

# Intravesical Alkalinized Lidocaine (PSD597): Relief from symptoms of interstitial cystitis/painful bladder syndrome

J. Curtis Nickel<sup>1</sup>; Richard A. Henry<sup>1</sup>; Michael G. Wyllie<sup>2</sup>

<sup>1</sup> Queens University, Kingston General Hospital, Ontario, Canada; <sup>2</sup> Plethora Solutions PLC, London, UK

## INTRODUCTION

**Interstitial cystitis (IC)** is a debilitating urological disorder characterised by urinary frequency, urgency, and bladder pain without an identifiable cause. It is poorly understood, poorly characterised, and treatment is mostly empirical and unsatisfactory. IC predominantly afflicts young and middle-aged women, although its prevalence in males is probably underestimated.

**Painful bladder syndrome (PBS)**, as defined by the International Continence Society, is "the complaint of suprapubic pain related to bladder filling, accompanied by other symptoms, such as increased daytime and nighttime frequency, in the absence of proven urinary infection or other obvious pathology". Although overlapping with IC, PBS is a clinical description of disease based on the patient's symptoms, and does not depend on urodynamic or cystoscopic findings.

Local anaesthetics have been administered in the bladder for many years, although no currently available IC therapy achieves immediate symptom relief without destroying the nerve endings or using narcotics. There is an unmet need for an IC treatment that offers immediate relief of symptoms and operates directly to downregulate the bladder sensory nerves without any rebound effect.

Theoretically, intravesical administration of the local anaesthetic lidocaine could help to control the pain and inflammation associated with IC, returning the neuropathic bladder to a more normal state with time. However, local anaesthetics are weak bases (pKa + 8.0) and are generally provided in an acidic aqueous solution of an ionised, water soluble form of the drug. Tissue penetration occurs when the injected solution is buffered by the surrounding tissue and the drug converts into the lipid soluble base form. When instilled into the bladder, this conversion to the base form may not occur since urine is usually acidic (pH 5 to 6), leaving most local anaesthetic essentially 'ion trapped' within the bladder.

A number of small studies have been carried out based on the hypothesis that lidocaine would be sufficiently and predictably absorbed from the human bladder if urine pH was buffered to 8.0 [1-3]. These studies have indicated that alkalinized lidocaine has therapeutic potential in symptomatic treatment of IC/PBS.

PSD597 consists of 200 mg lidocaine (as 5 ml of 4% lidocaine hydrochloride solution) instilled into an empty bladder via a urinary catheter followed by 5 ml 8.4% sodium bicarbonate solution to make a final concentration in the bladder of > 2% lidocaine. The catheter is clamped and the instillate left in situ for 1 hour before drainage and removal of the catheter.

## PATIENTS AND METHODS

This phase II placebo-controlled clinical study of PSD597 was undertaken in USA and Canada. A total of 102 patients (99 Female, mean age 46.8 years, 70.6% Caucasian) with symptoms of IC/PBS for  $\geq 3$  months, and who had pain at study entry of  $\geq 4$  on a 10-point Likert scale were entered into the study. The study included a double-blind treatment period including 5 days dosing and 10 days follow up. Patients could then opt to enter an open treatment period when all patients received PSD597 for a further 5 days (Figure 1).

The primary objective was 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 (measured by 10-point Likert scale), frequency (measured by a voiding log), changes in symptoms and problems associated with IC measured by the O'Leary Sant Interstitial Cystitis Symptom and Problem indices and to assess the safety and tolerability of PSD597 instilled into the bladder.

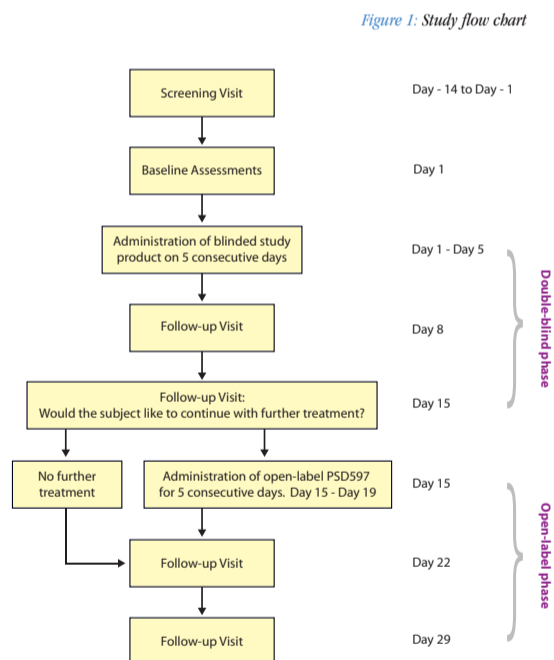
## RESULTS

### Initial treatment period

Symptoms of IC/PBS rapidly improved (see Table 1). At Day 8, 15 patients (30%) in the intent-to-treat (ITT) population reported moderate or marked improvement in GRA after PSD597 treatment compared with 5 patients (9.6%) randomized to placebo ( $p=0.012$ ).

For the primary efficacy variable, a greater number of PSD597 treated subjects (24%) compared with placebo treated subjects (11.5%) were GRA responders ten days after last treatment on Day 15 ( $p=0.102$ ).

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 (Table 2).



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

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

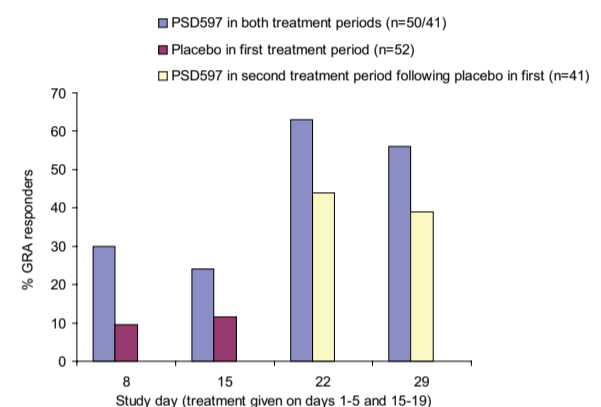
Positive results were also seen in all other secondary endpoints with improvements reported in bladder pain, urinary frequency and urgency, whether assessed as individual symptoms or combined into the O'Leary Sant Interstitial Cystitis Symptom and Problem indices.

### 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). The results obtained during the open-label treatment phase of the study were consistent with those obtained during the double-blind phase of the study (Figure 2).

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 2: 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 the systemic side effects often experienced with oral drugs (Table 3). 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).

The adverse events reported during the open-label follow-up phase were broadly consistent with the double-blind phase, although the most frequently reported adverse event was headache reported by 11 (27.2%) subjects in total.

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 3: 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)
		4 (8.0)	3 (5.8)
Infections and infestations	Any Urinary tract infection	3 (6.0)	6 (11.5)
		1 (2.0)	4 (7.7)
Musculoskeletal and connective tissue disorders	Any Back pain	2 (4.0)	4 (7.7)
		1 (2.0)	3 (5.8)
Nervous system disorders	Any Dizziness	6 (12.0)	8 (15.4)
	Headache	4 (8.0)	3 (5.8)
		2 (4.0)	4 (7.7)
Renal and urinary disorders	Any Bladder pain	13 (26.0)	10 (19.2)
	Dysuria	7 (14.0)	3 (5.8)
	Urethral pain	2 (4.0)	3 (5.8)
		1 (2.0)	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

- Henry, R., et al., Absorption of alkalinized intravesical lidocaine in normal and inflamed bladders: a simple method for improving bladder anesthesia. J Urol, 2001. 165(6 Pt 1): p. 1900-3.
- Parsons, C.L., Successful downregulation of bladder sensory nerves with combination of heparin and alkalinized lidocaine in patients with interstitial cystitis. Urology, 2005. 65(1): p. 45-8.
- Henry, R.A., et al., Alkalinized intravesical lidocaine to treat interstitial cystitis: absorption kinetics in normal and interstitial cystitis bladders. Urology, 2001. 57(6 Suppl 1): p. 119.

This work was funded by Plethora Solutions Ltd.