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TITLE: Comparison of Bladder-Directed and Pelvic Floor Therapy in Women With Interstitial Cystitis/Bladder Pain Syndrome

PRINCIPAL INVESTIGATOR: Kenneth M. Peters MD

RECIPIENT: WILLIAM BEAUMONT HOSPITAL INC
ROYAL OAK MI 48073-6712

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6. AUTHOR(S)

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7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)

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Approved for public release; distribution is unlimited

13. SUPPLEMENTARY NOTES

14. ABSTRACT

Interstitial cystitis/bladder pain syndrome (IC/BPS) is a debilitating constellation of symptoms including urinary urgency, frequency, and pain related to the bladder, which predominantly affects women. Although symptoms appear to be bladder related, there has been little solid evidence linking IC/BPS with a dysfunctional bladder epithelium unless ulcers are present. There is growing evidence that the bladder may be an innocent bystander in a more diffuse syndrome with a complex interplay of various systems/factors. It is our *objective* to assess the role of the pelvic floor muscles as a major contributor to pelvic pain and voiding dysfunction in adult women with IC/BPS symptoms. During Year 2, our primary focus was on study recruitment and enrollment. Due to the national shortage of one of the medications that are used for bladder instillations (bladder focused therapy), we only enrolled 1 of 128 total women (64 in each treatment arm) in the first project year. In August 2017 we obtained a limited supply of the medication, and study recruitment and enrollment resumed. In Year 2, recruitment activities have been expanded to increase enrollment. Identification of enrollment barriers and possible resolutions are ongoing. Although our targeted enrollment goals are not met, enrollment has been growing steadily.

15. SUBJECT TERMS

Cystitis, Interstitial; Pelvic pain; Lower Urinary Tract Symptoms; Pelvic Floor Disorders; Pain, Chronic; Biomarkers

16. SECURITY CLASSIFICATION OF:			**17. LIMITATION OF ABSTRACT**	**18. NUMBER OF PAGES**	**19a. NAME OF RESPONSIBLE PERSON**
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1. INTRODUCTION:

Although severe urinary urgency, frequency, and pelvic pain symptoms are present in interstitial cystitis/bladder pain syndrome (IC/BPS), there has been little solid evidence linking symptoms with a dysfunctional bladder epithelium unless ulcers are present. Our *objective* is to assess the role of the pelvic floor muscles as a major contributor to pelvic pain and voiding dysfunction in adult women with IC/BPS symptoms. The project aims to randomize 128 women (64 in each arm) with IC/BPS to bladder instillations (bladder focused therapy) or pelvic floor physical therapy. Participants will be followed with symptom and biomarker assessments for up to 3 years.

2. KEYWORDS:

Cystitis, Interstitial; Pelvic pain; Lower Urinary Tract Symptoms; Pelvic Floor Disorders; Pain, Chronic; Biomarkers

3. ACCOMPLISHMENTS:

What were the major goals of the project?

Specific Aim 1: **Evaluate the effects of bladder directed therapy twice weekly (bladder instillation) and twice weekly PFPT on IC/BPS symptoms.**

Major Task 1: Study Start Up

Completed, all milestones achieved by 12 months:

- Research protocol finalized, Local IRB and HRPO approval obtained, Research staff trained, Flow chart implemented for all study steps, data collection and database requirements)

Major Task 2: Participant Recruitment, Therapy, Participant Evaluation

Milestones to be achieved by 24 months:

- Seventy-two (72) participants consented, screened and enrolled
- Year 2, Actual: Twelve (12) women consented to study participation: 7 patients were enrolled, randomized and treated; 1 patient was enrolled, randomized and withdrew prior to treatment; and 4 patients consented and failed screening
- To date, four (4) patients have completed all treatment visits and are in follow-up

Major Task 3: Data analysis

- 0% achieved

Specific Aim 2: **Improve clinician assessment of IC/BPS**

Major Task 1: Evaluate pelvic floor assessment between multiple clinicians

- 0% achieved

Major Task 2: Explore methods for improving clinician assessment in military and other health care settings

- 0% achieved

Specific Aim 3: **Improve biomarker based evaluation of IC/BPS before, during and after therapy**

Major Task 1: Collect biological sample for testing

Milestone achieved:

- All study personnel have completed training

What was accomplished under these goals?

All study start-up activities are completed. Although enrollment has been steadily increasing, our enrollment goal of 72 participants (7 patients enrolled/treated through August 2018) has not been met. A major reason for this shortfall, was due to the initial delay in enrollment due to the nationwide sodium bicarbonate shortage, which has since been resolved. To increase enrollment, numerous and varied recruitment initiatives were implemented during this reporting period. These activities are specifically described in Section 5).

Additionally, quarterly research meetings and an intradepartmental study audit was conducted to support and enhance research performance.

What opportunities for training and professional development has the project provided?

Nothing to Report.

How were the results disseminated to communities of interest?

Nothing to Report.

What do you plan to do during the next reporting period to accomplish the goals?

We will expand our marketing and recruitment efforts to achieve enrollment goals. For example, in Fall 2018, an invitation to study participation will be sent to approximately 500 Beaumont Health patients diagnosed with IC/BPS.

4. IMPACT:

What was the impact on the development of the principal discipline(s) of the project?

Nothing to Report

What was the impact on other disciplines?

Nothing to Report

What was the impact on technology transfer?

Nothing to Report

What was the impact on society beyond science and technology?

Nothing to Report

5. CHANGES/PROBLEMS:

Changes in approach and reasons for change

Nothing to Report

Actual or anticipated problems or delays and actions or plans to resolve them
Although approximately 160 potential study participants were contacted and pre-screened in Year 2, the study enrollment rate remains lower than anticipated. Therefore, study staff will continue to review the reasons for non-participation, including screen failures, to determine methods to improve enrollment. Recruitment efforts have been significantly increased in Year 2. Research staff developed a list of possible recruitment activities to support enrollment, and most of those activities have been implemented. Study information was disseminated to potential referral sources, including Beaumont and non-Beaumont physicians and mid-level providers. These providers receive Beaumont Urology Research updates quarterly, as a reminder of studies that are seeking patients. We also partnered with National organizations, including the Interstitial Cystitis Network (ICN), the Interstitial Cystitis Association (ICA), to promote the study. Previous IC/BPS research subjects and current IC/BPS patients, who are members of our health system, were contacted and invited to participate in the study. Study information was also provided to IC support groups throughout Michigan. In effort to increase our connection to the IC/BPS community, we are also currently working with Patient Wing to reach potential patients on-line. Other recruitment initiatives include radio ads, and posting study information on Beaumont's employee and public research websites. Lastly, Dr. Peters provided a presentation on bladder pain to Beaumont nurses (during Nurses' Week), which resulted in one study referral.

Additionally, two changes were implemented which may positively impact enrollment; the addition of a patient stipend and a revision to the eligibility criteria. Due to the distance some of our patients travel to/from the study site, as well as the frequency of the visits, providing a stipend could be helpful for recruitment and retention, as well as overall study compliance. The eligibility criteria were also revised to include patients that had previous bladder instillations and/or pelvic floor physical therapy at least 12 months before the date of enrollment.

Changes that had a significant impact on expenditures
As stated previously, enrollment was initially limited by the national shortage of bicarbonate. Subsequently, the rate of enrollment has been slower than anticipated. Therefore, cumulative expenses are less than expected, despite increased spending related to recruitment initiatives. There is a cost saving in salary, travel, patient care, subcontract and other miscellaneous costs. We anticipate that expenditures will increase, as study enrollment increases. Budgeted funds will be needed to cover patient care costs and achieve the aims of the study.

Significant changes in use or care of human subjects, vertebrate animals, biohazards, and/or select agents
None

Significant changes in use or care of human subjects
There have been no changes in the use or care of human subjects. IRB continuing review and approval was obtained for an additional 12 months on 31-May-2018.

Significant changes in use or care of vertebrate animals.
N/A

Significant changes in use of biohazards and/or select agents
N/A

6. PRODUCTS:
Publications, conference papers, and presentations

Journal publications.
Nothing to Report

Books or other non-periodical, one-time publications.
Nothing to Report

Other publications, conference papers, and presentations.
Nothing to Report

Website(s) or other Internet site(s)
Nothing to Report

Technologies or techniques
Nothing to Report

Inventions, patent applications, and/or licenses
Nothing to Report

Other Products
Nothing to Report

7. PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS
What individuals have worked on the project?

Name: Kenneth Peters, MD, Principal Investigator
No Change

Name: Larry Sirls, MD, Investigator
No Change

Name: Deborah Hasenau RN, MS, Project Role: Project Manager
No Change

Name: Lydia Kosovich RN, BSN, Lead Study Coordinator
No Change

Name: Sandra McColley, Data Manager
No Change

Has there been a change in the active other support of the PD/PI(s) or senior/key personnel since the last reporting period?

Updated Other Support August 2017-September 2018; Key Personnel

Kenneth M. Peters

Closed:

Title:	The LEADERSHIP 301 Trial: A 12-Week, Randomized, Multi-Center, Double-Blind, Placebo-Controlled, 3-Arm, Parallel-Group, Phase 3 Trial to Evaluate the Efficacy and Safety of 2 Doses of AQX-1125 Targeting the SHIP1 Pathway in Subjects with Interstitial Cystitis/Bladder Pain Syndrome Followed by an Extension Period
Effort:	N/A part of dedicated research time; Role: PI
Supporting Agency:	Aquinox Pharmaceuticals (commercial sponsor)
Grants Officer:	N/A
Performance period:	8/1/2016 to 8/1/2018
Funding Amount:	$16,236.35
Project Goals:	The primary objective of this study is to evaluate the effect of 12 weeks of treatment with 2 different doses of oral AQX-1125 (100 mg or 200 mg) administered once daily compared to placebo on the change in maximum daily bladder pain in subjects with interstitial cystitis/bladder pain syndrome (IC/BPS)
Overlap:	This project recruits from a similar patient population but there is no scientific, financial, or level of effort overlap.

New:

Title:	Axonics SacRal NeuromodulaTIon System for UrinAry Urgency Incontinence TreatmeNt: ARTISAN-SNM
Effort:	N/A part of dedicated research time; Role: PI
Supporting Agency:	Axonics Modulation Technologies, Inc. (commercial sponsor)
Grants Officer:	N/A
Performance period:	January 2018 – June 2020
Funding Amount:	$302,790
Project Goals:	To evaluate the safety and effectiveness of the Axonics Sacral Neuromodulation System as an aid in the treatment of the symptoms of Urinary Urge Incontinence (UUI) designed to gain pre-market approval in the United States.
Specific Aims:	To evaluate the technical performance and health economics of the Axonics SNM System and the quality of life of patients in the treatment of the symptoms of UUI.

Overlap:	None

Title:	Double-Blind, Placebo-Controlled, Parallel Design, Phase 2 Study to Assess Clinical Activity and Safety of Enobosarm (GTx-024) in Postmenopausal Women with Stress Urinary Incontinence
Effort:	N/A part of dedicated research time; Role: PI
Supporting Agency:	GTx, Inc. (commercial sponsor)
Grants Officer:	N/A
Performance period:	September 2017 – October 2018
Funding Amount:	$98,504
Project Goals:	To evaluate the efficacy and safety of GTx-024 (1 mg and 3 mg) compared to placebo in the treatment of postmenopausal women with stress urinary incontinence
Specific Aims:	To evaluate the safety and efficacy of GTx-024
Overlap:	None

Larry Sirls MD

Closed:

Title:	The LEADERSHIP 301 Trial: A 12-Week, Randomized, Multi-Center, Double-Blind, Placebo-Controlled, 3-Arm, Parallel-Group, Phase 3 Trial to Evaluate the Efficacy and Safety of 2 Doses of AQX-1125 Targeting the SHIP1 Pathway in Subjects with Interstitial Cystitis/Bladder Pain Syndrome Followed by an Extension Period
Effort:	N/A part of dedicated research time; Role: subinvestigator
Supporting Agency:	Aquinox Pharmaceuticals (commercial sponsor)
Grants Officer:	N/A
Performance period:	8/1/2016 to 8/1/2018
Funding Amount:	$16,236.35
Project Goals:	The primary objective of this study is to evaluate the effect of 12 weeks of treatment with 2 different doses of oral AQX-1125 (100 mg or 200 mg) administered once daily compared to placebo on the change in maximum daily bladder pain in subjects with interstitial cystitis/bladder pain syndrome (IC/BPS)
Overlap:	This project recruits from a similar patient population but there is no scientific, financial, or level of effort overlap.

New:

Title:	Double-Blind, Placebo-Controlled, Parallel Design, Phase 2 Study to Assess Clinical Activity and Safety of Enobosarm (GTx-024) in Postmenopausal Women with Stress Urinary Incontinence
Effort:	N/A part of dedicated research time; Role: Co-Investigator
Supporting Agency:	GTx, Inc. (commercial sponsor)
Grants Officer:	N/A
Performance period:	September 2017 – October 2018
Funding Amount:	$98,504
Project Goals:	To evaluate the efficacy and safety of GTx-024 (1 mg and 3 mg) compared to placebo in the treatment of postmenopausal women with stress urinary incontinence
Specific Aims:	To evaluate the safety and efficacy of GTx-024
Overlap:	None

Michael Chancellor, MD:

Closed:

Title: A Double-Blind, Randomized Study of Safety and Efficacy of OnabotulinumtoxinA	Analysis of Urine Specimens From A Double-Blind, Randomized Study Of The Safety And Efficacy Of Onabotulinumtoxin A (Onabont-T) Versus Oral Oxybutynin In Spinal Cord Injured Patients With Neurogenic Detrusor Overactivity
Effort:	1 Calendar Months (5%); Role: PI
Supporting Agency:	Baylor College of Medicine/DOD
Grants Officer:	N/A
Performance period:	4/26/2016-7/27/2018
Funding Amount:	$83,698
Project Goals:	The main purpose of this proposal that incorporates novel urine biomarker testing into existing clinical methodologies is to: 1) evaluate the efficacy of 200 U BoNT-A injected into the detrusor versus oral oxybutynin for the treatment of urinary incontinence (UI) caused by neurogenic detrusor overactivity (NDO) in spinal cord injured patients and 2) to determine the potential role of urine biomarkers in guiding the process of patient selection and
Overlap:	None

Christopher Smith, MD: No Changes
Mireya Diaz PhD: No Changes
Laura Lamb PhD: No Changes

What other organizations were involved as partners?

Baylor College of Medicine
Houston, Texas
Contribution: During the past year, Dr. Smith actively participated in quarterly teleconferences along with other key study personnel. He assists in protocol review and the contributes to the development of the patient recruitment plan. Dr. Smith also helps to design strategies to troubleshoot anticipated and unanticipated issues as the study progresses. Finally, he remains engaged with military and Veteran's Affair communities in anticipation of eventual transition of study findings to their IC/BPS patient populations.

8. SPECIAL REPORTING REQUIREMENT COLLABORATIVE AWARDS:
Not Applicable

QUAD CHARTS:
Not Applicable

9. APPENDICES:
None