MECHANISMS AND URODYNAMIC EFFECTS OF A POTENT AND SELECTIVE EP4 RECEPTOR ANTAGONIST (MF191) ON CYCLOPHOSPHAMIDE AND PROSGLANDIN E2 INDUCED BLADDER OVERACTIVITY IN RATS

Hypothesis / aims of study
Upregulation of the prostaglandin E2 (PGE2) receptor subtype 4 (EP4) in the bladder has been suggested to involve in bladder overactivity. We investigated the mechanism and urodynamic effects of a potent and selective EP4 receptor antagonist (MF191) on cyclophosphamide (CYP) or PGE2 induced bladder overactivity in rats.

Study design, materials and methods
Experimental and control rats were injected with CYP (200 mg/kg intraperitoneally) or saline on day 1. Continuous cystometrogram (CMGs) were performed on day 3. In group 1, MF191 (vehicle, 0.1 and 1 mg/kg) was given intravenously. The bladder was then harvested for histology. Some bladders were harvested for analysis of EP4 expression by western Blotting. In group 2, MF191 (vehicle, 10 nM, and 100 nM) was continuously infused into bladder. In group 3, bladder overactivity was produced by intravesical instillation of PGE2 (200 uM) and vehicle or MF191 (1 mg/kg) was given intravenously.

Results
CYP induced bladder inflammation, EP4 upregulation, and overactivity. The CYP effects were suppressed by MF191 (1mg/kg) intravenous injection (intercontraction interval, ICI- 39.4% increase, inflammatory cells infiltration score- 26.1% decrease, and EP4 expression- 89.9% decrease). Intravesical instillation MF191 (100 nM) suppressed CYP induced bladder overactivity (ICI- 71.8% increase). PGE2 induced bladder overactivity was suppressed by MF191 (ICI- 43.2% increase). MF191 had no significant effects on other CMG parameters and on control rats.

Interpretation of results
EP4 receptor antagonist MF 191 may have effects on the bladder urothelium and inflammatory cells infiltration and suppressed CYP or PGE2 induced bladder overactivity.

Concluding message
Systemic or intravesical MF 191 administration may be promising for treatment of overactive bladder in humans.

References
3. Blouin M., Han Y., Burch J. et al. The Discovery of 4-[(1-((2,5-Dimethyl-4-4-(trifluoromethyl)benzyl)-3-