

**Food and Drug Administration
Center for Drug Evaluation and Research**

**Summary Minutes of the of the
Bone, Reproductive and Urologic Drugs Advisory Committee Meeting
December 7, 2017**

Location: FDA White Oak Campus, Building 31 Conference Center, the Great Room (Rm. 1503), 10903 New Hampshire Avenue, Silver Spring, Maryland.

Topic: The committee discussed appropriate patient selection criteria and clinical trial design features, including acceptable endpoints, for demonstrating clinical benefit for drugs intended to treat interstitial cystitis and bladder pain syndrome. The committee also discussed whether bladder pain syndrome and interstitial cystitis reflect overlapping or different populations, and whether it is appropriate to assess efficacy in the same way for both conditions.

These summary minutes for the December 7, 2017, meeting of the Bone, Reproductive and Urologic Drugs Advisory Committee of the Food and Drug Administration were approved on January 22, 2018.

I certify that I attended the December 7, 2017, meeting of the Bone, Reproductive and Urologic Drugs Advisory Committee of the Food and Drug Administration and that these minutes accurately reflect what transpired.

/s/

Kalyani Bhatt, BS, MS
*Designated Federal Officer,
BRUDAC*

/s/

Vivian Lewis, MD
Chairperson, BRUDAC

Summary Minutes
Bone, Reproductive and Urologic Drugs Advisory Committee Meeting
December 7, 2017

The following is the final report of the Bone, Reproductive and Urologic Drugs Advisory Committee meeting held on December 7, 2017. A verbatim transcript will be available in approximately six weeks, sent to the Division of Bone, Reproductive and Urologic Products and posted on the FDA website at:

<https://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/ReproductiveHealthDrugsAdvisoryCommittee/ucm573659.htm>

All external requests for the meeting transcript should be submitted to the CDER Freedom of Information Office.

The Bone, Reproductive and Urologic Drugs Advisory Committee of the Food and Drug Administration, Center for Drug Evaluation and Research met on December 7, 2017, at the FDA White Oak Campus, Building 31 Conference Center, the Great Room (Rm. 1503), 10903 New Hampshire Avenue, Silver Spring, Maryland. Prior to the meeting, the members and temporary voting members were provided the briefing materials from the FDA and Industry (Aquinox Pharmaceuticals, Inc. and Urigen Pharmaceuticals, Inc.). The meeting was called to order by Vivian Lewis, MD (Chairperson). The conflict of interest statement was read into the record by Kalyani Bhatt, PharmD (Designated Federal Officer). There were approximately 90 people in attendance. There were eight (8) Open Public Hearing speaker presentations.

Issue: The committee discussed appropriate patient selection criteria and clinical trial design features, including acceptable endpoints, for demonstrating clinical benefit for drugs intended to treat interstitial cystitis and bladder pain syndrome. The committee also discussed whether bladder pain syndrome and interstitial cystitis reflect overlapping or different populations, and whether it is appropriate to assess efficacy in the same way for both conditions.

Attendance:

Bone, Reproductive and Urologic Drugs Advisory Committee Members Present (Voting): Douglas C. Bauer, MD; Roger T. Dmochowski, MD (attended via phone); Matthew T. Drake, MD, PhD; Vivian Lewis, MD (Chairperson); Christian P. Pavlovich, MD; Pamela A. Shaw, PhD; Sarah E. Sorscher, JD, MPH (Consumer Representative)

Bone, Reproductive and Urologic Drugs Advisory Committee Members Not Present (Voting): Anne E. Burke, MD, MPH; Beatrice Edwards, MD, MPH; Margery Gass, MD

Bone, Reproductive and Urologic Drugs Advisory Committee Member Present (Non-Voting): Gerard G. Nahum, MD, FACOG (Industry Representative)

Temporary Members (Voting): Tamara G. Bavendam, MD, MS; Barbara Berney (Patient Representative); David Cella, PhD; Toby Chai MD; Thomas Chelimsky, MD; Monica M. Christmas, MD, FACOG, NCMP; Stuart S. Howards, MD; Timothy Ness, MD, PhD

FDA Participants (Non-Voting): Audrey Gassman, MD; Debuene Chang, MD; Selena Daniels, PharmD, MS; Suresh Kaul, MD, MPH

Open Public Hearing Speakers: Amy Macnow; Michael H. Hsieh MD, PhD; Laura Santurri, PhD, MPH, CPH; Patricia Garchinsky; Angie Slane (video presented by Devra Densmore); Henry S. Berks and Erma Berks (video presented by Devra Densmore); Stephanie Fox-Rawlings, PhD (National Center for Health Research); Lee K. Lowery, MPA, CAE (Interstitial Cystitis Association)

The agenda was as follows:

Call to Order and Introduction of Committee

Vivian Lewis, MD
Chairperson, BRUDAC

Conflict of Interest Statement

Kalyani Bhatt, BS, MS
Designated Federal Officer, BRUDAC

FDA Opening Remarks

Audrey Gassman, MD
Deputy Director, Division of Bone, Reproductive and Urologic Products (DBRUP)
Office of Drug Evaluation III (ODE III)
Office of New Drugs (OND), CDER, FDA

INDUSTRY PRESENTATION #1

Aquinox Pharmaceuticals

Introduction

Barbara Troupin, MD, MBA
Chief Medical Officer
Vice President, Clinical Development & Regulatory Affairs
Aquinox Pharmaceuticals, Inc.

Defining an IC/BPS Population for Clinical Study

Robert Moldwin, MD
Professor of Urology - The Smith Institute for Urology
Zucker School of Medicine at Hofstra/Northwell
Lake Success, New York

Endpoint Selection for Clinical Trials in IC/BPS

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

Conclusion

Barbara Troupin, MD, MBA

INDUSTRY PRESENTATION #2

Introduction

Urigen Pharmaceuticals, Inc.

Dan Vickery, PhD

President, Urigen Pharmaceuticals, Inc.

IC/BPS Disease, Pathophysiology and Diagnosis

Joel Teichman, MD, FRCSC

Professor, Department of Urologic Sciences

University of British Columbia

Vancouver, Canada

Clinical Trial Patient Enrollment and Assessment
Criteria

C Lowell Parsons, MD

Chairman, Urigen Pharmaceuticals, Inc.

Professor Emeritus of Urology

School of Medicine

University of California, San Diego

Conclusion

Dan Vickery, PhD

Clarifying Questions for both Industry
Presentations

BREAK

FDA PRESENTATIONS

Clinical Perspective: Clinical Trials for Interstitial
Cystitis/Bladder Pain Syndrome

Debuene Chang, MD

Medical Officer

DBRUP, ODE III, OND, CDER, FDA

Regulatory Approach to Clinical
Outcome Assessment Review for Drug
Development

Selena Daniels, PharmD, MS

Team Leader, Clinical Outcome Assessments Staff

OND, CDER, FDA

Clarifying Questions to FDA

LUNCH

OPEN PUBLIC HEARING

Clarifying Questions to Industry or FDA

BREAK

Questions to the Committee/Committee Discussion

ADJOURNMENT

Questions to the Committee:

1. **DISCUSSION:** Discuss the key inclusion and exclusion criteria, including diagnostic procedures, for trials evaluating drugs intended to treat interstitial cystitis.

Committee Discussion:

For inclusion criteria, the committee commented that classic interstitial cystitis (IC) should focus on patients with Hunner's lesions and pain associated with bladder fullness relieved by emptying. Several panel members recommended office cystoscopy, instead of cystoscopy under anesthesia, to identify Hunner's lesions, although this technique would not allow for bladder expansion/filling as described in the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) criteria. Some Urologist panel members stated that for their patients, they recommended cystoscopy with anesthesia, primarily for patient comfort and tolerance.

For exclusion criteria, some committee members stated that patients with certain urinary tract and pelvic diseases that can cause bladder/voiding pain similar to IC should be excluded. These disease states include bladder cancer, post-radiation cystitis, infection, myofascial pain, post-hysterectomy pain, cervicitis and vaginitis (along with those conditions listed in the American Urological Association (AUA) guidelines). Other panel members stated that there is no need to exclude conditions that can cause symptoms similar to IC if the patient has Hunner's lesions, as these lesions are considered pathognomonic findings for classic IC.

Please see the transcript for details of the committee discussion.

2. **DISCUSSION:** Discuss the key inclusion and exclusion criteria, including diagnostic procedures, for trials evaluating drugs intended to treat bladder pain syndrome.

Committee Discussion:

For inclusion criteria, the majority of the panel members stated that the hallmark criteria should be pain associated with urinary symptoms. Committee members stated that the definition of pain should be expanded, with patient input, to include symptoms that patients might not call pain such as discomfort and burning. Some committee members noted that at least a six-month history of symptoms should be part of the inclusion criteria because of the episodic nature of the symptomatology. Some panel members discussed the need for developing, or adapting, and validating available pain scores systems (such as the visual analog score or VAS) to incorporate the way patients with Bladder Pain Syndrome (BPS) experience their symptoms. There was no consensus about definitions of the severity or frequency of symptoms that would be necessary as an inclusion factor. The use of the European Society for the Study of Bladder Pain Syndrome or AUA diagnostic criteria was also suggested.

For exclusion criteria, the committee agreed that these are essentially the same as those for an IC study population. Some of the panel members stated it is not critical to exclude patients with comorbid conditions such as fibromyalgia.

Please see the transcript for details of the committee discussion.

3. **DISCUSSION:** 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.

Committee Discussion:

The committee commented that expanded definitions of bladder pain should be developed, with patient input, to include burning, pressure and discomfort. Voiding diaries should be used that incorporate urinary symptoms such as nocturia and urinary frequency. Other recommendations included capturing the impact of bladder symptoms on sexual functioning.

The majority of members agreed that urinary symptom relief should be the primary endpoint. Improvement in pain (broadly defined) was the main focus of the discussion. It was noted that this should include measures of magnitude, frequency and type of pain. Most of the panel agreed that instruments that capture other patient reported outcomes (PROs) would be critical for secondary endpoints. A few committee members thought PROs should be co-primary endpoints.

Some committee members stated that a minimum of 6 months of treatment would be needed to capture both flares and steady state. Other recommendations included that pivotal trials should be randomized and placebo-controlled, and use diaries. The committee members also expressed the need to ensure adequate representation of some populations including men, racial and ethnic minorities. Because the enrolled population will undergo cystoscopy, committee members stated it will be critical to incorporate quality control measures that ensure reliable and reproducible definitions of whether lesions are present and to rule out artifact. Patients who undergo cystoscopy and have Hunner's lesions are also likely to be treated at the same time and may have symptomatic improvement, which committee members stated should be taken into account when designing the study.

Please see the transcript for details of the committee discussion.

4. **DISCUSSION:** 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.

Committee Discussion:

The committee agreed that the key symptoms and signs that should be defined and assessed for BPS are the same as IC. In addition, the committee agreed that the endpoints for demonstrating clinical benefit should be the same for BPS and IC.

Please see the transcript for details of the committee discussion.

- 5. **DISCUSSION:** When assessing efficacy for drugs intended to treat patients with interstitial cystitis and bladder pain syndrome, discuss whether clinical trials should 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, or
 - b. One set of PRO instruments used both for patients with interstitial cystitis and those with bladder pain syndrome.

Committee Discussion:

The committee recommended one set of PRO instruments when assessing efficacy for drugs intended to treat patients with IC and BPS. One committee member recommended obtaining additional patient-derived data to confirm the appropriateness of using the same PRO for IC and BPS.

Please see the transcript for details of the committee discussion.

- 6. **DISCUSSION:** When assessing efficacy for drugs intended to treat patients with 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.

Committee Discussion:

For advantages, the committee commented that symptoms of both disorders are similar, that the same instruments can be used to assess efficacy in both populations, and that combining the populations is consistent with clinical care.

For disadvantages, the committee commented that there is risk of combining two different groups of patients and that if too much heterogeneity is introduced it may be difficult to detect a treatment effect, even if one exists among some of the patients.

Please see the transcript for details of the committee discussion.

7. **VOTE:** Should patients with interstitial cystitis and those with bladder pain syndrome be combined in clinical trials?

Discuss the rationale for your vote.

Yes: 15 No: 0 Abstain: 0

Committee Discussion: The committee members unanimously agreed that patients with IC and BPS be combined in clinical trials. Committee members noted that populations can be stratified and that symptoms for IC and BPS appear to be indistinguishable.

Please see the transcript for details of the committee discussion.

The meeting was adjourned at approximately 4:30 p.m.