

# **A Perspective on Clinical Trial Development for Interstitial Cystitis / Bladder Pain Syndrome (IC/BPS)**

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**Bone, Reproductive, and Urologic Drugs Advisory Committee  
December 7, 2017**

**Aquinox Pharmaceuticals (Canada), Inc.**

# Introduction

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**Barbara Troupin, MD, MBA**

Chief Medical Officer, VP Clinical Development & Regulatory Affairs  
Aquinox Pharmaceuticals, Inc.

## **Aquinox Pharmaceuticals, Inc.**

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- ◆ **Clinical-stage pharmaceutical company**
- ◆ **Vancouver, BC and San Bruno, CA**
- ◆ **IC/BPS focus since 2013**
- ◆ **Lead product candidate – AQX-1125**

# Sponsor Perspective on Today's BRUDAC Meeting on IC/BPS

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## ◆ Clarifying IC/BPS nomenclature

- Single patient population
- Unified symptom complex, defined by AUA criteria

## ◆ Clinical trial population should be symptom-defined

- Inclusive of patients with IC/BPS with Hunner lesions (“Classical IC”)
- Cystoscopy with hydrodistension under anesthesia or bladder biopsies not required for patient selection

## ◆ Consistent treatment goal – reduction in bladder pain – further supports one population, one trial

# Today's Agenda

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## Defining an IC/BPS Population for Clinical Study

### **Robert M Moldwin, MD, FACS**

*Professor of Urology - The Arthur Smith Institute for Urology,  
Zucker School of Medicine at Hofstra/Northwell  
Lake Success, NY*

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## Endpoint Selection and Trial Design in IC/BPS

### **J Curtis Nickel, MD, FRCRC**

*Professor of Urology, Queen's University  
CIHR Canada Research Chair in Urologic Pain and  
Inflammation, Kingston General Hospital*

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## Summary

### **Barbara Troupin, MD, MBA**

*Aquinox Pharmaceuticals, Inc.*

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*Expert Speakers have been compensated by Aquinox for their participation in this meeting.*

## Additional Expert

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**Tara Symonds, PhD**

*Strategic Lead, Clinical Outcome Assessment  
Clinical Outcome Solutions*

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*Clinical Outcome Solutions experts work as vendor partners with Aquinox.*

# Defining an IC/BPS Population for Clinical Study

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**Robert M Moldwin, MD**

*Professor of Urology*

*The Arthur Smith Institute for Urology*

*Zucker School of Medicine at Hofstra/Northwell*

*Lake Success, NY*



# Disclosures

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- ◆ **National Institutes of Health**      **Peer-reviewed funding**
- ◆ **Allergan Pharmaceuticals**      **Consultant, PI**
- ◆ **Aquinox Pharmaceuticals**      **Consultant, PI**
- ◆ **Urogen Pharmaceuticals**      **Consultant, PI**



## What is IC/BPS?

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***An unpleasant sensation (pain, pressure, discomfort) perceived to be related to the urinary bladder, associated with lower urinary tract symptoms of more than 6 weeks duration, in the absence of infection or other identifiable causes.***

**American Urological Association (AUA) Guideline  
2014 Update**

# Symptoms of IC/BPS

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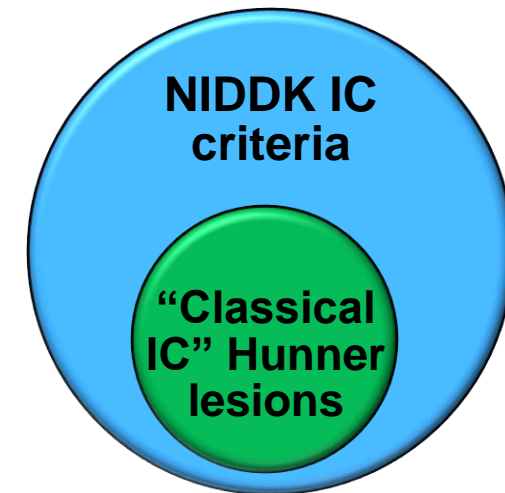
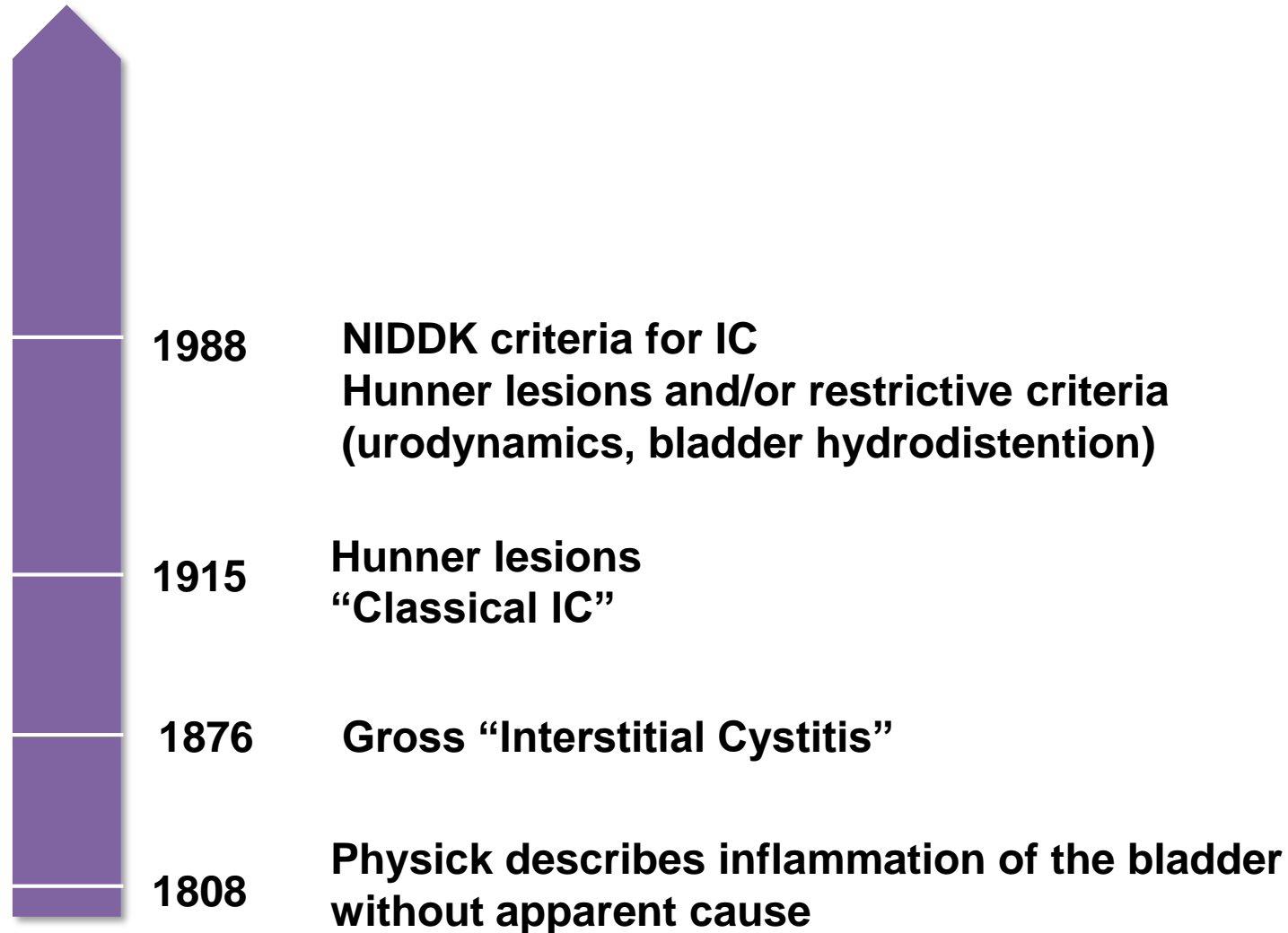
## ◆ Bladder pain

- Most bothersome symptom
- Usually worsens with bladder filling
- Predictive of poor health-related QOL

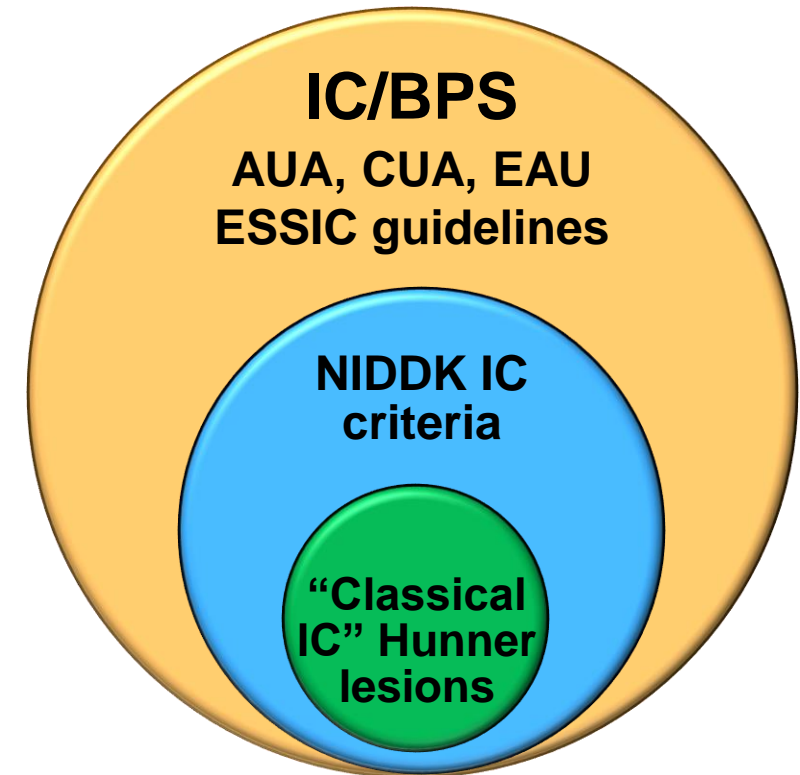
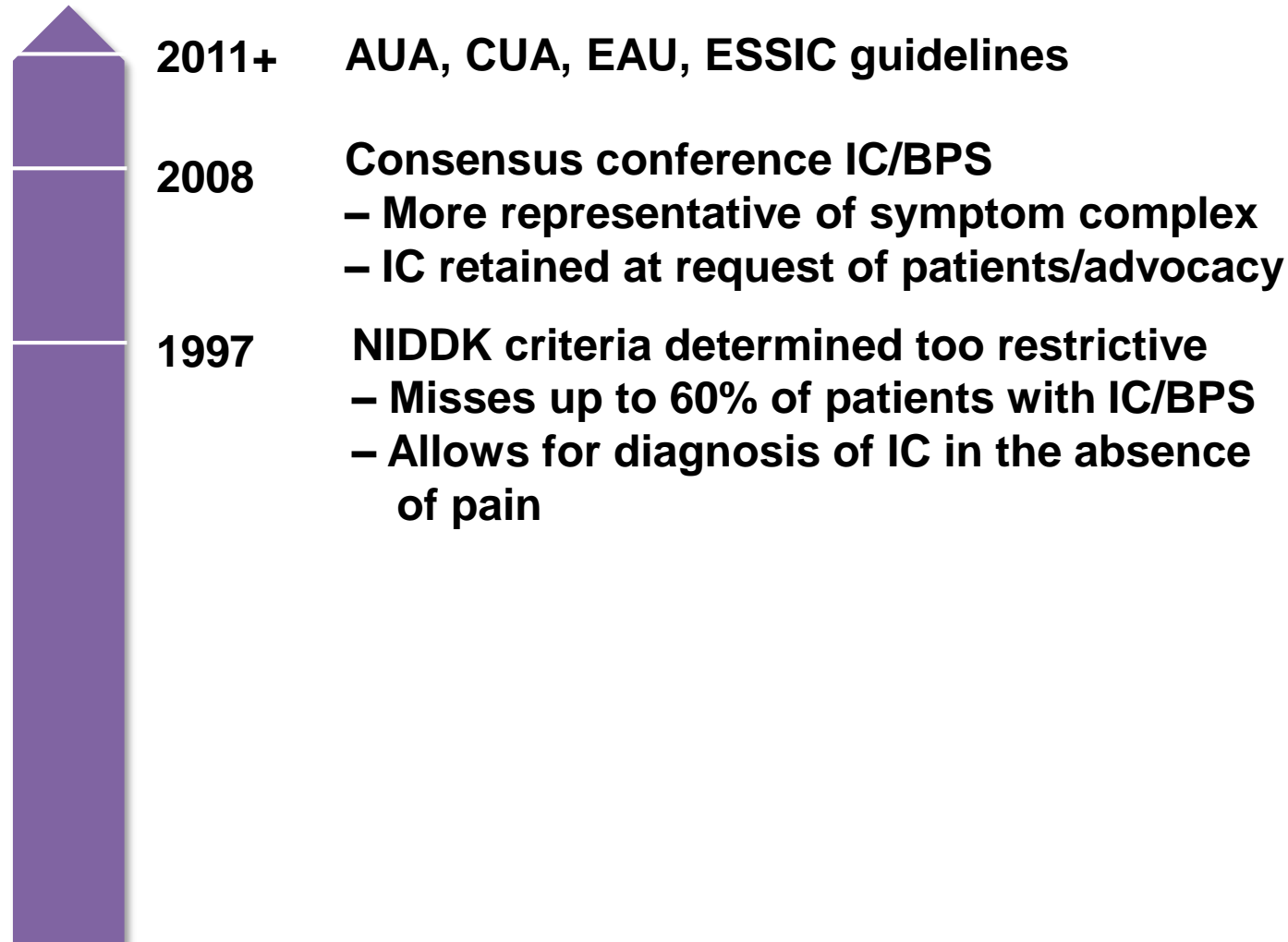
## ◆ Urinary symptoms

- Frequency (daytime and nighttime) and urgency
- Used to avoid bladder pain by some patients
- May also reflect low bladder capacity

# Evolution of the Term “IC/BPS” and the Patient Population



# Evolution of the Term “IC/BPS” and the Patient Population



## Treatments for IC/BPS Offer Limited Efficacy

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### ◆ Only 2 FDA-approved therapies

- Oral – Elmiron<sup>®</sup> (pentosan polysulfate sodium) approved in 1996
- Intravesical – RIMSO-50<sup>®</sup> (DMSO) approved in 1978

### ◆ Other drugs used with limited clinical evidence

- Oral – amitriptyline and hydroxyzine
- Intravesical – lidocaine and heparin
- Opioids often needed for pain management

### ◆ Procedural approaches

- Fulguration

# Defining the IC/BPS Population for Clinical Trials

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- ◆ **Diagnosis per AUA guidelines**
- ◆ **Moderate to severe bladder pain**
- ◆ **Significant urinary symptoms**
  - Voiding frequency or urgency

# Key Entry Criteria for Clinical Trials for IC/BPS

Key Criteria	IC/BPS
Diagnosis per AUA guidelines	✓
Bladder pain - moderate to severe	✓
Urinary symptoms - frequency/urgency	✓
Rule out confusable disorders (UTI, OAB)	✓
Exclusion of confounding medications	✓
Exclusion of recent invasive therapies	✓

# Key Entry Criteria for Clinical Trials if Split into Designations of “Classical IC” and BPS

Key Criteria	IC/BPS	“Classical IC”	BPS
Diagnosis per AUA guidelines	✓	✓	✓
Bladder pain - moderate to severe	✓	✓	✓
Urinary symptoms - frequency/urgency	✓	✓	✓
Rule out confusable disorders (UTI, OAB)	✓	✓	✓
Exclusion of confounding medications	✓	✓	✓
Exclusion of recent invasive therapies	✓	✓	✓



# The Role of Cystoscopy in IC/BPS

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## ◆ Cystoscopy with hydrodistention/biopsy

- Requires general anesthesia
- Risks – infection, bleeding, and bladder perforation
- Low predictive value

## ◆ Office cystoscopy

- Can be used to rule out confounding diseases in complicated cases
- A study protocol should include the collection of cystoscopy data for subpopulation analysis

## Studying the IC/BPS Population

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- ◆ **Single population sharing similar bladder pain and urinary symptoms**
  - Subpopulation analyses based on baseline characteristics, if conducted, may inform future clinical trial design, regulatory review, and clinical use
  - Option to study specific subpopulations based on mechanism of action or early clinical data
- ◆ **Based on symptom presentation using AUA criteria**
  - Replace NIDDK approach with more inclusive criteria that reflect clinical practice patterns

# Endpoint Selection and Trial Design in IC/BPS

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**J. Curtis Nickel, MD, FRCSC**

*Professor of Urology, Queen's University*

*CIRH Canada Research Chair in Urologic Pain and Inflammation*

*Kingston General Hospital*

# Disclosures

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## Peer-Reviewed Funding

Canada Institute for Health Research  
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## Consultant

Allergan Pharmaceuticals  
Alvio Therapeutics  
Farr Labs  
Interface Biologics  
Medifocus  
PureTech Health  
Seikagaku Corp

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## Consultant/Scientific Study/Trial

Aquinox Pharmaceuticals  
Astellas Pharma, Inc

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# Bladder Pain as a Primary Endpoint

- ◆ **Hallmark symptom of IC/BPS, experienced by virtually all patients**
- ◆ **IMMPACT recommendation**
  - “For most clinical trials of chronic pain treatments, a measure of pain intensity will provide the primary outcome measure”
  - Convened July 2017 to discuss chronic pelvic pain including IC/BPS
- ◆ **Maximum (worst) daily bladder pain**
  - Easier for patients to recall than average pain
  - DAAAP recommends an instrument that assesses worst pain over a relatively short recall period

IMMPACT = Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials: a collaborative effort from Academia, FDA, EMA, US NIH, consumer support and advocacy groups (including Chronic Pain Research Alliance), and industry.

Hanno PM, et al. AUA Guideline. *J Urol.* 2014;1-45; Dworkin RH, et al. *J Neuroimmunol.* 2005;113:9-19; Schneider S, et al. *Pain.* 2011;12:228-235; FDA Guidance for Industry Analgesic Indications: Developing drugs and biological products, draft guidance. 2014

# Assessing Bladder Pain Intensity in IC/BPS

## ◆ 11-point numerical rating scale (NRS)

- Recommended by IMMPACT as a robust tool
- Assessed by daily bladder diary, short recall period (24 hour)

<b>Select the number that best describes your worst bladder pain during the past 24 hours.</b> <i>(Circle one number only)</i>												
No bladder pain	0	1	2	3	4	5	6	7	8	9	10	Worst possible bladder pain

## ◆ Alternative method: visual analogue scale (VAS)

- Assessed by daily bladder diary, short recall period (24 hour)

# Hierarchical Secondary Endpoints in IC/BPS

## ◆ Urinary symptoms

- Quantitative measures of urinary frequency (daytime and nighttime)
  - Voiding diary or frequency volume chart
- Measures of urinary urgency

## ◆ Composite questionnaires

- BPIC-SS
- Legacy measures

Selection of secondary and even primary endpoints may vary by MOA

# Supportive Endpoints & Assessments in IC/BPS

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## ◆ Health-related QOL measures

- SF-12
- Disease specific measures of QOL

## ◆ Global response – PGI-C or GRA

- Allows assessment of clinically meaningfulness of key endpoints via anchor based analyses

## ◆ Rescue medication use

- Can help isolate treatment effect



## Other Considerations – Clinical Trial Duration and Geography

- ◆ **12 weeks is an appropriate duration to establish efficacy in chronic therapies**
  - IC/BPS symptoms may vary but consistency of effect can be seen in 12 weeks
  - DAAAP/IMPACT recommend 12-week trials for chronic pain studies
  
- ◆ **IC/BPS trials can be multi-regional**
  - US, Canada, and Europe share overlapping disease definitions and clinical guidelines
  - Country and region selection for clinical trials should be based on consistency in clinical standard of care

# Patients with IC/BPS Should be Studied in a Single Trial

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## ◆ Advantages

- Inclusive of all patients based on symptom presentation
- Treatment goals consistently focus on bladder pain/symptom relief
- Measurement tools to assess achievement of treatment goals identical
- Potential for subgroup analyses based on baseline characteristics, e.g. cystoscopy data

## ◆ Disadvantages

- If sub-populations represent a non-responsive group, efficacy in total population may be impacted

## Endpoints for Clinical Trials for IC/BPS

Endpoints	IC/BPS	“Classical IC”	BPS
Bladder pain – maximum (worst) daily (NRS)	✓	✓	✓
Urinary symptoms (voiding diaries)	✓	✓	✓
Composite questionnaires (BPIC-SS or other)	✓	✓	✓
Health related QOL measures (SF-12 or disease specific)	✓	✓	✓
Global response (PGI-C or GRA)	✓	✓	✓
Rescue medication use	✓	✓	✓

If split into designations of “Classical IC” and BPS, endpoints would remain the same

## Clinical Trial Design Considerations – Summary

- ◆ **Study the IC/BPS patient population in one trial**
  - Capturing baseline characteristics expands disease knowledge and enables characterization of treatment response
- ◆ **Primary endpoint of bladder pain is of greatest relevance to patients and clinicians**
  - Secondary endpoints further characterize treatment benefit
  - Selection of endpoints and hierarchy can be tailored based on mechanism of action or prior clinical data

Ultimate goal is to bring safe and effective treatments to patients to address their symptoms where there is an unmet need

# Summary

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*Chief Medical Officer, VP Clinical Development & Regulatory Affairs  
Aquinox Pharmaceuticals, Inc.*

## Perspective on Clinical Development in IC/BPS

- ◆ **IC/BPS is a single condition and best studied in a single inclusive trial**
  - Region selection based on consistency of patient population
- ◆ **Endpoint approach to follow COA best practices**
  - Primary endpoint of bladder pain – sufficient basis for approval
  - Secondary endpoints help characterize overall benefit
- ◆ **Trial design and duration consistent with other chronic pain studies**
  - 12 weeks in duration

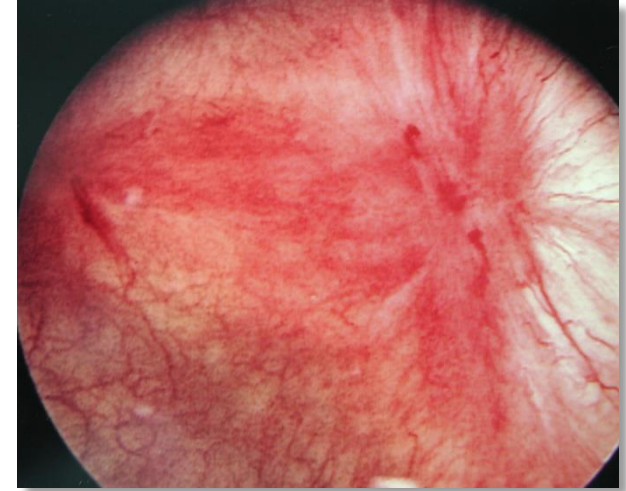
Clarity of regulatory guidance critical in supporting clinical development in IC/BPS

# Supporting Slides

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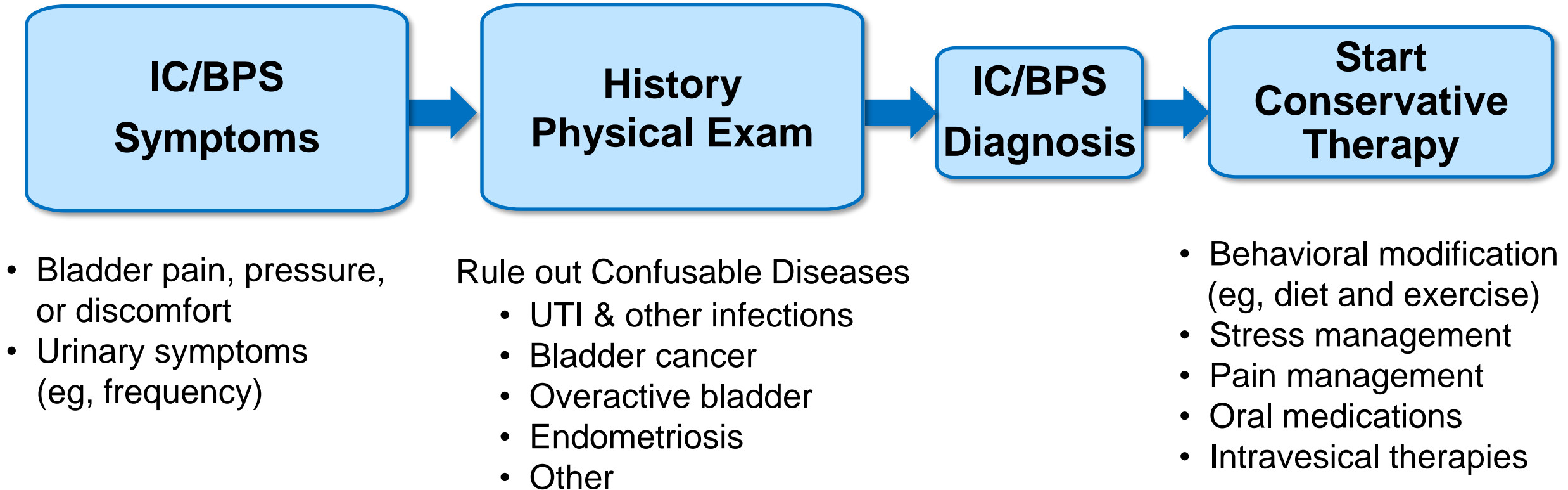
# Bladder Hydrodistention Not Required for Hunner Lesion Identification

- ◆ **Hunner lesions can be identified by office cystoscopy**
  - Number and size of lesions can be quantified
- ◆ **Original description never included need to over distend bladder**
  - Lesion identification through bladder trauma?
- ◆ **Bleeding and bladder wall tearing often occur with hydrodistention**
  - How to monitor for disease status?





# Current Management Approach Aligned with AUA Guidelines



# BPIC-SS

Concept	Sub-concept	In the Past 7 Days:
Urge to urinate	Persistent/constant need to urinate	How often did you still feel the need to urinate just after you urinated?
	The necessity to urinate driven by bladder pain	When you urinated, how often was it because of pain in your bladder?
		How often did you urinate to avoid pain in your bladder from getting worse?
Urinary frequency	Bother associated with daytime urinary frequency	How bothered were you by frequent urination during the daytime?
	Bother associated with nighttime urinary frequency	How bothered were you having to get up during the night to urinate?
Bladder pain and pressure	N/A	How often did you have a feeling of pressure in your bladder?
		How often did you have pain in your bladder?
		Select the number that describes your worst bladder pain in the past 7 days.

# Defining an IC/BPS Patient Population for Clinical Trials

## ◆ Baseline Characteristics

- Medical history, medication use, co-morbidities, duration of symptoms, cystoscopic findings

## ◆ Key Inclusion

- Male and female patients, age  $\geq 18$  and  $\leq 80$  years at Screening
- Diagnosis, or consistent history, of IC/BPS for  $>3$  months, AUA guideline
- BPIC-SS of  $\geq 19$  (differentiate from OAB)
- ICSI of  $\geq 7$  (enriches for symptoms of IC/BPS)
- Pelvic floor pain  $< 7/10$  on the 11-point NRS pain scale
- Average daily pain score of  $\geq 5$  out of 10 (mean of the av. daily pain score recorded at each of the 7 days prior to Visit 2) with minimum of 5 records within 7 days prior to Visit 2 must be recorded
- $\geq 8$  voids in a 24-hour period recorded within 72 hours prior to Visit 2