Interstitial Cystitis/Bladder Pain Syndrome (IC/BPS): Establishing Effectiveness of Drugs for Treatment

Guidance for Industry

DRAFT GUIDANCE

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U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

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Interstitial Cystitis/Bladder Pain Syndrome (IC/BPS): Establishing Effectiveness of Drugs for Treatment Guidance for Industry[1]

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I. INTRODUCTION

This guidance provides recommendations for establishing effectiveness for drugs intended to treat patients with interstitial cystitis/bladder pain syndrome (IC/BPS).

This guidance incorporates recommendations the FDA received at a December 2017 advisory committee meeting[2] on trial design features, including enrollment criteria and acceptable effectiveness endpoints for drugs intended to treat IC/BPS.

In general, FDA's guidance documents do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

II. BACKGROUND

IC/BPS is a complex, poorly understood syndrome of unknown etiology. In general, the diagnosis requires the following:

- Chronic bladder pain or discomfort

[1] This guidance has been prepared by the Division of Bone, Reproductive, and Urologic Products in the Center for Drug Evaluation and Research at the Food and Drug Administration.

[2] See the meeting materials on the FDA's December 7, 2017: Meeting of the Bone, Reproductive, and Urologic Drugs Advisory Committee web page at https://www.fda.gov/advisory-committees/advisory-committee-calendar/december-7-2017-meeting-bone-reproductive-and-urologic-drugs-advisory-committee-12062017-12062017.

- Accompanying lower urinary tract symptom(s), such as urinary frequency, urgency, or nocturia

- Exclusion of other disorders that have similar presentations such as malignancy, endometriosis, chronic prostatitis, and bladder outlet obstruction

Cystoscopy may show bladder inflammation, including Hunner's lesions[3] (mucosal lesions or ulcerations seen with or without hydrodistention of the bladder), or other pathology but can be normal.

III. CLINICAL TRIAL DESIGN FEATURES — KEY CONSIDERATIONS

A. Enrollment Criteria

Sponsors of investigational drugs intended to treat IC/BPS should consider the following for patient enrollment criteria in clinical trials:

- Patients should have bladder pain/discomfort.
  - The description of the bladder pain/discomfort can vary among patients. For example, some patients describe constant bladder pain/discomfort, whereas other patients describe bladder pain/discomfort when voiding or as a burning sensation between voids as the bladder fills with urine. Clinical trials should not exclude patients based on the description of their symptoms.
  - Patients should have at least 6 months duration of bladder pain/discomfort symptom(s) before enrollment to exclude other disorders with similar presentations that have a shorter time course.
- Patients should also have at least 6 months duration of one accompanying lower urinary tract symptom, such as urinary frequency, urgency, or nocturia. The accompanying lower urinary tract symptom(s) can vary among patients and may be intermittent or persistent.
- Patients should have cystoscopy at screening (if not obtained within the preceding 6 months) to exclude other conditions (e.g., transitional cell carcinoma of the bladder, endometriosis).
  - Patients are not required to have Hunner's lesions on bladder cystoscopy. Sponsors that do require this should consider the following:
    - If a sponsor incorporates an inclusion criterion for Hunner's lesions, the baseline appearance of the bladder pathology should be documented in a standardized

[3] Hunner G., 1918, A Rare Type of Bladder Ulcer: Further Notes, with a Report of Eighteen Cases, JAMA, 70(4):203–212.

fashion during screening. For this purpose, sponsors can opt to use a standard representative bladder diagram, photographic imagery, or videography.

  - Because Hunner's lesions are rarely identified in the United States but are more commonly identified in other countries, sponsors that choose to use this pathologic finding for trial entry should discuss the approach in advance with the Division of Bone, Reproductive, and Urologic Products (the Division), particularly for multinational trials.

- A symptom or symptoms that will be assessed as a primary endpoint or endpoints should be of sufficient severity (intensity or frequency) at baseline to show a clinically meaningful improvement with the drug.

- Patients can have received prior treatment(s) for IC/BPS, including those who have had surgical procedures, such as fulguration. In general, the Division recommends including these patients in the trials to improve generalizability of the results unless a compelling effectiveness or safety reason exists for excluding them. During the trial design phase, the sponsor should discuss with the Division the extent to which such patients should be included in the trials.

- Patients should undergo rigorous evaluation to exclude other conditions or diseases that can cause similar symptoms, using information from medical history, physical examination findings, laboratory studies (e.g., negative urine bacterial culture), and other previously performed procedures (e.g., urodynamics, cystoscopy, laparoscopy, radiological studies).

B. Effectiveness Endpoints

Sponsors of investigational drugs intended to treat IC/BPS should consider the following for effectiveness endpoints in clinical trials:

- Ideally, treatments intended for IC/BPS should improve both the bladder pain/discomfort and the accompanying lower urinary tract symptoms.

  – Because symptoms can vary among patients, one approach is to ask all patients to self-identify at baseline their most bothersome bladder pain/discomfort symptom and their most bothersome lower urinary tract symptom. The change from baseline for each patient's self-identified most bothersome bladder pain/discomfort symptom can be assessed as one coprimary effectiveness endpoint, and the change from baseline for each patient's self-identified most bothersome lower urinary tract symptom can be assessed as the other coprimary effectiveness endpoint.

  – Other approaches may be appropriate based on the specifics of the development program. For example, if a drug is not expected to improve lower urinary tract symptoms based on the mechanism of action, it would be appropriate to use a single primary effectiveness endpoint related to bladder pain/discomfort.

127
128 – Even if trials use the most bothersome symptom approach, sponsors should still
129 measure the other bladder pain/discomfort symptoms and lower urinary tract
130 symptoms related to IC/BPS. We recommend having prospectively planned
131 measurements and analyses of these IC/BPS symptoms, regardless of whether the
132 symptom is included in the primary effectiveness endpoint(s), because it is important
133 to assess for any potential effect (including a detrimental one) on the core symptoms
134 of IC/BPS. Sponsors should discuss with the Division whether any of these analyses
135 should be included in a multiple testing strategy.
136
137 • It is critical that sponsors use fit-for-purpose[4] patient-reported outcome (PRO)
138 instruments to assess IC/BPS symptoms.[5] We encourage sponsors to seek FDA input as
139 early as possible and at important milestones throughout the drug development process to
140 ensure the inclusion of fit-for-purpose PRO instruments in phase 3 trials.
141
142 Sponsors should consider the following for PRO instruments:
143
144 – Currently, the FDA is not aware of any specific PRO instruments that are adequate
145 for regulatory use to assess symptom improvement in IC/BPS. The FDA is open to
146 evaluating existing or modified PRO instruments for this use. For example, sponsors
147 may be able to use or adapt existing numeric or verbal rating scales for pain, urinary
148 frequency diaries, and nocturia diaries. The FDA encourages development of a
149 publicly available, fit-for-purpose PRO instrument that can be used across multiple
150 drug development programs.[6]
151
152 – Piloting the proposed PRO instrument in phase 2 trials provides the sponsor an
153 opportunity to evaluate the instrument's measurement properties (reliability, validity,
154 and ability to detect change), to consider guidelines for clinically meaningful within-
155 patient change in scores, and to confirm the endpoint definition before use in phase 3
156 trials.
157
158 • If the sponsor plans to evaluate Hunner's lesions, results of posttreatment cystoscopy
159 may or may not provide additional support for the effectiveness of the drug to treat for
160 IC/BPS. Sponsors that would like to use cystoscopy for additional support for
161 effectiveness should discuss the approach with the Division in advance.
162

[4] For purposes of this guidance, the term *fit-for-purpose* is defined as a conclusion that the level of validation associated with a tool is sufficient to support its context of use. See the BEST (Biomarkers, EndpointS, and Other Tools) Resource, available at https://www.ncbi.nlm.nih.gov/books/NBK326791/?report=reader.

[5] For general recommendations regarding PRO instruments and documents to be provided to the FDA for review, see the guidance for industry *Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims* (December 2009). We update guidances periodically. To make sure you have the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/regulatory-information/search-fda-guidance-documents.

[6] See the guidance for industry and FDA staff *Qualification Process for Drug Development Tools* (January 2014).

C. Other Critical Trial Design Considerations

Sponsors of investigational drugs intended to treat IC/BPS should also consider the following for trial design:

- Sponsors should discuss with the Division the planned proportion of men and women to be enrolled in the clinical trials, taking into account the underlying proportion of men and women in the IC/BPS population or subpopulation targeted by the drug.

- In general, a sponsor should conduct two randomized, double-blind, placebo-controlled trials. Each trial should demonstrate that the drug provides statistically and clinically meaningful improvement in IC/BPS symptoms.

- The randomized, controlled treatment duration should be at least 6 months to adequately assess persistence of benefit because IC/BPS patients can have intermittent symptomatic flares.

- Sponsors should prespecify how flares will be defined, documented, and treated during clinical trials.

- The use of rescue medications to treat bladder pain/discomfort or lower urinary tract symptom(s) could affect the interpretation of the efficacy results. The sponsor should pre-specify in the protocol and statistical analysis plan the permitted type(s), dose(s), and frequency of rescue medication and the timing of pain/discomfort assessment relative to rescue medication administration and how these medications will be accounted for in the efficacy analyses.