agents to treat bladder pain is based on in vitro and clinical observations [1,2], which suggest that these agents may reduce pain due to a blocking or desensitization effect on C-fibers. Based on these factors, a randomized, placebo-controlled, multicenter, Phase II clinical trial of the VR1 agonist resiniferatoxin (RTX) was undertaken. We hypothesized that RTX would be an effective agent for patients with IC by desensitizing bladder C-fibers that transmit painful stimuli producing urinary frequency and urgency.

Study design, materials and methods
Eligible subjects had IC diagnosed by cystoscopy with bladder overdistention under anesthesia, no other disease process to explain the symptoms as listed in the NIDDK exclusion criteria [3], and current active symptoms manifest by a pain score of ¡Ý 4 (on a 9-point scale) and urinary frequency of ¡Ý 8/day while awake. Urodynamic studies were not performed. Subjects were randomized to one of four treatment groups: placebo, RTX 10 nM, RTX 50 nM, RTX 100 nM. All treatments were given as a single 50 cc instillation to be held in the bladder for 30 min in an office setting after anesthetizing the bladder with topical lidocaine. Supplemental analgesia was permitted but conscious sedation was not employed. Assessments were performed at 1, 4, 8, and 12 weeks. The primary efficacy endpoint was the Global Response Assessment (GRA) at week 4, a 7-point symmetrical scale ranging from markedly worse (score of 1) to markedly improved (score of 7). Secondary efficacy endpoints included percentage of subjects either moderately or markedly improved on GRA at week 4 (Responders), percentage of subjects with ¡Ý 50% reduction in pain at week 4, voiding diary variables, and the O'Leary-Sant Symptom and Problem Indices. Tolerability was assessed by the percentage of patients able to hold study drug for the required 30 minute treatment and instillation pain.

Results
Detailed results are displayed below. 163 subjects were recruited from 30 clinical centers; baseline disease severity and demographic factors were well balanced between the four treatment arms. There was no evidence of efficacy at any dose studied in overall symptoms, frequency, urgency, nocturia, or average voided volumes. There was no overall improvement in pain recorded in diaries. RTX resulted in a dose-dependent increase in pain during instillation and pain-related adverse events. The ability to retain study drug was improved by changing from lidocaine 2% 50 mL held for 10 min to 4% 100 mL held for 30 min (data not shown). There was one treatment-related serious adverse event (lower abdominal pain), occurring with RTX 10 nM.