Demonstrating Clinical Benefit for Drugs Intended to Treat Interstitial Cystitis/Bladder Pain Syndrome (IC/BPS)

Meeting of the Bone, Reproductive and Urologic Drugs Advisory Committee (BRUDAC)

December 7, 2017
Introduction

Dan Vickery, PhD
President
Urigen Pharmaceuticals
### Telephone Surveys Designed to Diagnose the Symptoms of IC/BPS

**IC/BPS Prevalence**  
% U.S. Adult Population<sup>1</sup>

<table>
<thead>
<tr>
<th></th>
<th>Women</th>
<th>Men</th>
<th>Total Average</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low Estimate</td>
<td>2.7%</td>
<td>1.9%</td>
<td></td>
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<tr>
<td>High Estimate</td>
<td>6.5%</td>
<td>4.2%</td>
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</table>

#### Patient Population<sup>2</sup>

<table>
<thead>
<tr>
<th></th>
<th>Low Estimate</th>
<th>High Estimate</th>
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</thead>
<tbody>
<tr>
<td>Women</td>
<td>3.5M</td>
<td>8.6M</td>
</tr>
<tr>
<td>Men</td>
<td>2.4M</td>
<td>5.3M</td>
</tr>
<tr>
<td>Total Average</td>
<td>5.9M</td>
<td>13.9M</td>
</tr>
</tbody>
</table>

<sup>1</sup> Americans aged 15 years or older; <sup>2</sup> Based on 2015 UN Population Division
Interstitial Cystitis/Bladder Pain Syndrome (IC/BPS)

• Single disease state

• Pain is the hallmark symptom
  ‣ Varies in intensity from mild to severe
  ‣ Can be chronic, acute, or intermittent

• Urinary frequency and urgency accompany the pain

• Symptoms can be severe and debilitating

• Diagnosis has evolved to be based on symptomatology
  ‣ There is no diagnostic test with high predictive value for IC/BPS
  ‣ Diagnosis also requires the exclusion of other causes of the symptoms
Need New Treatment Options

- Approved in US
  - Elmiron® (pentosan polysulfate sodium); only approved oral drug; 1996
  - Rimso-50® (dimethyl sulfoxide; DMSO) 50% w:w aqueous solution for intravesical instillation; 1978

- Pain medications

- Other drugs are used off label, recommended in guidelines
  - Amitriptyline, Hydroxyzine, Cimetidine, Heparin and Lidocaine instillation, GAG instillations

- Initial therapies are pain management and behavioral

- Treatments become more invasive and risky with progression

- Need for new therapies
  - Acute: Rapidly relieve acute symptoms and flares
  - Chronic: Reduce symptoms and flares over time
<table>
<thead>
<tr>
<th>Agenda</th>
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<tbody>
<tr>
<td>Introduction</td>
<td>Dan Vickery, PhD</td>
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<tr>
<td></td>
<td>President, Urigen Pharmaceuticals</td>
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<tr>
<td>One Disease</td>
<td>Joel Teichman, MD, FRCSC</td>
</tr>
<tr>
<td>Pathophysiology</td>
<td>Professor, Department of Urologic Sciences</td>
</tr>
<tr>
<td>Diagnosis</td>
<td>University of British Columbia, Vancouver</td>
</tr>
<tr>
<td>Patient Selection Criteria</td>
<td>C Lowell Parsons, MD</td>
</tr>
<tr>
<td></td>
<td>Professor Emeritus of Urology, School of Medicine</td>
</tr>
<tr>
<td></td>
<td>University of California, San Diego</td>
</tr>
<tr>
<td>Endpoints and Assessments</td>
<td>Dan Vickery, PhD</td>
</tr>
<tr>
<td></td>
<td>President, Urigen Pharmaceuticals</td>
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</tbody>
</table>
One Disease
The Name Changes but the Symptomology Remains the Same

Joel Teichman, MD, FRCSC
Professor, Department of Urologic Sciences
University of British Columbia, Vancouver
IC/BPS: One Disease

• Defined by pain and urinary frequency and urgency
  ‣ Spectrum of disease severity and presentation

• Nomenclature describes etiology and symptomatology
  ‣ Joseph Parrish 1836, described a condition that he called “tic doloureux of the bladder”
  ‣ Samuel Gross, 1855, described it as a common disease with increasing pain and voiding
    – Recognized that rare ulcers can occur in some patients (1855 2nd ed)
    – First known use of “Interstitial Cystitis” (1876 3rd ed)

• Past attempts to separate into different conditions
  ‣ Not supported by evidence
  ‣ Risk limiting or delaying treatments

• Single approach to diagnosis and treatment
  ‣ Better recognition of the disease
Spectrum of Symptomatology

IC/BPS

Mild

Pain Cycles

Urinary Symptoms

Mild/intermittent/urgency/frequency

Can be severe and debilitating on their own
Pathophysiology

Joel Teichman, MD, FRCSC
Professor, Department of Urologic Sciences
University of British Columbia, Vancouver
IC/BPS Theorized Causes

- Infection
- Autoimmunity
- Mast Cell Activation
- Neurogenic Pain
- Dysfunctional Urothelium
Normal Urothelium

- GAG Layer
- Blood Vessel
- Toxic Urinary Solutes
- Umbrella Cells
- Urothelium Cells
- Basal Layer
- Interstitial Cells
- Detrusor Muscle
- Nerves

*J Urol* 1993; 149: 716
Dysfunctional Urothelium and Inflammation in IC/BPS

Healthy Bladder

IC/BPS Bladder

GAG Layer

Toxic Urinary Solutes

Umbrella Cells
Urothelium Cells
Basal Layer
Interstitial Cells
Detrusor Muscle

Nerves

Blood Vessel
Dysfunctional Urothelium and Inflammation in IC/BPS

- Toxic Urinary Solutes
- GAG Layer
- Blood Vessel
- EDEMA
- Nerves
- MAST Cells
- Sensory Nerves
- Blood Vessels
- Leukocyte Migration
- Umbrella Cells
- Urothelium Cells
- Basal Layer
- Interstitial Cells
- Detrusor Muscle

CC-14
Diagnosis

Joel Teichman, MD, FRCSC
Professor, Department of Urologic Sciences
University of British Columbia, Vancouver
Diagnosis

• Diagnosis is based on symptoms and exclusion of other causes
  ‣ Combination of pain and urinary frequency and urgency
• Typical history begins with urinary symptoms followed by pain
• Pain is the usual presenting complaint
• Many patients are undiagnosed or misdiagnosed
  ‣ Initial manifestations resemble other bladder disorders
  ‣ Patients may not receive a correct diagnosis until years after their initial symptoms
• **Statement 1**
  ‣ The basic assessment should include a careful history, physical examination, and laboratory examination to document symptoms and signs that characterize IC/BPS and exclude other disorders that could be the cause of the patient’s symptoms

• **Statement 2**
  ‣ Baseline voiding symptoms and pain levels should be obtained in order to measure subsequent treatment effects

• **Statement 3**
  ‣ Cystoscopy and/or urodynamics should be considered when the diagnosis is in doubt; these tests are not necessary for making the diagnosis in uncomplicated presentations
Cystoscopy with Hydrodistension Under Anesthesia

- Not required for diagnosis
- Potential therapeutic effect
- Used in past as diagnostic to show presence of lesions (Hunner’s) or glomerulations
- Lesions in 5-12% of symptomatic IC/BPS cases
  - Highly variable methods with potential for misinterpretation
  - Mostly seen in older patients
- Glomerulations in ≤60% of diagnosed patients
  - Non-specific: Present in other bladder diseases as well as asymptomatic controls
- Low predictive value (positive and negative) for IC/BPS
- Risks related to procedure and anesthesia
Patient Selection

C Lowell Parsons, MD
Professor Emeritus of Urology
School of Medicine
University of California, San Diego
Chairman, Urigen Pharmaceuticals
Inclusion Criteria
Based on Pain as Primary Outcome

• Have had a previous diagnosis of IC/BPS as per current AUA guidelines
• Be male and/or female of appropriate age based on trial design
• Have moderate-to-severe pain symptoms of IC/BPS for at least 6 months prior to the study (may or may not include symptoms of frequency and urgency as appropriate for specific trial)
• Pain score on validated VAS scale deemed appropriate for trial
• Symptom score of IC/BPS through appropriate assessment
  ▶ Three current assessments (O’leary-Sant, BPICSS, PUF) should be acceptable for inclusion with assessment grade appropriate for study
• May or may not have received a cystoscopy in association with their diagnosis of interstitial cystitis/bladder pain syndrome prior to or at time of screening
• Additional inclusion criteria may be warranted depending on type of intervention or study duration
Exclusion Criteria
Based on Pain as Primary Outcome

• Bacterial infection of the urinary tract
• Prescription pain medications
• Neurologic disease
• Other conflicting pain disease/disorder
• Actively Bleeding Lesions
• Has/had other conditions of the bladder that could interfere with study goals i.e.
  ‣ History of pelvic irradiation or radiation cystitis
  ‣ History or presence of uterine, cervical, pelvic, rectal, ovarian or vaginal cancer
  ‣ History of benign or malignant bladder tumors
  ‣ Current chemotherapy
  ‣ History or presence of tuberculous cystitis
  ‣ History or presence of chemical cystitis, including that due to cyclophosphamide
  ‣ History or presence of urinary schistosomiasis
  ‣ Bladder or ureteral calculi
  ‣ Clinically significant infectious vaginitis
  ‣ Currently uncontrolled genital herpes
Symptomatology Considerations

• Different therapies may target different patients based on symptomatology

• Pain is most bothersome and debilitating symptom
  ‣ Severity
    – Mild, moderate, severe
  ‣ Chronicity
    – Acute, chronic, intermittent
    – Pattern and duration of symptoms

• Urgency can also be bothersome

• Frequency, including nocturia, can be disruptive
Endpoints

C Lowell Parsons, MD
Professor Emeritus of Urology
School of Medicine
University of California, San Diego
Chairman, Urigen Pharmaceuticals
Pain

- Primary Endpoint
- Most bothersome symptom
- Drives patients to seek treatment
- Mild to severe, chronic, acute and/or intermittent
- Can change over time
  - Influenced by many factors that can affect placebo response
- **Assessment by validated Visual Analog / Numerical Rating Scales (VANRS)**
  - Long term therapies can use change in pain over weeks to months
  - Short term acute treatments show change in pain over hours to days

Please circle the number that best describes the PAIN ASSOCIATED WITH YOUR BLADDER you are **EXPERIENCING NOW**.

<table>
<thead>
<tr>
<th>None</th>
<th>BLADDER PAIN</th>
<th>worst ever</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>1</td>
<td>2</td>
</tr>
</tbody>
</table>
Urinary Symptoms

• Typical secondary endpoints

• Frequency
  ‣ Reduction assessed with voiding diary
  ‣ Nocturia

• Urgency
  ‣ VANRS
  ‣ Patient Perception of Intensity of Urgency Scale (PPIUS)
Global Assessments/Quality of Life

• Possible secondary endpoints for longer term trials
• May include assessment of combinations of individual symptoms
• May help determine how bothersome the symptoms are
• May detect symptomatic or overall improvement
• Assessments include:
  ‣ Pelvic Pain and Urgency/Frequency (PUF) questionnaire
  ‣ O'Leary-Sant Symptom and Problem Indices (OLS)
  ‣ Patient Overall Rating of Improvement of Symptoms (PORIS) questionnaire
  ‣ Genitourinary Pain Index (GUPI)
  ‣ Bladder Pain/Interstitial Cystitis Symptom Score (BPIC-SS)
  ‣ Global Response Assessment (GRA)
  ‣ Patient Perception of Bladder Condition (PPBC)
  ‣ Overactive Bladder Questionnaire (OAB-q)
Conclusions

Dan Vickery, PhD
President, Urigen Pharmaceuticals
Conclusions

• One disease
  ‣ Many names
  ‣ Spectrum of symptom severity and chronicity

• Diagnosis by symptomatology
  ‣ Exclude other causes

• Cystoscopy not required for diagnosis or study entry
  ‣ Low predictive value (positive and negative) for IC/BPS diagnosis
  ‣ May be useful to rule out other causes if diagnosis inconclusive
  ‣ Recent cystoscopy may affect symptom assessment

• Enroll patients based on symptoms and diagnosis

• Evaluate change in symptoms
  ‣ Pain is primary endpoint
  ‣ Secondary endpoints may include urinary symptoms and global assessments
Available to Address Questions

Dan Vickery, PhD  
President, Urigen Pharmaceuticals

Joel Teichman, MD, FRCSC  
Professor, Department of Urologic Sciences  
University of British Columbia, Vancouver

Lowell Parsons, MD  
Professor of Urology  
University of California, San Diego

Robert J. Evans, MD  
Associate Professor, Urology  
Wake Forest School of Medicine, Winston-Salem
Backup Slides Shown
IC/BPS Possible Confusable Diseases/Conditions

- Uterine, cervical, pelvic, rectal, ovarian, prostate or vaginal cancer
- Benign or malignant bladder tumors
- Radiation cystitis
- Tuberculous cystitis
- Bacterial cystitis
- Vaginitis
- Chemical induced cystitis
- Symptomatic urethral diverticulum
- Active herpes
- Bladder or lower ureteral calculi
- Overactive Bladder
- Endometriosis
- Urogenital prolapse
Cystoscopy Is Not Predictive of IC/BPS

And should not be considered a reliable procedure for conduct of clinical trial trials

- **Lesions**
  - Hunners lesion reported in 5-12% of patients
  - Confusion over ulcers which do not have intact urothelium and classic Hunners lesion which does: can be misdiagnosed as biopsy scars or fulguration sites
  - The absence of lesions does not preclude the diagnosis of IC/BPS
  - Trained observers can identify classic Hunners lesion using awake cystoscopy but not known whether this ability is widespread
  - Limited consistent findings
    - More common in older patients
    - Increased nocturia
    - Higher pain scores

- **Glomerulations**
  - Present in 30% to 60% of IC/BPS patients, and many of those are scant
  - May arise from cystoscopic trauma or trauma of hydrodistension
  - Reported to be equally present in both IC patients and asymptomatic controls
  - There is a poor correlation between observed severity and symptomology
  - Interrater reliability is poor

Diagnosis (AUA Guidelines)

IC/BPS
An unpleasant sensation (pain, pressure, discomfort) perceived to be related to the urinary bladder, associated with lower urinary tract symptoms of more than six weeks duration, in the absence of infection or other identifiable causes

Basic Assessment
- History
- Frequency/volume chart
- Post-void residual
- Physical examination
- Urinalysis, culture
- Cytology if smoking history
- Symptom questionnaire
- Pain evaluation

Signs/symptoms of complicated IC/BPS
- Incontinence/OAB
- GI signs/symptoms, microscopic/gross, hematuria/sterile pyuria
- Gynecologic signs/symptoms

Consider:
- Urine cytology
- Imaging
- Cytoscopy
- Urodynamics
- Laparoscopy
- Specialist referral (urologic or non-urologic appropriate)

Confirmed or uncomplicated IC/BPS
TREAT FOR IC/BPS
TREAT and REASSES

Dx urinary tract infection

TREAT and REASSES
Inflammation Cycle

Bladder Insult (Loss of Protective GAG Layer)

More Injury

Mast Cell Activation and Histamine Release

Epithelial Layer Damage

Potassium Leak into Interstitium

Activation of C-fibers and Release of Substance P
Acute Relief of IC/BPS Symptoms Can be Measured

**URG101 Pharmacodynamic Study**

% Change in Pain Over Time, n=18 patients

- Placebo Avg
- URG101 Avg

* Statistically significant

Parsons et al. *J Sex Med* 2012;9:207–212
Patient Overall Rating of Improvement in Symptoms Questionnaire

Please check the category that BEST describes your condition NOW in COMPARISON to your condition BEFORE you started study medication.

1. Please check the category that best describes the OVERALL CHANGE in PAIN associated with your pelvic/bladder pain now compared to before receiving study medication. (Check one box)
   - [ ] Worse
   - [ ] No better (0% improvement)
   - [ ] Slightly improved (25% improvement)
   - [ ] Moderately improved (50% improvement)
   - [ ] Greatly improved (75% improvement)
   - [ ] Symptoms gone (100% improvement)

2. Please check the category below that best describes the OVERALL CHANGE in URGENCY to urinate associated with your bladder now compared to before receiving the study medication. (Check one box)
   - [ ] Worse
   - [ ] No better (0% improvement)
   - [ ] Slightly improved (25% improvement)
   - [ ] Moderately improved (50% improvement)
   - [ ] Greatly improved (75% improvement)
   - [ ] Symptoms gone (100% improvement)

3. Considering your response to items 1 and 2, please check the category below that best describes the OVERALL CHANGE in your problem COMPARED TO BEFORE YOU RECEIVED the study medication. (Check one box)
   - [ ] Worse
   - [ ] No better (0% improvement)
   - [ ] Slightly improved (25% improvement)
   - [ ] Moderately improved (50% improvement)
   - [ ] Greatly improved (75% improvement)
   - [ ] Symptoms gone (100% improvement)

PUF – Pelvic Pain and Urgency/Frequency Scale

Please circle the answer that best describes how you feel for each question.

<table>
<thead>
<tr>
<th>Symptom Score</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Better Score</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

1. How many times do you go to the bathroom during the day?
   - (Add scores from top column: 1, 2a, 3a, 4a, 5a, 6a)
   - SYMPTOM SCORE =

2. a. How many times do you go to the bathroom at night?
   - (Add scores from top column: 2b, 3b, 5b, 6b)
   - BOTHER SCORE =

3. a. Do you now or have you ever had pain or symptoms during or after sexual intercourse?
   - Never | Occasionally | Usually | Always

4. Do you have pain associated with your bladder or in your pelvis (e.g., uterine, labia, lower abdomen, urethra, perineum, testes, or scrotum)?
   - Never | Occasionally | Usually | Always

5. a. If you have pain, is it usually
   - Mild | Moderate | Severe

6. b. Does your pain bother you?
   - Never | Occasionally | Usually | Always

7. a. If you have urgency, is it usually
   - Mild | Moderate | Severe

8. b. Does your urgency bother you?
   - Never | Occasionally | Usually | Always

9. Are you sexually active?
   - Yes | No

TOTAL SCORE (Symptom Score + Bother Score) =
## IC/BPS Prevalence in Woman
### RICE Study


<table>
<thead>
<tr>
<th>Estimated Prevalence Rates</th>
<th>High Sensitivity Definition Prevalence (95% CI)</th>
<th>High Specificity Definition Prevalence (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>0.065 (0.063, 0.068)</td>
<td>0.027 (0.025, 0.029)</td>
</tr>
<tr>
<td><strong>Race</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>0.067 (0.065, 0.070)</td>
<td>0.030 (0.028, 0.032)</td>
</tr>
<tr>
<td>Black</td>
<td>0.058 (0.050, 0.065)</td>
<td>0.019 (0.015, 0.023)</td>
</tr>
<tr>
<td>Hispanic</td>
<td>0.065 (0.055, 0.075)</td>
<td>0.020 (0.015, 0.026)</td>
</tr>
<tr>
<td>Other</td>
<td>0.065 (0.054, 0.076)</td>
<td>0.026 (0.019, 0.033)</td>
</tr>
<tr>
<td>Refused/no response</td>
<td>0.033 (0.021, 0.046)</td>
<td>0.021 (0.011, 0.032)</td>
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<tr>
<td><strong>Census region</strong></td>
<td></td>
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<tr>
<td>Northeast</td>
<td>0.056 (0.051, 0.062)</td>
<td>0.022 (0.019, 0.026)</td>
</tr>
<tr>
<td>North Central</td>
<td>0.063 (0.058, 0.069)</td>
<td>0.027 (0.024, 0.031)</td>
</tr>
<tr>
<td>South</td>
<td>0.072 (0.068, 0.077)</td>
<td>0.029 (0.027, 0.032)</td>
</tr>
<tr>
<td>West</td>
<td>0.063 (0.057, 0.069)</td>
<td>0.026 (0.023, 0.030)</td>
</tr>
<tr>
<td><strong>Age</strong></td>
<td></td>
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<tr>
<td>18-29</td>
<td>0.057 (0.050, 0.064)</td>
<td>0.022 (0.018, 0.026)</td>
</tr>
<tr>
<td>30-39</td>
<td>0.067 (0.060, 0.075)</td>
<td>0.026 (0.021, 0.030)</td>
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<tr>
<td>40-49</td>
<td>0.075 (0.069, 0.080)</td>
<td>0.032 (0.028, 0.036)</td>
</tr>
<tr>
<td>50-59</td>
<td>0.074 (0.069, 0.079)</td>
<td>0.034 (0.031, 0.038)</td>
</tr>
<tr>
<td>60-69</td>
<td>0.068 (0.063, 0.074)</td>
<td>0.028 (0.025, 0.032)</td>
</tr>
<tr>
<td>70-75+</td>
<td>0.048 (0.042, 0.053)</td>
<td>0.017 (0.014, 0.020)</td>
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# RICE High Sensitivity and High Specificity Case Definitions for IC/BPS

<table>
<thead>
<tr>
<th>Exclusion Criteria*</th>
<th>Female</th>
<th>Male</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Bladder cancer, urethral diverticulum, spinal cord injury, stroke, Parkinson’s disease, multiple sclerosis, spina bifida, cyclophosphamide treatment, radiation treatment to pelvic area, tuberculosis affecting the bladder, genital herpes</td>
<td>Uterine cancer, ovarian cancer, vaginal cancer, pregnancy</td>
</tr>
</tbody>
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<table>
<thead>
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<th>High Sensitivity Definition</th>
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<th>Male</th>
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<td>Pain, pressure, or discomfort in the pelvic area and Daytime urinary frequency 10+ or urgency due to pain, pressure, or discomfort, not fear of wetting</td>
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</tbody>
</table>

(81% Sensitivity, 54% Specificity)

<table>
<thead>
<tr>
<th>High Specificity Definition</th>
<th>Female</th>
<th>Male</th>
</tr>
</thead>
<tbody>
<tr>
<td>High Sensitivity Definition plus pain worsens as bladder fills and Symptoms did not resolve after treatment with antibiotics and No treatment with hormone injection therapy for endometriosis</td>
<td></td>
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</tbody>
</table>

(48% Sensitivity, 83% Specificity)