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Phase II, multicentre, randomised, double blind, placebo conntrolled pilot study to determine proof of efficacy, safety, tolerablility and pharmacokinetics of intravesical PSD597 in the symptomatic management of interstitial cystitis /painful bladder syndrome

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Registration date	**Overall study status**	[_] Statistical analysis plan
11/08/2006	Completed	[X] Results
Last Edited	**Condition category**	[_] Individual participant data
07/01/2021	Urological and Genital Diseases	

Plain English summary of protocol
Not provided at time of registration

Contact information

Type(s)
Scientific

Contact name
Ms Crystal Richardson

Contact details
Clinical Research Associate
United BioSource Corporation
3822 Summit
Kansas City
United States of America
MO 64111
+1 816 421 6400 ext. 2208
crystal.richardson@unitedbiosource.com

Additional identifiers

Protocol serial number

PSD597-PP-001

Study information

Scientific Title
Phase II, multicentre, randomised, double blind, placebo conntrolled pilot study to determine proof of efficacy, safety, tolerablility and pharmacokinetics of intravesical PSD597 in the symptomatic management of interstitial cystitis/painful bladder syndrome

Study objectives
Interstitial Cystitis (IC) is a chronic, painful inflammatory condition of the bladder wall, first characterized in 1914 by Dr Hunner. The disease is poorly understood, poorly characterised, and treatment is mostly empirical and unsatisfactory. Estimates of prevalence of the disease may vary widely. In 1990 it was thought to affect as many as 500,000 U.S. citizens, with 25% of patients under the age of 25. Estimates in 2002, using expanded definitions of IC, and estimates of the chronic pelvic pain population and chronic prostatitis group that probably have IC, now exceed 10 million. Quality of life with IC can be worse than end stage renal disease. Treating the IC patient has proven to be one of the greatest challenges of health care providers managing chronic pelvic pain disorders. Relief of symptoms and disease remission are the primary goals of any management plan. Unfortunately, most pharmacologic therapies are non-disease specific, instituted in a trial and error manner, with few randomised, placebo-controlled trials to support their efficacy.

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 night-time frequency, in the absence of proven urinary infection or other obvious pathology." Although overlapping with interstitial cystitis, PBS is a clinical description of disease based on the patient’s symptoms, and does not depend on urodynamic or cystoscopic findings. These symptoms can be quite variable among patients, leading to several proposed etiologic theories including:
1. Increased bladder epithelial permeability.
2. Activation of bladder mast cells.
3. Allergic or autoimmune processes.
4. Toxic substance(s) in the urine.
5. Occult infection.
6. Neuropathic changes.
7. Neurogenic inflammation.
However, none of these mechanisms have been conclusively shown to be responsible for interstitial cystitis and/or the painful bladder syndrome.

Little is known about the natural history of PBS, especially the rate of spontaneous remission following first identification of symptoms. Consequently, clinicians have little evidence-based guidance in choosing which treatments may be most beneficial for the newly diagnosed PBS patient. Various PBS treatments are used, some directed specifically to one of the proposed etiologies, whereas other therapies are purely empirical. Treatment choices typically are made by first trying the safest and least invasive options, and then progressing to other treatments (which have more potential morbidity) if the initial treatments do not relieve symptoms effectively.

Local anaesthetics have been administered in the bladder for many years and specifically as an intravesical agent for short-term pain relief in IC. No currently available IC therapy achieves

immediate symptom relief without destroying the nerve endings or using narcotics. Intravesical agents have been used for many years as adjuncts to oral treatment regimens or as second-line therapies for IC. The most widely used is heparin, which is effective in approximately 50% of patients treated, however, not producing immediate and sustained relief of IC symptoms. An IC treatment that offers immediate relief of symptoms and operates directly to down regulate the bladder sensory nerves without any rebound effect continues to be needed.

Local anaesthetics are increasingly recognised as having powerful broad-spectrum anti-inflammatory effects, including stabilising mast cells and blocking histamine release. Theoretically they appear to be ideally suited to suppress the neuroinflammatory cycle occurring in IC. As weak bases (pKa ± 8.0), local anaesthetics are generally provided in an acidic aqueous solution of an ionized 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 5-6), leaving most local anaesthetic essentially ion trapped within the bladder. Pharmacokinetic studies confirm that intravesical lidocaine is not sufficiently absorbed by human bladders to achieve a significant serum level or deep local anaesthetic effect. Henry et. al. demonstrated in an animal model that the optimal absorption of intravesical lidocaine is achieved when bladder content pH is approximately 8.0, and further showed that similar effects could be achieved in normal and inflamed bladders. Intravesical alkalised lidocaine may offer a therapeutic approach to treat the pain and bladder inflammation associated with interstitial cystitis and painful bladder syndrome and may be useful to help differentiate the anatomical site of non-specific pelvic pain.

This Phase II, multicentre, randomised, double-blind, placebo-controlled pilot study will employ PSD597: 200 mg lidocaine (as 5 ml of 4% lidocaine solution) instilled into an empty bladder followed by 5 ml of 8.4% sodium bicarbonate.

Ethics approval required
Old ethics approval format

Ethics approval(s)
Ethical Review Committee, Inc., approval received on 15/02/2006.

Study design
Phase II, multicentre, randomised, double-blind, placebo-controlled, parallel group, pilot study.

Primary study design
Interventional

Study type(s)
Treatment

Health condition(s) or problem(s) studied
Interstitial cystitis/painful bladder syndrome

Interventions
Eligible subjects will be randomly allocated (1:1) to receive blinded treatment with PSD597 or a placebo during the double-blind treatment phase of the study:
Group one: PSD597 treatment will consist of 5 ml of 4% lidocaine instilled into an empty bladder via a ten French urinary catheter, followed by 5 ml of 8.4% sodium bicarbonate solution. The

bladder will be drained via the urinary catheter before commencing the instillation. Following instillation the catheter will be clamped and the instillate left in situ for one hour before drainage and removal of the catheter (N.B.: If a subject cannot tolerate the catheter remaining in situ for this period it may be removed and the subject re-catheterised at one hour to drain the instillate. The instillate should not be voided by the subject to avoid unnecessary urethral pain which may result from voiding of the bicarbonate. Where possible the catheter should remain in situ during the hour of treatment. In cases where an increased number of catheterisations are required, the investigator may wish to consider use of prophylactic antibiotics). Subjects will receive daily instillations of PSD597 on five consecutive study days (days one to five, Monday - Friday), administered in hospital as an outpatient.
Group two: Placebo treatment will consist of 10 ml of ordinary saline instilled into an empty bladder as two 5 ml instillates. Subjects will receive daily instillations of placebo using an identical dosing schedule and administration procedure to that used for PSD597.

In both cases, lidocaine must not be used as local anaesthetic when inserting the urinary catheter.

At the day 15 follow-up visit all subjects will be offered the option of open-label treatment with PSD597 for five consecutive days (days 15-19, Monday to Friday) to be administered in hospital as an outpatient.

Intervention Type
Drug

Phase
Phase II

Drug/device/biological/vaccine name(s)
PSD597 (lidocaine, sodium bicarbonate), placebo (saline solution)

Primary outcome(s)
To assess the percentage of patients who respond to PSD597, assessed as 'moderately improved' or 'markedly improved' measured by a GRA, compared to placebo, at day 15 following a five consecutive day course of treatment.

Key secondary outcome(s))
1. To assess changes in GRA measured by a seven point scale.
2. To assess changes in bladder pain measured by ten point Likert scale.
3. To assess changes in frequency measured by a voiding log.
4. To assess changes in urgency measured by ten point Likert scale.
5. To assess changes in symptoms and problems associated with interstitial cystitis measured by the O'Leary Sant Interstitial Cystitis symptom and problem indexes.
6. To assess the safety and tolerability of PSD597 instilled into the bladder.

7. To characterise the pharmacokinetics of single and multiple doses of intravesical PSD597 in a sub-group of patients.

Completion date
31/12/2006

Eligibility

Key inclusion criteria
1. Male or female patients aged between 18 and 75 years of age.
2. Women of child bearing potential or men with partners of child bearing potential willing to commit to the use of a reliable form of contraception during the course of the study (e.g contraceptive pill or condoms).
3. Symptoms of bladder pain/discomfort of more than four on a ten point Likert scale, described as suprapubic pain related to bladder filling accompanied by other symptoms including increased daytime and night-time frequency (more than eight or more than two respectively) in the absence of infection or other pathology, with or without the typical cystoscopic appearance of IC.
4. Symptoms of abnormal urinary frequency and bladder pain/discomfort must have been present for at least three months prior to study entry.
5. Anterior vaginal wall/bladder wall pain on bimanual examination.
6. Able to understand and complete a Likert Scale, Global Risk Assessment (GRA) and O'Leary Sant Interstitial Cystitis symptom and problem indexes.
7. Willing and able to provide written informed consent.

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Adult

Lower age limit
18 years

Upper age limit
75 years

Sex
All

Total final enrolment
102

Key exclusion criteria
1. Known allergy to, or intolerance of, amide type local anaesthetics.
2. Currently receiving local anaesthetic analogue therapy.
3. Treatment for IC/PBS (e.g., Elmiron, dimethyl sulfoxide [DMSO] or intravesicular therapy) within four weeks prior to baseline visit.
4. History of cardiac arrhythmias, other cardiac conduction disturbances, and/or significant cardiovascular disease.
5. History of liver disease.
6. Inability to void spontaneously.
7. Severely debilitating or urgent concurrent medical condition.
8. History of pelvic radiation therapy, tuberculous cystitis, neurologic disease affecting bladder function, bladder cancer, or carcinoma in situ, or urethral cancer.

9. Presence of bladder, urethral, or ureteral calculi.
10. Clinical evidence of urethritis.
11. Presence of urethral diverticulum.
12. Unlikely to be compliant due to unmanaged medical or psychological problem, including neurological, psychological or speech/language problems that will interfere with ability to complete the study.
13. Substance abuse or dependency problem within the past two years for which treatment has not been received.
14. Imminent change in residence or other social factors that could compromise compliance with the protocol.
15. Clinically significant abnormal blood clinical chemistry or haematology.
16. Evidence of significant eletrocardiogram (ECG) abnormality such as prolonged QTc.
17. Previously failed therapy with alkalinised lidocaine.

Exclusion criteria for men only:
1. Current treatment for chronic bacterial prostatitis, as documented by a positive urine culture or prior history of recurrent bacterial urinary infections.
2. Unevaluated suspicious prostate examination.
3. History of any prostate cancer.

Exclusion criteria for women only:
1. Currently pregnant or breastfeeding.
2. Symptoms of bladder pain/discomfort and urinary frequency present only during menstruation.

Deferral Criteria: There are several conditions for which a participant will be deferred from entry into the study. Once it is formally ascertained that the condition is not present or has subsided according to the time frame identified, the participant will be reconsidered for entry into the trial. The following list identifies some of the conditions for deferment:
1. Positive urine culture at screening. Participant will be deferred until treated and the repeat urine culture is negative.
2. Gross haematuria. Participant will be deferred until they are without the condition.
3. Currently enrolled in another intervention study, or has received an investigational drug or device within three months prior to screening. Participant will be deferred until they have been off study for at least three months.
4. Active genital herpes, or history thereof, within the prior 12 weeks. Participant will be deferred until they have been without the condition for at least 12 weeks.

Deferral criteria for men only:
1. Recent Transurethral Resection of the Prostate (TURP), Transurethral Incision of the Prostate (TUIP), Transurethral Incision of the Bladder Neck (TUIBN), Transurethral Microwave Thermotherapy (TUMT), Transurethral Needle Ablation (TUNA), balloon dilation of the prostate, open prostatectomy or any other prostate surgery or treatment, such as cryotherapy or thermal therapy. He will be deferred until at least six months from the date of the procedure.

Deferral criteria for women only:
1. Active vaginitis. She will be deferred until she is free of the condition.
2. Recent vaginal delivery or caesarean section. She will be deferred until at least six months from the date of childbirth.

Date of first enrolment
01/07/2006

Date of final enrolment
31/12/2006

Locations

Countries of recruitment
United States of America

Study participating centre
Clinical Research Associate
Kansas City
United States of America
MO 64111

Sponsor information

Organisation
Plethora Solutions Ltd. (UK)

ROR
https://ror.org/02y9vw172

Funder(s)

Funder type
Industry

Funder Name
Plethora Solutions Ltd

Results and Publications

Individual participant data (IPD) sharing plan

IPD sharing plan summary
Not provided at time of registration

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Results article	results	01/04/2009	07/01/2021	Yes	No