

# Immediate and sustained relief from the symptoms of interstitial cystitis/painful bladder syndrome (IC/PBS) with intravesical alkalized lidocaine (PSD597): Results of a phase II multi-centre placebo-controlled trial

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## INTRODUCTION

**Intravesical local anaesthetics in the treatment of interstitial cystitis / painful bladder syndrome (IC/PBS):** Although local anaesthetics have been administered in the bladder for many years, none achieve immediate symptom relief without destroying the nerve endings or using narcotics. There is an unmet need for an IC/PBS treatment that offers immediate relief of symptoms and operates directly to down-regulate the bladder sensory nerves without any rebound effect.

When instilled into the bladder, the conversion of local anaesthetic from the ionised, water soluble form to the lipid soluble base form may not occur since urine is usually acidic (pH 5 to 6), leaving most local anaesthetic essentially 'ion trapped' within the bladder.

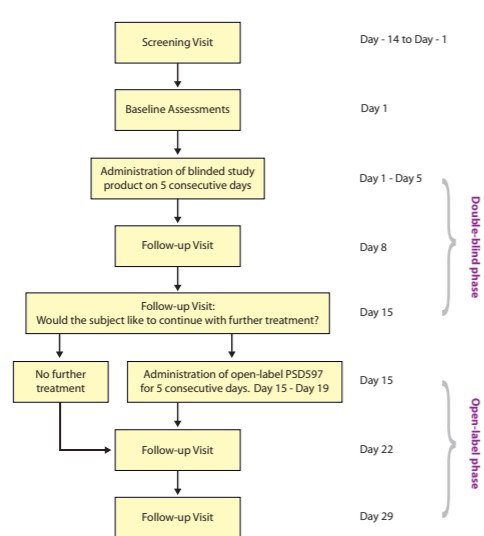


Figure 1: Study flow chart

A number of small studies, based on the hypothesis that lidocaine would be sufficiently and predictably absorbed from the human bladder if urine pH was buffered to 8.0, have indicated that alkalized lidocaine has therapeutic potential in symptomatic treatment of IC/PBS [2-4].

PSD597 consists of alkalized lidocaine instilled into an empty bladder. The catheter is clamped and the instillate left in situ for 1 hour before drainage and removal of the catheter.

## PATIENTS AND METHODS

This was a phase II double-blind, placebo-controlled study carried out in 19 centres in the USA and Canada. Subjects received 5 days daily dosing with PSD597 or placebo and were followed up for 10 days. All subjects were then offered open-label treatment with PSD597 for a further 5 days with 10 days follow up (see Figure 1).

### Entry criteria included:

- Male or female aged  $\geq 18$  and  $\leq 75$  years
- Symptoms of IC/PBS for  $\geq 3$  months
- Pain at study entry of  $\geq 4$  on a 10-point Likert scale

**Primary objective:** to assess the percentage of subjects who respond to PSD597, assessed as "moderately improved" or "markedly improved" measured by a patient-rated Global Response Assessment (GRA), compared to placebo at Day 15.

### Secondary objectives included:

- Changes in bladder pain and urgency (10-point Likert scale)
- Frequency (voiding log)
- Changes in symptoms and problems associated with IC (O'Leary Sant Interstitial Cystitis Symptom and Problem indices)
- Safety and tolerability of PSD597 (collection of adverse event data)

## RESULTS

### Patients and demographics:

- Comparable demographic and baseline characteristics in both treatment groups
- 97.1% female
- Mean age overall 46.8 years
- 72 (70.6%) Caucasian

### Initial treatment period

A significantly greater number of PSD597-treated subjects compared with placebo-treated subjects were GRA responders (moderate or marked improvement) 3 days after the end of treatment on Day 8 ( $p=0.012$ ; Table 1).

For the primary efficacy variable, a greater number of PSD597-treated subjects compared with placebo-treated subjects were GRA responders on Day 15, although this did not reach statistical significance ( $p = 0.102$ ; Table 1).

Analysing the response across all GRA categories, the difference with PSD597 treatment at Day 15 was highly significantly different from placebo ( $p=0.005$ ), with 29 subjects (65.9%) in the PSD597 treatment group reporting improved GRA scores compared to 20 subjects (41.7%) in the placebo group (Figure 2).

Positive results were also seen in all other secondary endpoints with improvements reported in bladder pain, urinary frequency and urgency, whether assessed as individual symptoms or combined into the O'Leary Sant Interstitial Cystitis Symptom and Problem indices.

### Voluntary open-label phase

Of the 95 patients who completed the double-blind placebo-controlled phase, 82 patients (86%) elected to receive open-label treatment with PSD597 for 5 days (days 15-19).

At Day 22, 63% (26/41) of those patients who had received PSD597 in the initial double-blind study phase reported moderate or marked improvement in GRA after the second course of treatment; of the patients who previously were randomised to placebo, 44% (18/41) now responded to active treatment. By Day 29, GRA response rates were still maintained at 56% (23/41) and 39% (16/41) in the two groups (Figure 3).

Table 1: Percentage of GRA responders ("moderately improved" or "markedly improved"): ITT population

		PSD597 (n = 50)	Placebo (n = 52)
Day 8	GRA Responders, n	15 (30.0%)	5 (9.6%)
	odds ratio 95% CI	4.30 (1.38 - 13.46) $p = 0.012$	
Day 15	GRA Responders, n	12 (24.0%)	6 (11.5%)
	odds ratio 95% CI	2.48 (0.83 - 7.40) $p = 0.102$	

Table 1: Percentage of GRA responders ("moderately improved" or "markedly improved"): ITT population

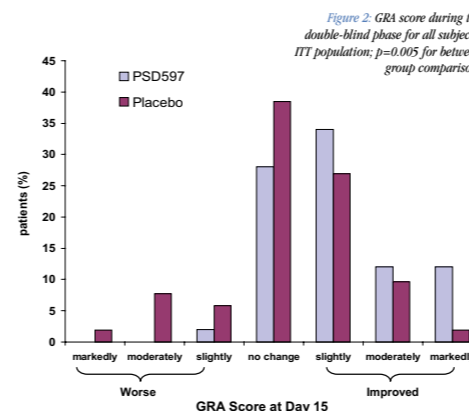


Figure 2: GRA score during the double-blind phase for all subjects: ITT population;  $p=0.005$  for between group comparison.



Figure 3: Percentage of GRA responders ("moderately improved" or "markedly improved") following daily double-blind treatment with PSD597 or placebo on days 1-5. All patients completing the placebo-controlled phase were then offered open treatment with PSD597 on days 15-19.

## SAFETY AND TOLERABILITY

PSD597 was well tolerated, appeared safe, and was devoid of systemic side effects often experienced with oral drugs (Table 2). Total adverse events and severe adverse events were very similar in number and pattern between the two treatment groups except for bladder pain (14.0% PSD597 and 5.8% placebo).

Three (6.0%) subjects, all in the PSD597 treatment group, withdrew because of adverse events during the double-blind phase of the study: 2 episodes of bladder pain and 1 of urethral irritation. A further 2 (4.9%) subjects who had been in the placebo treatment group withdrew because of adverse events during the open-label phase. The adverse events were urinary tract infection and burning pain in bladder.

Table 2: Most common ( $\geq 5\%$  subjects) adverse events (double-blind phase): safety population

Primary system organ class	Preferred term	Double-Blind Treatment Group; n (%)	
		PSD597 (n = 50)	Placebo (n = 52)
Any adverse event		27 (54.0)	25 (48.1)
General disorders & administration site conditions	Any Fatigue	8 (16.0)	5 (9.6)
	Any Urinary tract infection	4 (8.0)	3 (5.8)
Infections and infestations	Any Urinary tract infection	3 (6.0)	6 (11.5)
	Any Back pain	1 (2.0)	4 (7.7)
Musculoskeletal and connective tissue disorders	Any Back pain	2 (4.0)	4 (7.7)
	Any Headache	1 (2.0)	3 (5.8)
Nervous system disorders	Any Dizziness	6 (12.0)	8 (15.4)
	Any Headache	4 (8.0)	3 (5.8)
Renal and urinary disorders	Any Bladder pain	2 (4.0)	10 (19.2)
	Any Dysuria	7 (14.0)	3 (5.8)
	Any Urethral pain	2 (4.0)	3 (5.8)

## CONCLUSIONS

Patients who received PSD597 showed clear and substantial improvements in GRA (the primary endpoint measure) 8 and 15 days after a 5-day course of treatment. Positive results were also seen in all other secondary endpoints with improvements reported in bladder pain, urinary frequency and urgency and the O'Leary Sant Interstitial Cystitis Symptom and Problem indices. The fact that 86% of patients who completed the double-blind treatment phase elected to receive a further course of open (active) treatment provides direct evidence of treatment acceptability and the lack of alternative treatment options. Further improvements seen after the second dosing period suggest that the benefits of PSD597 were sustained for a considerable period after treatment and secondly, confirm that clinical benefit can be increased with repeated dosing. PSD597 was also found to be safe and well tolerated when instilled into the bladder.

### References

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