Development of Drugs Intended for Treatment of Interstitial Cystitis (IC) and Bladder Pain Syndrome (BPS)

Opening Remarks

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Agenda

• Brief Overview of Today’s Meeting
• Industry presentations
• FDA presentations
• Open Public Hearing
• Questions to the Panel
Introduction

• Interstitial Cystitis (IC)
  – Patients report pain referable to the bladder made worse by bladder filling and relieved by bladder emptying
  – First described in 1887
  – Clinical definition expanded with 1988 NIDDK criteria
  – Diagnosis focused on bladder symptoms and clinical findings (i.e. cystoscopic findings)
  – Treatment focused on symptom relief
Bladder Pain Syndrome (BPS)

– Definition is similar to IC
– Recent broadening of the concept of IC
– Diagnosis on clinical symptomatology and exclusion of other confounding conditions
– Treatment is symptomatic
– Current target populations in worldwide clinical guidelines appear to be heterogeneous
American Urological Association (AUA) Guideline for IC/BPS

• Describes basic assessment, laboratory examinations
• Recommends documenting symptoms and signs of IC/BPS
• Presents a framework for clinical evaluation:
  – Determine whether the bladder is the source of pain
  – Identify if other urologic sources for pain (e.g. stones)
  – Identify if source of pain is outside urinary tract
AUA Guideline for IC/BPS (continued)

• Cystoscopy and/or urodynamics should be considered when the diagnosis in doubt

• Provides treatment recommendations:
  – Therapies should proceed from most to least conservative
  – Surgical therapy recommended only after other therapies are ineffective
  – Pain management should be considered throughout course of therapy with goal of maximizing function and minimizing pain and side effects
What is substantial evidence of effectiveness for the purposes of drug approval

- Approval requires adequate and well controlled trials
- Requirements for these trials include, but are not limited to:
  - Valid comparison with control (e.g. placebo)
  - Subjects have condition of interest
  - Minimize bias and assure comparable treatment groups
  - Well-defined methods for analyzing treatment response
Issues for IC/BPS Drug Development

– IC/BPS is a heterogeneous population of patients because:
  • Diagnosis of exclusion
  • Symptoms overlap with other conditions
  • No known etiology
  • No biomarker(s) or “gold standard” to identify patient population
  • No agreed on urodynamic/cystoscopic findings using diagnostic modalities available in the office
  • Simple cystoscopy will not identify Hunner’s lesions and/or other pathology – requires cystoscopy with hydrodistension under anesthesia
Meeting Goals

Today’s discussion will focus on:

• How to best define the population(s) that will optimize drug development in this field

• How to select endpoints that demonstrate clinically meaningful benefit
Discussion and Voting Questions
Question 1

• Discuss the key inclusion and exclusion criteria, including diagnostic procedures, for trials evaluating drugs intended to treat interstitial cystitis.
Question 2

• Discuss the key inclusion and exclusion criteria, including diagnostic procedures, for trials evaluating drugs intended to treat bladder pain syndrome.
Question 3

• For drugs intended to treat patients with interstitial cystitis, discuss:
  
a. How the key symptoms and signs should be defined and assessed

b. Acceptable endpoints for demonstrating clinical benefit

c. Other key trial design features that should be considered
Question 4

• For drugs intended to treat patients with bladder pain syndrome, discuss:
  a. How the key symptoms and signs should be defined and assessed
  b. Acceptable endpoints for demonstrating clinical benefit
  c. Other key trial design features that should be considered
Question 5

• When assessing efficacy for drugs intended to treat patients with interstitial cystitis and bladder pain syndrome, should clinical trials use:
  
a. One set of patient reported outcome (PRO) instruments for patients with interstitial cystitis and a different set of PRO instruments for those with bladder pain syndrome?
  
b. One set of PRO instruments used both for patients with interstitial cystitis and those with bladder pain syndrome?
Question 6

• When assessing drugs intended to treat interstitial cystitis and bladder pain syndrome, discuss:
  a. The advantages of enrolling patients with interstitial cystitis and bladder pain syndrome in the same trial
  b. The disadvantages of enrolling patients with interstitial cystitis and bladder pain syndrome in the same trial
VOTING QUESTION:

• Should patients with interstitial cystitis and those with bladder pain syndrome be combined in clinical trials?
• Discuss the rationale for your vote
Clinical Perspective: Clinical Trials for Interstitial Cystitis/ Bladder Pain Syndrome (IC/BPS)

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HISTORICAL DESCRIPTIONS OF INTERSTITIAL CYSTITIS (IC):

1887 Inflammation of bladder wall described by AJ Skene

1918 Dr. Guy Hunner described IC as:
1) bladder pain related to bladder filling AND
2) a cystoscopic bladder lesion-Hunner’s lesion

50 years – Diagnosis of IC
CYSTOSCOPY WITH HYDRODISTENSION UNDER ANESTHESIA

Procedure generally described to provoke a Hunner’s lesion:

1) Fill bladder under gravity to 80 cm H₂O for 2-3 minutes

2) Establish total bladder capacity under anesthesia

3) Repeat filling of bladder with one or two additional milder hydrodistensions to incite “waterfall” bleeding and atypical edema
HUNNER’S LESION

BEFORE: Cystoscopic view of a Hunner lesion. Findings are non-specific for Hunner’s lesion before distension

AFTER: Same lesion after hydrodistension. A deep rupture is seen in the bladder wall

cystoscopy with hydrodistension

Initial phase of bladder distension: waterfall-like bleeding from discrete Hunner lesion

Contributed by Dr. Magnus Fall from his patient collection.
Initial phase of bladder distension: waterfall-like bleeding from discrete Hunner lesion

Contributed by Dr. Magnus Fall from his patient collection.

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Post distension edema

Contributed by Dr. Magnus Fall from his patient collection.

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Post distension edema

Contributed by Dr. Magnus Fall from his patient collection.

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Marked post distension edema

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Marked post distension edema

Hunner’s lesion outline

Contributed by Dr. Magnus Fall from his patient collection.

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Expansion of the IC Population: Development of the NIDDK Criteria

- 1970’s recognition of more diverse forms of IC
- 1988 National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) developed research criteria
INTERSTITIAL CYSTITIS

- Understanding of this condition relied on expert opinion
- No precise definition for interstitial cystitis
- Interstitial cystitis is a syndrome characterized by urinary frequency, nocturia, urgency, suprapubic pressure and pain with bladder filling relieved by emptying
- Unknown etiology and pathogenesis of the disease
- Rates in women are higher than men by ratio 10:1
- Urine cultures and cytologies are negative
NIDDK CRITERIA

Automatic inclusions:
Hunner's lesion

Positive factors (at least 2 positive factors for inclusion):
1) Pain on bladder filling relieved by emptying
2) Other pain (e.g. suprapubic, pelvic, urethral or perineal)
3) Glomerulations on endoscopy
4) Decreased compliance on urodynamic evaluation
NIDDK EXCLUSION CRITERIA

These criteria attempted to exclude overlapping diseases with similar symptoms and signs

**Significant Exclusions Included:**

- Daytime frequency < 5 times in 12 hours
- Nocturia < 2 times
- Duration < 12 months
RULE-OUT OVERLAPPING DISEASES WITH SIMILAR PRESENTATIONS

Includes:

- Endometriosis
- Pelvic pain syndrome
- Benign or malignant bladder tumors
- Radiation cystitis
- Viral (herpes) or urinary tract infections
- Neurogenic bladder
- Overactive bladder
- Abdominal disorders with similar symptoms
- ETC.

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After publication of the NIDDK criteria:

- Use of NIDDK criteria for clinical diagnosis although intended for research purposes
- 60% of patients with bladder pain symptoms NOT included in NIDDK criteria patients
- Evolution of bladder pain syndrome to include patients with and without bladder lesions or obvious bladder inflammation with similar symptoms
EXPANSION INTO BLADDER PAIN SYNDROME

Heterogeneous patient population includes:
1) Classical IC patients with Hunner’s lesions
2) NIDDK criteria patients
3) Similar symptoms but do not fulfill NIDDK criteria (BPS)
RELEVANCE OF HUNNER’S LESION PATIENTS (CLASSICAL IC)

- Pathognomonic Bladder Finding on Provoked Cystoscopy with Hydrodistension
- Older Patients with Smaller Bladder Capacities
- Increased Mast Cells in all Cell Wall Layers on Bladder Biopsies
- Higher Rates of Bladder Frequency Symptoms
- Suggestion of More Severe Disease Process with Fibrosis of Bladder Walls at Diagnosis
HUNNER’S LESION TREATMENTS

Treatment Options:

- Ablation of Lesions (e.g. fulguration and transurethral resection of lesions, etc.)
  - Reported up to 90% symptom relief in 50% of patients for up to three years
- No FDA-approved drugs to treat Hunner’s lesions

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SEPARATION OF CLASSICAL IC FROM BLADDER PAIN SYNDROME (BPS)

Distinct Patient Populations
HUNNER’S LESION RATES
WORLDWIDE DIFFERENCES

US Clinicians Rates Estimated 3-20%
(Some US Clinicians Doubt Existence)

European and Asian Clinicians Publish Rates 30-57%

WHY???

a) Genetics?
b) Referral Base?
c) Cystoscopy and Hydrodistension (with Biopsies)
d) All of the Above
e) Some of the Above or None of the Above

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Countries and regions with high rates of cystoscopy with hydrodistension (e.g. Asia, Sweden, Scandinavia, and Russia, etc.) report the highest rates of Hunner’s lesions.

In the US, cystoscopy and hydrodistension is not widely practiced in many clinical centers as the widening patient target population no longer requires bladder findings to be included in the diagnosis for treatment.

Does cystoscopy with hydrodistension equal higher detection rates of Hunner’s lesions?
Worldwide harmonization for IC/BPS has coalesced around similar clinical definitions but with some notable differences

The following tenants are generally in the current American and European clinical definitions:

- Chronic pain related to the bladder
- Accompanying urinary symptoms
- Exclusion of other diseases or disorders with similar presentations
CLINICAL TRIAL PATIENT POPULATION

Target Population:

• Well-defined patient population suitable for enrollment in studies and trials

• Identify symptoms of patients at baseline for drug targets, accounting for waxing/waning course and pain flares

• Rule-out overlapping and other diseases/disorders with similar symptoms
TARGET PATIENT POPULATION

- Study only classical IC patients:
  - Advantages: well-defined population makes it more likely detect treatment effect
  - Disadvantages: narrow patient population and precludes other patients who could benefit

- Study both classical IC patients and the general IC/ BPS patients with documentation of Hunner’s lesions by hydrodistension in all patients for subgroup analysis
CAPTURING TARGET POPULATION
CAPTURING TARGET POPULATION
CAPTURING TARGET POPULATION

BPS

NIDDK IC Criteria

Classical IC
CAPTURING TARGET POPULATION

BPS

NIDDK IC Criteria

Classical IC
ELIGIBILITY CRITERIA CONSIDERATIONS

1) Bladder pain perceived to be from the bladder or pain on bladder filling which is relieved upon emptying, etc.

2) Urinary Symptoms such as frequency and nocturia

3) Pain Flares-consider how to measure waxing/ waning pain episodes

4) Other Considerations:
   - Duration of disorder- > 6 months?
   - Other urinary symptoms such as urgency
   - Objective findings such as maximal voided volume
ELIGIBILITY CRITERIA CONSIDERATIONS

- IC/ BPS remains a diagnosis of exclusion of overlapping diseases and disorders

- Importance of baseline history, physical exams, laboratory studies and other procedures to rule-out other disease and disorders as in the NIDDK criteria

- The IC/BPS population remains heterogeneous and differences in subgroups may impact drug development
PROTOCOL DESIGN CONSIDERATIONS

- Efficacy endpoints should be able to show clinically meaningful benefits of treatment

- Different patients may have different severity of pain and different associated urinary symptoms

- Specify pain therapies:
  1) Pre-specify acceptable baseline and maintenance pain therapy
  2) Define pain flares, pain severity and minimal threshold for pain rescue therapy
  3) Pre-specify any rescue medication regimens
EFFICACY ENDPOINT CONSIDERATIONS

One Approach → Co-Primary Endpoints:
Bladder pain symptoms + Key urinary tract symptom change

Alternative Approach:
- Primary endpoint- bladder pain symptom (e.g. pain perceived from the bladder, bladder pain increased with filling, relieved with emptying, etc.)
- Key secondary endpoint- changes in urinary tract symptoms such as urinary frequency
PATIENT REPORTED OUTCOMES (PROs)

• PROs to capture bladder pain, related to pain on filling, emptying and other aspects (e.g. frequency, nocturia, etc.)

• PROs may capture disease or disorder aspects not felt to be previously quantifiable or discernible

• Following presentation will focus more on ways to capture these important aspects
OTHER STUDY CONSIDERATIONS

- Pain flare treatment could confound studies – pre-specify the assessments, treatments, and how rescue medications will be handled with regard to the key efficacy endpoints

- Concerns using generalized abdominal pain or lower abdominal pain as primary efficacy - overlaps with other diseases/ disorders such as vulvodynia, chronic pelvic pain, and endometriosis

- Sufficient treatment duration (e.g. 24 weeks) because of pain flares to ensure that relief is sustained
TAKE HOME MESSAGES

1) IC/ BPS is a syndrome generally defined as pain attributed to the bladder with variable associated urinary tract symptoms

2) Classical IC with Hunner’s lesions, identified by cystoscopy with hydrodistension, has possible therapeutic options. Is it a distinct population?

3) Classical IC cannot be distinguished from BPS by signs and symptoms alone

4) IC/ BPS remains a diagnosis of exclusion in a heterogeneous patient population with unknown etiology
DISCUSSION QUESTIONS

Discuss Separately for IC and BPS:

Questions 1 & 2: What are the key inclusion and exclusion criteria for trials evaluating drugs. Include diagnostic procedures necessary.

Questions 3 & 4:

a. How are the key symptoms and signs defined and assessed?

b. What are acceptable endpoints for demonstrating clinical benefit?

c. Other key trial design considerations
DISCUSSION QUESTIONS

Question 5: Should one set of PROs be used for both IC and BPS or one set of PROs for IC and a different one for BPS?

Question 6: What are advantages and disadvantages of enrolling patients with IC and BPS in the same trial?

ONE VOTING QUESTION:
Should patients with IC and BPS be combined in clinical trials?

Vote → YES or NO

Provide a rationale for your answer
Special Thanks

Dr. Magnus Fall

Dr. Jørgen Nordling
REGULATORY APPROACH TO
CLINICAL OUTCOME ASSESSMENT REVIEW
FOR DRUG DEVELOPMENT

MEETING OF THE BONE, REPRODUCTIVE AND UROLOGIC
DRUGS ADVISORY COMMITTEE (BRUDAC)
DECEMBER 07, 2017

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...the FDA is working to give patients a greater voice in medical product development and evaluation.

Success in these efforts could lead to tremendous advances in the understanding of health, disease, diagnosis, treatment, and recovery, **ultimately transforming patients’ experience of health care** by enabling physicians to tailor care to an individual’s specific needs and preferences.

Including clinical outcomes that are meaningful to patients can profoundly influence drug development by ensuring the patient voice is captured.”

**Hunter NL, O’Callaghan KM, Califf RM. JAMA 2015**
Purpose of an Outcome Assessment

• To determine whether or not a drug has been shown to provide **clinical benefit** to patients
  – A positive **clinically meaningful effect** of an intervention on how an individual feels, functions, or survives

• A conclusion of clinical benefit is described in labeling in terms of the concept of interest (outcome) measured
Types of Clinical Outcome Assessments

**ClinRO**
A measurement based on a report that comes from a trained health care professional after observation of a patient’s health condition.

**ObsRO**
A measurement based on a report of observable signs, events or behaviors related to a patient’s health condition by someone other than the patient or a health care professional.

**PRO**
A measurement based on a report that comes directly from the patient about the status of the patient’s health condition without interpretation of the patient’s response by a clinician or anyone else.

**PerfO**
A measurement based on a standardized task(s) performed by a patient that is administered and evaluated by an appropriately trained individual or is independently completed.
General reasons for a patient to want to take a drug:

- **Improved survival**
  - Resulted in a benefit that was detectable by the patient
    (improvement/slowed deterioration of symptoms or functioning)
  - **Decreased probability** of developing an undesirable complication (e.g., stroke)
1. Understanding the Disease or Condition

- Natural history
- Patient subpopulations
- Current clinical practice
- Patient/caregiver perspectives

2. Conceptualizing Clinical Benefit

- Identify measurement concepts (clinically important outcomes)
- Define context of use
- Determine planned endpoints

3. Selecting/Developing the COA

- Select COA type
- Search for existing COA
- Modify an existing COA
- Develop a new COA
I. Identify Context of Use and Measurement Concept

II. Draft Instrument and Evaluate Content Validity

III. Cross-sectional Evaluation of Other Measurement Properties

IV. Longitudinal Evaluation of Measurement Properties/Interpretation Methods

V. Modify Instrument

III. Cross-sectional Evaluation of Other Measurement Properties

Development of CLINICAL OUTCOME ASSESSMENTS

CONCEPT = CLAIM

SPOKE II
SPOKE III
SPOKE I
SPOKE IV
SPOKE V

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Updated on February 11, 2014
Clinical Outcome Assessment Review

- Was the instrument appropriately used in the trial?
- Is the instrument appropriate for the studied population?
- Does the instrument measure what is important to the patient?
- If there are multiple concepts/domains being measured, do they overlap?
- Is the instrument reliable?
- Does the instrument measure what it is supposed to measure?
- Is the instrument sensitive to detect change over time?
- Did one question drive the result?
- What does a score improvement of 2-points mean?
FDA PRO Guidance (2009)

- Defines **good measurement principles** to consider for “**well-defined and reliable**” (21 CFR 314.126) PRO measures intended to provide evidence of clinical benefit.

- All clinical outcome assessments can benefit from the good measurement principles described within the guidance.

- Provides optimal approach to PRO development; **flexibility** and judgment needed to meet practical demands.
Good Measurement Principles

- The assessment is **appropriate** for its **context of use**.
- The assessment directly/indirectly **measures** the **most important concepts** to the patient for that disease.
- The assessment’s **content/concepts** are **well-defined**.
- The assessment can **generate consistent** and **reproducible data**.
- The assessment can **measure what it is supposed to measure**.
- The assessment is **sensitive to detect change** whether it is improvement or deterioration.
- The assessment’s **score change is interpretable** and reflective of **meaningful changes**.
Considerations for Using COAs in IC/BPS

• Potential trial endpoints
  – Endpoints related to sign/symptom
  – Endpoints related to impacts on daily life

• Measuring sign/symptoms
  – Prioritize concepts to include core signs and symptoms
  – Enrich trial with symptomatic patients
  – Sufficient symptom score at enrollment

• Measuring impacts
  – Prioritize concepts to include core impacts attributed to disease
Considerations for Assessment of Pain in IC/BPS

• Pain type and location
  – Obtain patient input to understand how to describe and qualify pain (bladder empty/fullness)
  – Inclusion of pain type (e.g., localization of pain in the question stem)
  – Inclusion of pictures with location of pain

• Recall period/Frequency and timing of assessment
  – Select recall period that is suitable for how pain presents in the target population (e.g., variability, duration (chronic vs. episodic), frequency, and/or intensity).

• Analgesic use
  – Capture patients’ concomitant analgesic use (including analgesic type) at baseline and during trial, including rescue medications for “flares.”
Considerations for Measurement Strategy in IC/BPS

• **Pain**
  - 0-10 pain numeric rating scale (NRS) to assess specific pain type (e.g., bladder pain associated with bladder emptying/fullness)

• **Frequency of voids**
  - Patient-reported voiding diary

• **Nocturia frequency**
  - Patient-reported voiding diary

• **Urgency**
  - ? (Measurement Gap)
Existing COAs in IC/BPS

O’Leary-Sant Interstitial Cystitis Symptom Index (ICSI)

**STRENGTHS**

- Measures some core signs and symptoms of bladder pain syndrome (e.g., urinary frequency, nocturia frequency)

**LIMITATIONS**

- Susceptible to recall error (30 day recall)
- Response choices difficult to differentiate (e.g., usually vs. fairly often)
- Response choices do not appear to be balanced (i.e., more response options weighted toward higher frequency)
- Some questions measure two or more concepts (e.g., bladder pain or burning)
- Absence of data on what constitutes a meaningful score change in instrument

**Can benefit from modifications informed by patient and expert input**
**Existing COAs in IC/BPS**

**Bladder Pain/Interstitial Cystitis Symptoms Score (BPIC-SS)**

**STRENGTHS**

- Measures some core signs and symptoms of bladder pain syndrome and qualifies pain more descriptively (e.g., bladder pain associated with emptying, bladder pain at its worst)
- Distinct response choices
- Includes a 0-10 pain NRS (bladder pain at its worst)

**LIMITATIONS**

- Documentation of qualitative and quantitative research needed to support that it is ‘fit-for-purpose’ for the intended population(s)
  - *If not available, this info can be gathered in early stages of drug development*
- Absence of data on what constitutes a meaningful score change in instrument
Existing COAs in IC/BPS

• O’Leary-Sant Interstitial Cystitis Symptom Index (ICSI)

• Bladder Pain/Interstitial Cystitis Symptoms Score (BPIC-SS)

• Any other existing instruments

**Key takeaway:** Sponsors are encouraged to leverage and build upon existing instruments, literature, and data to fit the specific needs of the research question(s)/endpoints and improve measurement.
Pathways* for FDA Review & Advice: Clinical Outcome Assessments

1. **IND/NDA/BLA Pathway**
   - Within an individual drug development program
   - Investigational New Drug (IND) submissions to FDA
   - Potential to result in *labeling* claims

2. **DDT COA Qualification Pathway**
   - Outside of an individual drug development program
   - Development of novel COAs for use in multiple drug development programs
   - Potential to result in *qualification* of COA

3. **Critical Path Innovation Meetings Pathway**
   - Outside of an individual drug development program
   - Potential for *general advice* on specific methodology or technology (e.g., COA) in development stages

*Pathways specific for CDER
DDT = Drug Development Tool; COA = Clinical Outcome Assessment; PRO = Patient-Reported Outcome
NDA = New Drug Application; BLA = Biologics Licensing Application

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DDT = Drug Development Tool; COA = Clinical Outcome Assessment; PRO = Patient-Reported Outcome
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Helpful Links

• FDA’s Patient-Reported Outcome (PRO) Guidance for Industry:

• FDA’s DDT Qualification Program Guidance for Industry:

• FDA’s DDT Clinical Outcome Assessment Qualification Program webpage:
    • Includes Roadmap and Wheel and Spokes diagrams

• FDA’s Critical Path Innovation Meetings (CPIM) webpage: