STUDY PROTOCOL

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Protocol Title
Pilot Study Evaluating the Efficacy of Certolizumab Pegol for Interstitial Cystitis

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Purpose and Study Background

Interstitial cystitis/ bladder pain syndrome (IC/BPS) is a chronic, debilitating bladder disease characterized by suprapubic pressure or pain accompanied by urinary frequency and urgency, in the absence of an identifiable cause.[1-3] Population based studies have demonstrated a prevalence rate of 3 to 12 percent among women[4-6] and 2 to 4 percent for men.[4] The symptoms of IC/BPS result in a poor quality of life with sleep dysfunction, sexual dysfunction, depression, anxiety, and stress.[7-9]

The pathogenesis of IC/BPS is undefined. Treatments of IC/BPS have been empirical and inadequate.[10-12] Narcotics are the most commonly prescribed medication.[13] The direct cost of medical care for IC/BPS patients is > $11,000 per year.[14] There are also the indirect costs to society including work absenteeism and decreased productivity. Investigation of novel therapies is needed.

IC/BPS has been postulated to be one of the autoimmune diseases. Like autoimmune diseases, IC/BPS affects more women than men. Infection and stress worsen both conditions. Pregnancy improves symptoms for both IC/BPS and autoimmune diseases. There is a clinical concordance of IC/BPS with other established autoimmune diseases.[15] IC/BPS as an autoimmune disease is not a new theory. In 1938 Fister recognized the clinical and histopathologic similarities between IC/BPS and lupus erythematosus.[16] In the 1980 review article, Oravisto viewed IC/BPS as an autoimmune disease due to the very chronic course of the disease, the absence of infection, the pathological findings, the common occurrence of antinuclear antibodies, and the response to certain modalities of treatment.[17] Immunosuppressive drugs including methotrexate, prednisone, and cyclosporine A, routinely used to treat autoimmune diseases, have shown efficacy in selected IC/BPS patients.[18-20] There are more than 80 different documented autoimmune diseases affecting every organ and tissue in the body. IC/BPS may be the autoimmune disease of the bladder.

Selective release of tumor necrosis factor-alpha (TNFα) by mast cells (MC) plays a central role in the pathogenesis and pathophysiology of IC/BPS. Bladder biopsies of patients with IC demonstrate increase numbers of MC.[21-23] A selective release or degranulation of vasoactive and proinflammatory mediators by MC, a process called "activation", may explain IC/BPS pathogenesis.[24,25] MC activation elicits an inflammatory response in urothelial cell IC/BPS models with secreted product TNFα playing a central role.[26,27] Inflammation in experimental IC/BPS was mediated by TNFα.[26,28-30] Drugs that inhibited TNFα decreased this experimental IC/BPS bladder inflammation. Interruption of mast cell activation, with a decrease expression of TNFα, inhibited bladder inflammation in an autoimmune cystitis model.[31]

Elevated levels of TNFα in urine, serum, and tissue were found in patients with IC/BPS. TNFα, a proinflammatory cytokine released by immune cells, is central to the acute and chronic inflammation in autoimmune diseases.[32,33] Patients with clinically diagnosed IC/BPS, but no glomerulations observed with cystoscopy under anesthesia after hydrodistention, had elevated levels of TNFα in urine or bladder wash fluid.[34] However, patients with clinically diagnosed IC/BPS, but did have glomerulations observed with cystoscopy under anesthesia after hydrodistention, did not have elevated levels of TNFα in urine or bladder wash fluid compared to controls. Interestingly, cystoscopic findings were not felt to identify distinct subgroups of patients with IC/BPS symptoms.[35] TNFα was upregulated in urine of patients with overactive bladder[36], a syndrome that has been considered a milder form of IC/BPS.[37] Serum levels of TNFα were significantly higher in patients with IC/BPS.[38] Tissue levels of TNFα were significantly elevated in women with vulvar vestibulitis.[39] Vulvar vestibulitis, also known as vulvodynia is part of the symptom complex in women with IC/BPS.[40] TNFα is highly expressed in bladder urothelium tissue of patients with ulcerative IC/BPS and was suggested to be the causative etiology of IC/BPS.[41]

I recently completed a study (ClinicalTrials.gov Identifier NCT01295814) "A Randomized, Double-Blind, Placebo Controlled Trial of Adalimumab in the Treatment of Interstitial Cystitis/Bladder Pain Syndrome".[42] Adalimumab is one of several biological agents that are known as TNFα antagonists or TNFα blocking agents. Adalimumab is a recombinant, fully human, monoclonal antibody that neutralizes human TNFα. In this study adalimumab treatment demonstrated a statistically significant improvement in outcome measures compared to baseline in patients with moderate to severe IC/BPS. However, adalimumab failed to demonstrate positive proof of concept compared to placebo due to a significant placebo effect. This confounding result was evaluated and analyzed in my paper “Examination of the Significant Placebo Effect in the Treatment of Interstitial Cystitis/ Bladder Pain Syndrome”.[43] The

conclusions of this paper were that this greater "placebo effect" represented the benefits of advice, support, education, and behavior modification programs. The recommendation was that physicians should review standard advice with all IC/BPS patients before starting medical therapy or clinical trials. Future studies should include a washout period after subjects receive standard IC/BPS advice. Only those patients who do not improve with standard IC advice and therapy would be participants in clinical trials.

Current understanding of the TNFα blocking agents recognizes differences in each of their mechanism of action and clinical experience. Adalimumab may not theoretically be the best TNFα blocking agent for the treatment of IC/BPS. Adalimumab mediates complement-dependent cytotoxicity and antibody-dependent cell-mediated cytotoxicity. Adalimumab increases the proportion of cells undergoing apoptosis and the level of granulocyte degranulation.[44] This may not be therapeutically beneficial as IC/BPS histologically demonstrates a pancystitis with mast cell infiltration.[45] A total degranulation of these inflammatory cells with the release of histamine, cytokines, and proteolytic enzymes, typical of an anaphylactic reaction, may exacerbate bladder inflammation.

Certolizumab pegol (Cimzia) has some advantages over other TNFα blocking agents for the treatment of IC/BPS including better distribution in inflamed tissue[46], development of low levels of neutralizing autoantibodies[47], greater affinity to TNFα [48], and efficacy when used in monotherapy[49]. Patients with rheumatoid arthritis treated with certolizumab pegol demonstrated a rapid clinical response, often within 2 weeks. Certolizumab pegol inhibits cytokine production.[44] Certolizumab pegol has a unique mechanism of action that should be beneficial in the treatment of IC/BPS in that it has no complement-dependant cytotoxicity and antibody-dependant cell-mediated cytotoxicity.[44,50] IC/BPS histologically demonstrates a pancystitis with mast cell infiltration.[45] The polyethylene glycol moiety of certolizumab pegol inhibits mast cell degranulation.[51] TNFα blocking agents that do not cause cytolysis and prevents degranulation of these inflammatory cells should be therapeutically beneficial in the treatment of IC/BPS.

Most trials in IC/BPS use a patient-reported global response assessment (GRA) such as “Compared to when you began this trial, how would you rate your IC symptoms now?” as the primary endpoint.[52,53] The O'Leary-Sant Interstitial Cystitis Symptom Index and Problem Index (OSPI) questionnaire evaluates overall symptoms in IC/BPS patients.[54] The OSPI results confirm the clinical diagnosis of IC/BPS and establish the severity of the participants IC/BPS baseline symptoms. The Interstitial Cystitis Symptom Index (ICSI) is one of the two O'Leary-Sant Interstitial Cystitis Symptom and Problem Indexes. ICSI has been validated as a reliable

and responsive measure of changes in IC/BPS symptoms.[53,55] ICSI is recommended as an endpoint in IC clinical trials.

Research has searched unsuccessfully for an inflammatory urine biomarker for the diagnosis of IC/BPS. However, Felson[34] demonstrated elevated urine TNFα levels measured by ELISA in patients with IC/BPS compared to controls. It would be interesting to measure urine TNFα levels with modern techniques in IC/BPS patients and see if those levels go down with certolizumab pegol treatment.

The FDA asked for more outcome measures so ICPI and numeric rating scale for pain and urgency was added. They asked for monitoring of patient with outcome data to week 18. We also agreed to change the potential total number of patients from 44 to 42 as this would maintain the 2:1 study medication ratio.

Condition	Intervention	Phase
Cystitis, Interstitial Bladder Pain Syndrome	Biological: Certolizumab pegol (Cimzia) Other: Placebo	Phase III

Study Type: Interventional

Study Design: Randomized, Double-Blind, Placebo Controlled Treatment, Efficacy Study

Primary Outcome Measures

The primary endpoint is improvement in global response assessment (GRA) at week 2

Secondary Outcome Measures

Improvement in GRA at week 4, 10, and 18

Improvement in the Interstitial Cystitis Symptom Index (ICSI) Interstitial Cystitis Problem Index (ICPI) from baseline to week 2, 4, 10, and 18

11-point numeric pain and urgency scale at baseline, week 2, 4, 10, and 18

Midstream first void urine specimen level of TNFα normalized to urinary creatinine, at week 2, 4, 10, and 18 compared to baseline levels

Adverse events from time of Screening through the last clinic and phone call visit

Estimated enrollment 42 patients

After subjective evaluation of efficacy and safety in the initial 30 patients, the total study sample size will be 42 study patients.

Previous IC/BPS studies demonstrated an approximate 20% placebo response rate.[56] Monotherapy response rate of certolizumab pegol in rheumatoid arthritis was 45%.[49] To achieve an 80% power using 2:1 randomization and a 2-sided $p = .05$ a minimum of 39 subjects was required. The sample size was increased by 3 subjects to account for potential participant withdrawals.

Arms	Assigned Intervention
Group 1: Experimental	Biological: Certolizumab pegol (Cimzia) 400 mg pre-filled syringe loading dose given subcutaneously at week 0, 2, and 4 followed by a maintenance dose at week 8
Group 2: Placebo Comparator	Placebo: given subcutaneously at week 0, 2, 4, and week 8

Eligibility

Ages Eligible for Study: 18-65

Genders Eligible for Study: Female

Inclusion Criteria:

1. A diagnosis of IC/BPS defined based on AUA guidelines as the following: an unpleasant sensation (pain, pressure, discomfort) perceived to be related to the urinary bladder, associated with lower urinary tract symptoms of more than 6 months duration, in the absence of infection or identifiable causes, documented history or patient reported.
2. Only those patients with moderate to severe IC/BPS will be included in the study.
3. Able to provide informed consent to participate in the study and comply with study requirements
4. Able to provide written authorization for use and release of health and research study information
5. Written documentation of being provided California's Experimental Subject's Bill of Rights
6. Females ≥18 and ≤ 65 years of age previously diagnosed with interstitial cystitis/ bladder pain syndrome (IC/BPS) for a duration of greater than 6 months
7. Female patients of child-bearing potential must have a negative serum pregnancy test at Screening and use birth control while in the study.
8. O'Leary-Sant Interstitial Cystitis Symptom and Problem Indexes (OSPI) score ≥ 18
9. No history of any cancer.
10. No bacterial cystitis in previous 1 month
11. No active herpes in previous 3 months
12. Never treated with cyclophosphamide
13. No neurogenic bladder dysfunction (due to a spinal cord injury, stroke, Parkinson's disease, multiple sclerosis, spina bifida or diabetic cystopathy)
14. Absence of bladder, ureteral or urethral calculi for previous 3 months

Exclusion criteria:

1. Symptoms are relieved at one month reevaluation visit after receiving IC/BPS behavior modification advice at screening visit.
2. Symptoms are relieved by antimicrobials, antibiotics, or other medications for IC/BPS
3. Pregnant women, lactating mothers, nursing mothers, women suspected of being pregnant and woman who plan to be pregnant during the course of the clinical trial
4. Males
5. Patients with inadequate renal, hepatic, or cardiac function
6. Patients with history of gross hematuria within 2 years.
7. Patients with the following medical history: Lower urinary tract anatomical anomaly, pelvic radiotherapy, or active genital herpes
8. Patients with a history of tuberculosis (TB), recent exposure to TB, or recent travel to TB endemic regions. Patients should have a recent negative PPD (or negative CXR) prior to receiving treatment.
9. Patients who have undergone cystoscopy under anesthesia with bladder biopsy, hydrodistension, or fulguration of Hunner's ulcer within 3 months
10. Patients taking the following treatments for interstitial cystitis at Screening: Intravesical BCG, corticosteroid therapy, cyclosporine, or TNF-alpha inhibitors.
11. Patients with a history of receiving live vaccine including Flumist® influenza vaccine in the past 3 months.
12. Patients with a history of allergic or anaphylactic reaction to a therapeutic or diagnostic monoclonal antibody or IgG-fusion protein.

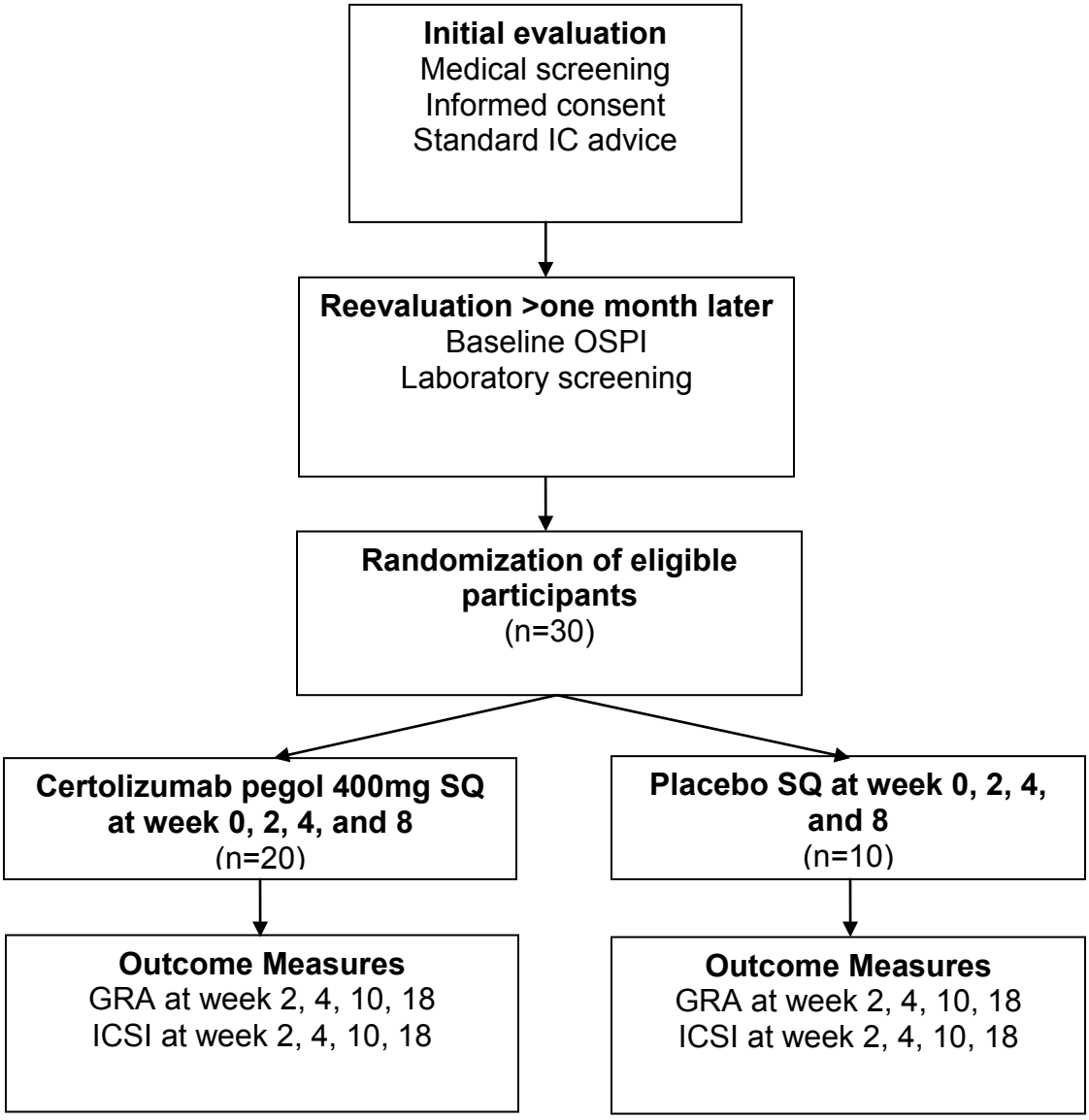
13. Patients with a history of alcohol, analgesic or drug abuse within 2 years of Screening.
14. Patients with a history of any cancer.
15. Patients with a history of active Hepatitis B, Hepatitis C, or Human Immunodeficiency Virus (HIV) infection, or who are known carriers (Hepatitis B).
16. Patients with a history of invasive fungal infections, recent travel to regions endemic for the following invasive fungal infections: San Joaquin Fever, aspergillosis, histoplasmosis, candidiasis, coccidiodomycosis, blastomycosis, and pneumocystosis.
17. Patients with a history of diabetes mellitus.
18. Patients with a history of a neurologic disease included but not limited to central demyelinating diseases, including multiple sclerosis; and a history of peripheral demyelinating disease, including Guillain-Barre syndrome.
19. Other severe acute or chronic medical or psychiatric condition or laboratory abnormality that may increase the risk associated with study participation or investigational product administration or may interfere with the interpretation of study results and, in the judgment of the Investigator, would make the patient inappropriate for entry into this study.

Study Design

Patients enter a one month Screening period to assess inclusion/exclusion criteria, sign informed consent, and determine study eligibility. At the initial screening visit, patients will be instructed in behavior modification techniques to improve IC/BPS symptoms.[43] Patients are reassessed at least one month later for inclusion/exclusion criteria and determine study eligibility. Patients who do not improve with standard IC/BPS advice and pass clinical and laboratory screening can be participants in the study. Baseline evaluation of the included patients will be done with the O'Leary-Sant Interstitial Cystitis Symptom Index and Problem Index (OSPI). At the baseline visit (week 0), all eligible IC/BPS patients will be randomized in a blinded fashion to receive in a 2:1 ratio either SQ certolizumab pegol 400mg or SQ placebo at weeks 0, 2, 4 followed by a maintenance dose at 8 weeks. The length of the study will be 18 weeks. The effectiveness of certolizumab pegol will be assessed at week 2, 4, 10, and 18 using GRA, ICSI, ICPI, and the numeric pain and urgency scale. After subjective evaluation of efficacy and safety in the initial 30 patients, the total study sample size will be 42 study patients.

A midstream urine will be collected at baseline and weeks 2, 4, 10, and 18 from all participants. Quest Diagnostics Nichols Institute, San Juan Capistrano, CA or similar lab will perform an ELISA TNFα and creatinine levels on these samples.

Pilot Study Evaluating the Efficacy of CZP for Interstitial Cystitis
Study Flow Chart



Trial Schedule

	Screen	>One Month Reevaluation	Baseline	Visit 1	Visits 2, 3	Visit 4	Phone Follow-up[6]	Phone Follow-up[6]
Study Day	-37	-7	0	14	28,56	70	98	126
Study Week	-5	-1	0	2	4,8	10	14	18
Study procedures:								
Obtain Informed Consent	X							
Medical History	X							
Medication Review	X	X	X	X	X	X		
Vitals[1]	X	X	X	X	X	X		
Physical Exam	X							
OSPI[2]	X	X						
anti-HCV, HBsAG		X						
PPD		X						X
CBC						X		X
Urinalysis	X	X	X	X	X	X		
Urine Culture		X	X	X	X	X		
Urine Pregnancy Test		X						
Eligibility Assessment	X	X						
Dispense Study Drug			X	X	X			
Injection Site Evaluation[3]			X	X	X			
Adverse Events			X	X	X	X	X	X
GRA[4]				X	X	X		X
ICSI, ICPI[5]				X	X	X		X
Numeric scale of pain and urgency	X	X	X	X	X	X		X

1. Height, weight, blood pressure, pulse, temperature
2. O'Leary-Sant Interstitial Cystitis Symptom Index and Problem Index
3. Monitor subjects for systemic and local hypersensitivity reactions for one hour after injection

4. Global response assessment
5. Interstitial Cystitis Symptom Index, Interstitial Cystitis Problem Index
6. In-office visit if determined to be clinically necessary

Statistical Analysis

All statistical summaries and 2-sample t-tests were performed using the Data Desk® version 6.3. Comparison of these changes between treatment groups are also shown as 95% confidence intervals (CI). The chi-square test or Fisher's exact test was applied to analyze baseline demographics, improvement with GRA treatment responders, and the proportion of patients with a reduction from baseline of 30% or greater in their pain intensity score between treatment groups.

Safety Evaluation

Patients will be assessed at office visits and by continuous availability by phone for adverse events. Adverse effects may include rhinitis, headache, rash, pruritus, injection site reaction, infections, tuberculosis, cancer, and demyelinating diseases.

Stopping Criteria for Adverse Events

Serious infections:
These include TB and infections caused by viruses, fungi, or bacteria. Symptoms related to TB include cough, low-grade fever, weight loss, or loss of body fat and muscle.

Allergic reactions:

Signs of a serious allergic reaction include skin rash, a swollen face, or trouble breathing.

Nervous system problems:

Signs and symptoms include numbness or tingling, problems with your vision, weakness in your arms or legs, and dizziness.

Blood problems:
Symptoms include a fever that does not go away, bruising or bleeding very easily, or looking very pale.

New heart failure or worsening of heart failure you already have:
Symptoms include shortness of breath or swelling of your ankles or feet, or sudden weight gain.

Immune reactions including a lupus-like syndrome:
Symptoms include chest discomfort or pain that does not go away, shortness of breath, joint pain, or rash on your cheeks or arms that gets worse in the sun.

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