

Intravesical Alkalized Lidocaine (PSD597)

offers immediate and sustained relief from the symptoms of

Interstitial Cystitis/Painful Bladder Syndrome (IC/PBS);

Results of a phase II, multicenter, placebo-controlled trial.

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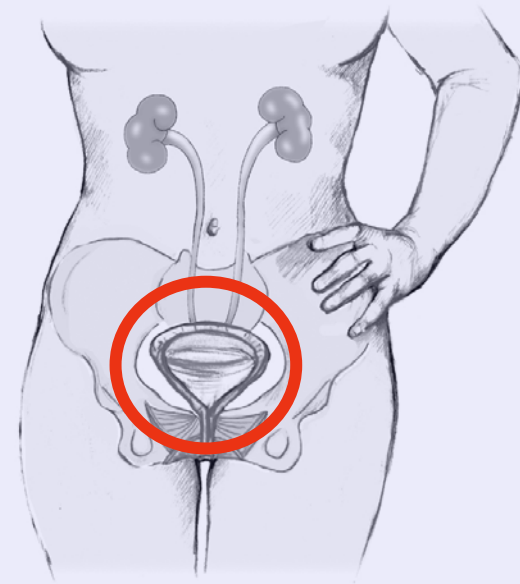
And the PSD597 Study Group

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Definition: Interstitial cystitis/painful bladder syndrome (IC/PBS)

“urgency, frequency and/or pain in the absence of a defined aetiology”



- **No identified bladder infection, stone or tumour**
- **Pain commonly associated with bladder filling & relieved on emptying**
 - **Increased frequency of urination and nocturia**
- **Etiology unknown, but peripheral and central sensitization is believed to be involved (“visceral allodynia”)**

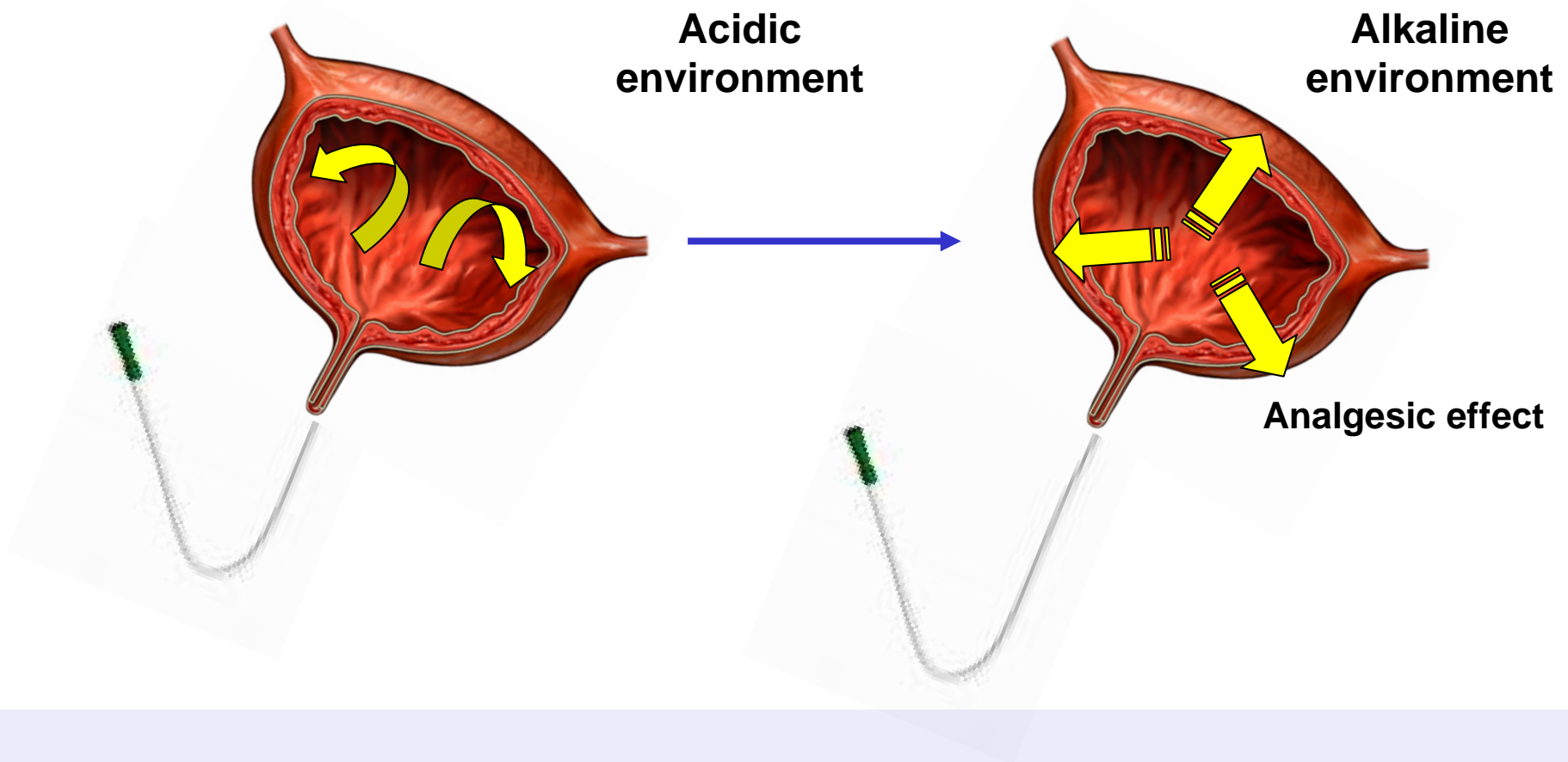
IC/PBS Treatment is.....

- **Lifestyle Changes**
 - Anecdotal benefit in some
- **Pharmacological Treatment**
 - Treatment response rates between 18-60%
BUT treatment effect is minimal or nonexistent
- **Physical Therapy**
 - Promising for patients with pelvic floor dysfunction
- **Cognitive Behavioral Therapy**
 - Promising for treatment refractory patients

PSD597: Rationale & Overview

- A clear, unmet need exists for a safe and effective means of providing relief from the acute and chronic symptoms of IC/PBS
- Established anaesthetics such as lidocaine have an obvious role in the control of IC/PBS pain but their efficacy is compromised by the acidic bladder environment
- PSD597 is designed to maximise lidocaine drug availability in the bladder

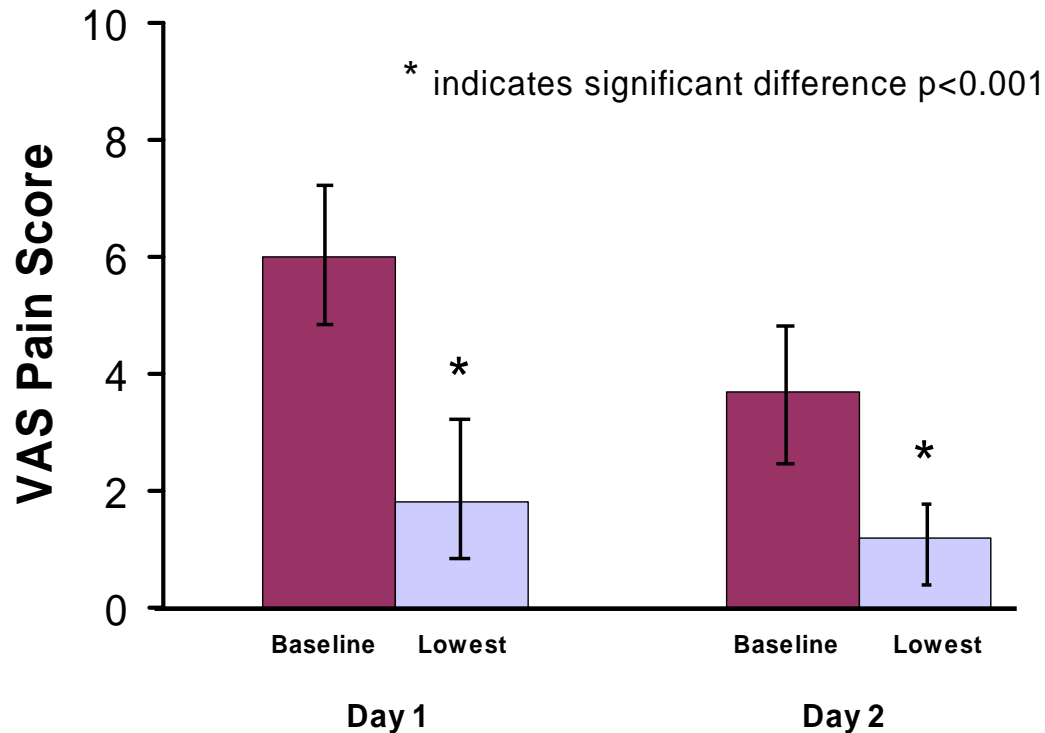
PSD597: Mechanism of Action



**1. Lidocaine instilled into bladder:
but cannot cross bladder
endothelium**

**2. Bicarbonate instilled into bladder:
lidocaine converts to non-ionic
bioavailable form**

Clinical Proof of Concept Study



Adapted from Henry, Nickel *et al.*
J Urol, 2001. 165(6 Pt 1): p. 1900-3

- Pilot study in 11 IC patients refractory to all prior treatments
- Treated by intravesicular instillation of PSD597 on two consecutive days
- Statistically significant reduction in mean pain scores as measured on the Visual Analog Scale after each treatment

Phase II Study: Study Design

	IC/PBS female patients (n=102)		
	<i>Randomised</i>		
	PSD597 (n = 50)	Placebo (n = 52)	
Days 0-5	Consecutive daily instillation X5		Placebo-controlled
Day 8	Follow-up		
Day 15	Follow-up		
Day 15 - 19	PSD597 Consecutive daily instillation X5 (n=82)		Open-label option
Day 22	Follow-up		
Day 28	Follow-up		

- **Primary Endpoints**

- Global Response Assessment (GRA)

- **Secondary Endpoints**

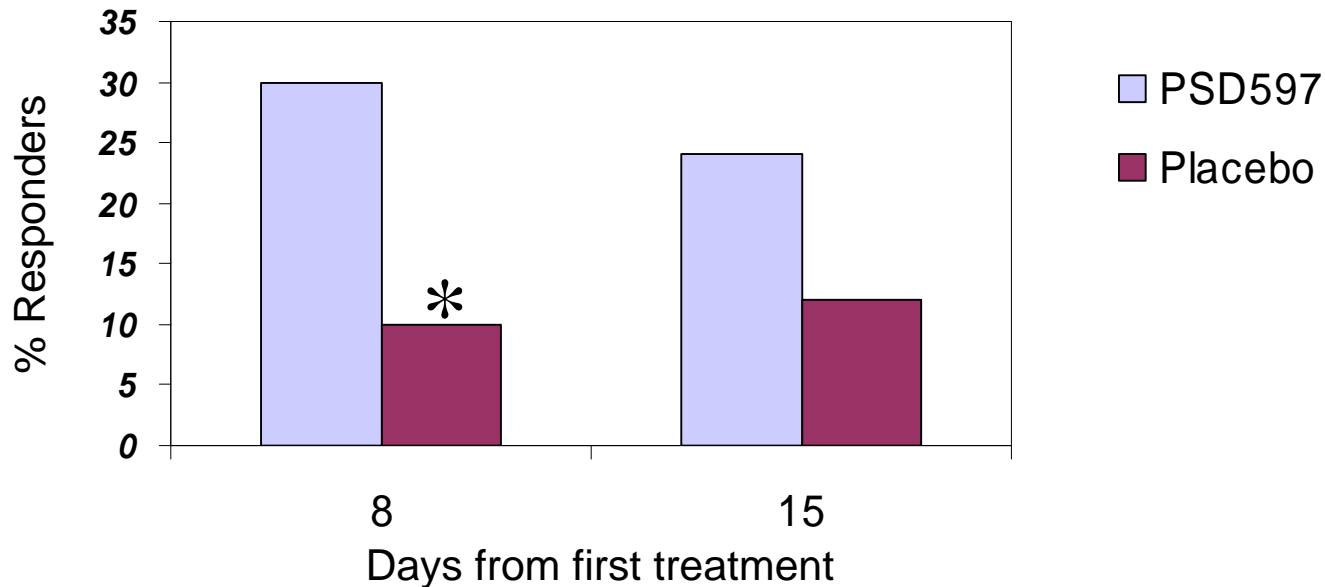
- IC symptoms (O'Leary Sant Index)
- Bladder pain (Likert scale)
- Haematology & clinical chemistry, urine microbiology, vital signs
- Pk (plasma lidocaine)

Phase II Study: Study Population

- 102 subjects enrolled at 19 centres in the US and Canada
 - Mean age 44.5 years (PSD597) and 49 years (placebo)
 - Mean duration of IC/PBS symptoms, 57.9 months (PSD597) and 56.8 months (placebo)
- Randomised 50:52 (PSD597:placebo)
- 93% (95/102) subjects completed the double-blind study
- 86% (82/95) subjects elected to enter the open-label study
- 98% completed the open-label study

Phase II Study: Response rates at Day 8 and 15

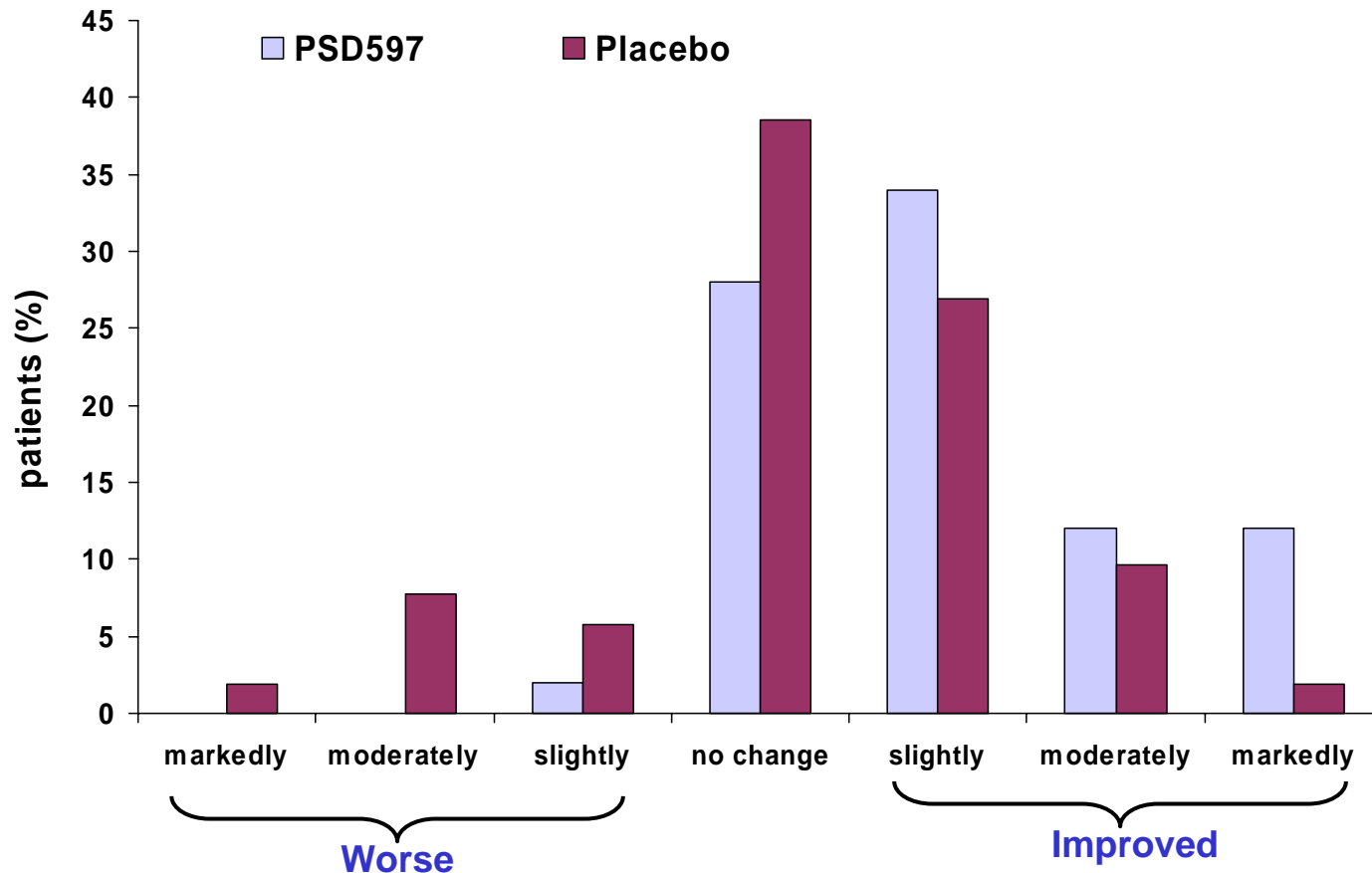
“responder”= subject reporting moderate or markedly improved GRA



Demonstrable improvement obtained with PSD597 over placebo at Day 8 and at Day 15

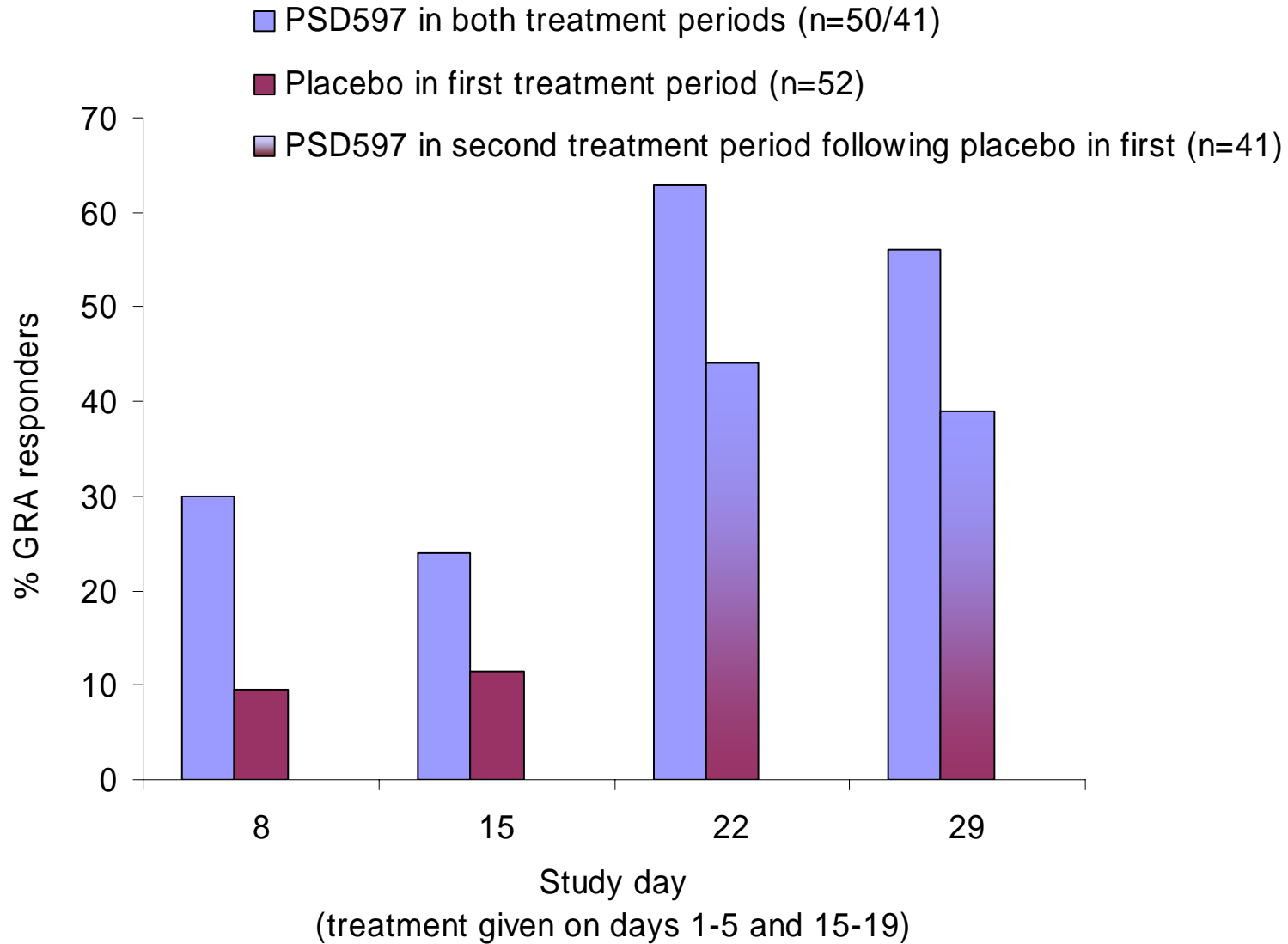
- **Day 8:** 30% responders to PSD597 vs 10% on placebo (* $p=0.012$)
- **Day 15:** 24% responders to PSD597 vs 12% on placebo ($p=0.102$)

Phase II Study: GRA Scores at Day 15



Significantly greater GRA scores and clinical improvement with PSD597 over placebo at Day 15 ($p=0.005$)

Phase II Study: Open Label Treatment Period



Phase II Study: Secondary Endpoints

	% decrease from baseline	
	Day 8	Day 15
O'L-S Symptoms index	PSD597 = 27.8% Placebo = 16.6%	PSD597 = 23.1% Placebo = 13.5%
<i>p</i> value	0.041	0.120
O'L-S Problems index	PSD597 = 31.6% Placebo = 12.6%	PSD597 = 27.8% Placebo = 14.2%
<i>p</i> value	<0.001	0.038
Pain scores	PSD597 = 39.1% Placebo = 33.4%	PSD597 = 35.5% Placebo = 21.1%
<i>p</i> value	0.442	0.076

Phase II Study: Safety Data – Double-blind

- No serious adverse events on PSD597
- Treatment-related AEs confined to urinary tract discomfort
 - Some bladder pain during first few days of treatment
- Number of severe AEs
 - 8% PSD597 vs 9.6% placebo
- Number of AEs resulting in study withdrawal
 - 2% PSD597 vs 0% placebo
- No changes in vital signs on treatment days
- No systemic lidocaine toxicity

No safety concerns

Conclusions

- PSD597 is effective for the treatment of the symptoms of IC/PBS
- Maintenance of treatment effect extends beyond the end of treatment
- Open label study suggests longer or repeated PSD597 treatment leads to a greater and sustained response rate
- Treatment has appropriate safety profile