ICCTG Protocol #2: A Randomized, Multicenter Clinical Trial to Evaluate the Efficacy of Intravesical Bacillus Calmette Guerin (BCG), for the Treatment of Interstitial Cystitis (IC)

Interstitial Cystitis Clinical Trials Group (ICCTG)

Version 3.0

Effective Date - May 28, 2002

(Incorporates Protocol Amendment #2)

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AGREEMENT PAGE

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I will provide copies of the protocol, any subsequent protocol amendments and access to all information furnished by the sponsor to study personnel under my supervision. I will discuss this material with them to ensure that they are fully informed about the investigational drug and the study protocol.

This agreement will now include Protocol Amendment #2 Effective May 28, 2002.

I agree to conduct this clinical trial according to the protocol described herein, except when mutually agreed to in writing. I also agree to conduct this study in compliance with all applicable federal, state and local regulations, as well as with the requirements of the appropriate Institutional Review Board and any other institutional requirements.

PRINCIPAL INVESTIGATOR: _____ _____

Signature) ***(Date)***

_____

NAME: ***(Please Print)***

_____

INSTITUTION:

Once signed, this original shall be maintained in the clinical center ICCTG RCT#2 Regulatory Binder and a copy faxed to the Project Manager at the DCC.

1 INTRODUCTION

Interstitial cystitis (IC) is an inflammatory disease of the bladder characterized by urinary urgency, frequency, and suprapubic pain. An estimated 1,000,000 persons are currently diagnosed with IC in the United States, however, the number of undiagnosed individuals affected may be much higher (1-3). Approximately ninety percent of IC sufferers are women (2;4). The mean age at diagnosis is 40 years with 25% of IC patients being younger than 30 years (5). Interstitial cystitis patients scored worse on quality of life questionnaires than patients on dialysis(5;6). Sixty percent of IC sufferers complain of pain with sexual intercourse, many so severe they abstained altogether (6;7). Fifty percent of IC patients are unable to work full time (8). On average, $170 million per year is spent for medical care of interstitial cystitis. While combining lost wages and medical expenses, the economic impact of IC has been estimated to be $1.7 billion per year (9). The cause of IC is unknown despite a century of study. Current treatments for IC have come largely from case reports and limited studies. The IC patient will often endure years of failed treatments before even some relief is achieved, if at all.

Symptoms form the basis for diagnosis of IC (4) since pathognomonic markers have yet to be identified. Several characteristics, while not diagnostic for IC, have appeared with relative frequency in advanced cases (10). These characteristics include the presence of glomerulations and/or petechial hemorrhages following bladder distention (11). Small urothelial fissures known as Hunner's ulcers have also been noted in severe cases (12)

Since the etiology and pathogenesis of IC are still undetermined (13), directing treatments towards the specific cause(s) of the symptoms is problematic. Various IC treatments are used. Some are directed specifically to one of the proposed etiologies, whereas others are purely empirical (14). At this time, there is very little knowledge to help clinicians choose which treatments may be most beneficial for specific patients (15).

The number of current treatments is large and ranges from simple bladder distention to cystectomy with urinary diversion. IC treatments can be grouped into five broad categories:

1. intravesical therapies (e.g., Clorpactin (11), DMSO (16;17), heparin, oxychlorosene sodium (18)),
2. oral medications (e.g., pentosan polysulfate (19), amitriptyline (17), hydroxyzine (20)),
3. local ablative or injection therapy (e.g., transurethral resection (21)),
4. neural ablative therapy (e.g., cystolysis (22)), and
5. other surgical procedures or alternative approaches (e.g., augmentation cystoplasty (23), electrical stimulation and biofeedback (24)).

In most cases of IC, treatment choices are made by first trying the safest and least invasive options, and then progressing to other treatments (which have more potential morbidity) if the initial treatments do not relieve symptoms effectively (14). Combining treatments is often needed to improve functional outcome (14;15).

Having failed conservative therapy, patients with refractory interstitial cystitis choose to undergo various intravesical treatments to obtain symptom relief. Many of these treatments, however, have failed to demonstrate sustained benefit (18).

Intavesical Bacillus Calmette-Guerin (BCG) is a novel therapy for the treatment of IC (25). Although this therapy has been used effectively in the treatment of bladder cancer, its exact mechanism of action is unknown (26-28). Preliminary studies evaluating its effect in the treatment of IC have shown promising results (25;29;30). Confirmation of these results require further clinical trial investigation with placebo control, and studies to evaluate mechanism of action and effect on putative IC markers (31-34).

2 STUDY DESIGN AND OBJECTIVES

The proposed randomized clinical trial (RCT #2) will utilize a 2 arm design to evaluate the efficacy of intravesical BCG in patients with interstitial cystitis, as compared to an intravesical placebo.

The primary objectives of this trial are:

1. To compare treatment with six (6) instillations of BCG to sham treatment with six (6) instillations of saline for effects on symptoms and overall well being in patients with interstitial cystitis (IC).

2. To evaluate changes in urinary markers over time and correlate these changes with changes in symptoms over the same period.

3. To evaluate measures of symptoms and quality of life, including the O'Leary-Sant and Wisconsin symptom indices, and validate their use as endpoints in clinical trials.

4. To obtain additional information on re-induction of intravesical BCG.

5. To obtain information on long-term response of those patients determined to be responders at the completion of Phase 1 of treatment.

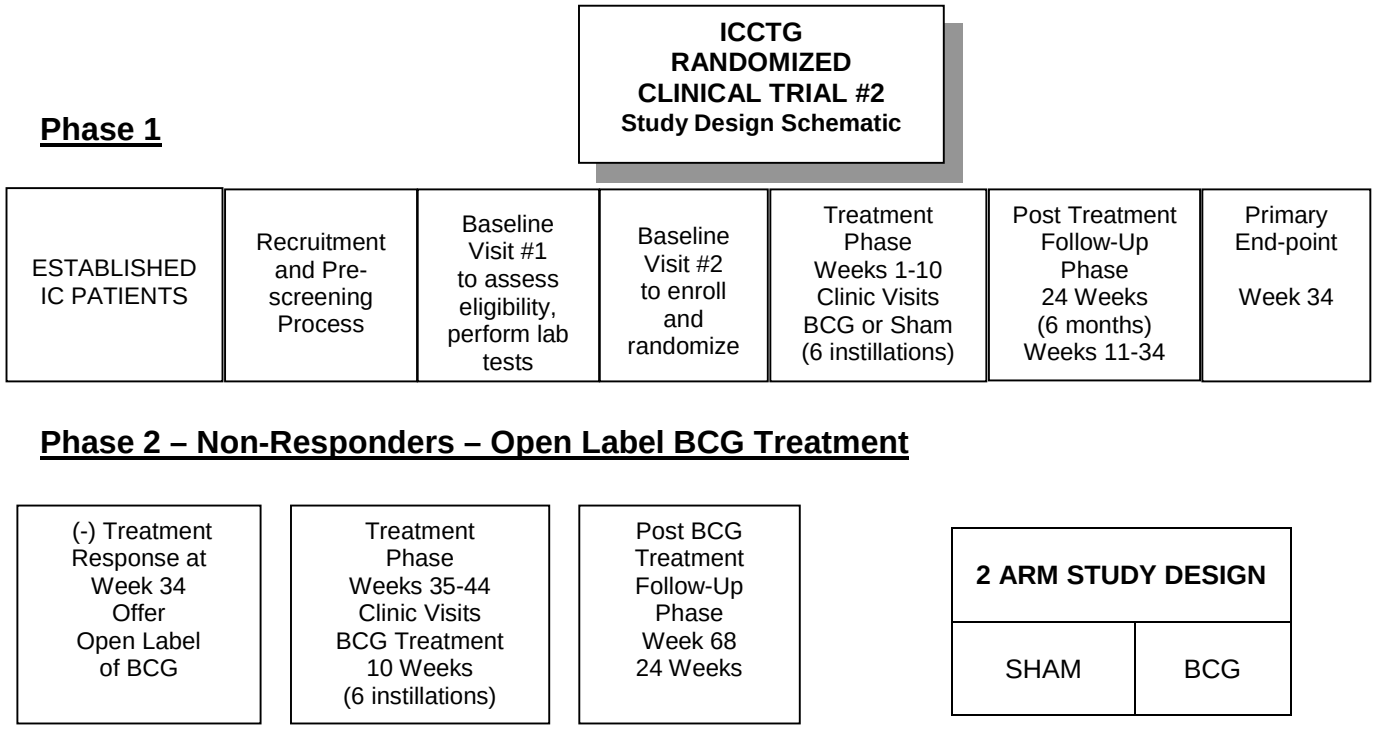
All participants who meet eligibility criteria at baseline screening (a two-to-four week period), will be stabilized on their current IC medications prior to randomization to one of the two treatment arms. Immediately after randomization, there will be a two-week window in which the first instillation must occur. The instillation regimen will require that the interval between treatments be a minimum of 6 days and a maximum of 3 weeks. No more than 3 weeks may lapse between instillations. Each patient is expected to receive total of six instillations (BCG or saline). Instillations will be scheduled according to the patient's tolerability. The six instillations can be given weekly within 6 consecutive clinic visits, but all instillations, even if fewer than six, must be administered within a 10 week visit schedule.

For the six months following the intravesical instillations, each patient will continue to be monitored for safety, use of concomitant medications (especially narcotics and medications for IC), quality of life, IC symptoms, and urinary biomarkers.

The primary endpoint will be evaluated at the patient's visit at week 34 following randomization in the post-treatment follow-up phase. Patients will be identified as responders and non-responders at week 34 based on their response to the global assessment question and their use of medications for IC symptoms.

The study consists of two phases as outlined below. The first phase, consisting of initial treatment and follow-up for primary and secondary endpoints, represents the primary phase of the study. Phase 2-Non-Responders will be primarily descriptive, and will provide additional information related to open-label BCG treatment for all "non-responders" in Phase 1 who choose to undergo a second course of treatment. Phase 2R-Responders will also be primarily descriptive. This phase will provide information on the long-term response of those patients determined to be "responders" at the completion of Phase 1 of treatment.

Figure 1



3 Study Agent and Rationale for Use in Interstitial Cystitis

3.1 Bacillus Calmette-Guerin (BCG)

Bacillus Calmette-Guerin is an attenuated strain of the bovine tuberculosis bacterium *(Mycobacterium bovis)*, originally developed as a vaccine against *Mycobacterium tuberculosis*, the cause of tuberculosis in humans. BCG administered intravesically, is a Food and Drug Administration approved treatment for superficial cancer of the bladder (26;27). Although its exact mechanisms of action are unknown, intravesical instillations of BCG have been shown to be effective treatment of and prophylaxis against recurrent stages Ta and T1 bladder tumors and therapy for carcinoma in situ (35). Intravesical BCG is a novel therapy for the treatment of IC. An open-label pilot study of BCG for the treatment of refractory IC was conducted by Zeidman and coworkers on patients who had failed conservative therapy. Results suggested that BCG immunotherapy may be efficacious in the treatment of IC symptoms (25). Peters and colleagues extended the work of Zeidman in a placebo-controlled study. The results from this study demonstrated a 60% BCG response rate compared to a 27% placebo response. The treatment regimen was six weekly instillations of BCG. A follow-up study suggested that the results were durable. Patients treated with intravesical BCG achieved remission and remained free of IC related symptoms for more than two years (29;30).

The mechanism of symptom relief is unknown. One theory is that BCG changes bladder inflammation from a predominantly T-helper cell type 2 (Th2) response to a Th1 response, which is more indolent (30). Another theory is that BCG may increase nitric oxide synthase activity in the bladder (30). The major concern with BCG is that this live organism occasionally causes sepsis when used to treat bladder cancer. To date, BCG sepsis has not occurred in the IC population (15).

Clear demonstration of the benefit of BCG immunotherapy would profoundly alter the current treatment options available for treating this enigmatic disease and provide insights into its etiology. Finally, a second induction of BCG for non-responders is a standard therapy for bladder cancer (36;37). If this proves to be fruitful in treating refractory IC, it will be of great benefit to those suffering from this disease.

4 Study Plan

4.1 Phase 1

The first phase, consisting of initial treatment and follow-up for primary and secondary endpoints, represents the primary phase of the study. This phase will utilize an intention-to-treat analysis to compare the proportion of responders between treatment arms, using a definition of response based on both patient assessment of global improvement and the use of "breakthrough" medications (see section 4.3.1) for symptoms.

4.2 Phase 2 and Phase 2R

Phase 2 of the study will include only patients who, after completing phase one study treatment and post-treatment follow-up, are classified as "non-responders" for the primary endpoint at week 34. These patients will be offered a second series of six (6) intravesical instillations with open-label BCG. For those patients originally randomized to saline, this will be the first BCG treatment. For those who originally received BCG, this will represent "reinduction therapy". The original treatment assignment will remain blinded, except for emergency situations, until the end of the study. Those patients who choose to undergo this second instillation will be followed using the same schedule as for Phase 1. Therefore, these patients will be followed a total of 34 weeks in the first treatment phase and 34 weeks in the second treatment phase for a total of 68 weeks.

Phase 2R of the study will include only patients who, after completing Phase 1 treatment and follow-up, are classified as "responders" for the primary endpoint at week 34. Three telephone contacts (or clinic visit contacts if the patient prefers) wherein the patient will be queried as to any (serious) adverse events, supplemented with mailing of data forms from the patient to the clinical center, will be conducted. At the primary endpoint of Phase 1 of the study (7.5 months from randomization), the principal investigator may choose to discuss with those patients who feel they are in excellent control of their symptoms the possibility of tapering medications for IC. The decision to initiate the discussion about medication taper, and any subsequent decision to taper medication or not, should be based on the principal investigator's impression of what is in the patient's best individual clinical interest, and will be completed only with qualified medical supervision.

For both Phase 2 and for Phase 2R, the overall global assessment of response, symptom index, and other endpoints (described in section 4.4) will be evaluated at week 68 and compared to both values at randomization and those at the end of Phase 1 (34 weeks). However, it is recognized that there is no control group for this second phase (phase 2 and phase 2R) of the study, and the analysis of these results will be primarily descriptive.

4.3 Treatment and Follow-up

In the first phase, patients will be randomized in equal proportions to receive six (6) instillations of either BCG or saline within a 10 week period of time. All patients will be followed for 34 weeks from randomization.

A variety of pharmacotherapeutic agents are utilized in the treatment of IC. This study will define as "IC Treatment Medications" those agents medically prescribed for treatment of IC symptoms in patients with an established diagnosis of interstitial cystitis. These medications are identified in the following therapeutic categories:

- Tricyclic Antidepressants
- Sedating Antihistamines (H1 Blocker)
- Anticonvulsants
- Alpha2-Adrenergic Agonist Agents
- Intravesical therapies (e.g. DMSO, Clorpactin, Heparin)

Prior to randomization, all patients will be stabilized on current medications. Medications prescribed for treatment of IC from these therapeutic categories will be specifically identified in the patients pre-study diary record and monitored in the patients concomitant medication record throughout the study. Additionally, if the patient is taking prescribed medications for treatment of IC that are not included in the above categories, these medications will also be identified and monitored as IC medications.

Patients randomized into the study will be requested to have no change in their pre-study medication regimen for IC throughout the treatment and follow-up period. It is strongly recommended that categories of medications (as listed above), prescribed for the treatment of IC, be ***avoided*** in managing the patients IC symptoms throughout the trial. Instead, *breakthrough* medications (as listed in 4.3.1) will be used to manage the patient's IC symptoms throughout the trial. Other than the specified intravesical treatment administered in this study, the administration of **any other intravesical treatment is prohibited during the course of this study.**

4.3.1 Definition and Classification of Breakthrough Medication

During the entire treatment and follow-up period (34 weeks), oral medications of the following therapeutic categories will be allowed, on a temporary as needed basis, for use as *"breakthrough"* medication for treating episodes of increase in pain, frequency, urgency/pressure (IC symptoms). For purposes of this clinical trial, *"breakthrough"*medication is defined as those agents utilized to symptomatically alleviate interstitial cystitis symptoms of pain, frequency, urgency/pressure as follows:

- Narcotic Analgesics
- Urinary Analgesics
- Urinary Antispasmodics
- Analgesics, nonsteroidal anti-inflammatory drugs (NSAIDS)
- Analgesics, salicylate and miscellaneous
- Anticholinergics
- Antibiotics (**except**: Aminoglycosides, Quinolones, Rifampin, Doxycycline, INH)

4.4 Study Endpoints

4.4.1 Primary Endpoint

The primary endpoint on which the comparative efficacy of BCG and saline will be evaluated is a combined endpoint with two components: the patient-reported global assessment of response and the use of IC medications during the follow-up period.

The global evaluation of improvement for the primary endpoint will occur at week 34 or withdrawal, whichever comes first, relative to IC symptoms at baseline via the question: "As compared to when you started the study, how would you rate your interstitial cystitis symptoms now?" A seven point scale centered at zero will be used: -3) markedly worse; -2) moderately worse; -1) slightly worse; 0) no change; +1 slightly improved; +2) moderately improved; and +3) markedly improved. Participants who answer either +2) moderately improved or +3) markedly improved on the global evaluation will be considered to have evidence of "clinical improvement"

The second component relates to changes (increase or addition) in the use of IC treatment medications from the level at which the patient was stabilized at the beginning of the study. Increased usage of pre-study IC medications or the initiation of new IC medications during the last four weeks of post-treatment follow-up (week 31 - 34 post-randomization) will cause the patient to be classified as a non-responder.

Use of *breakthrough* medications as described in Section 4.3.1 will be allowed **with the exception of narcotic analgesics.** New or increased use of narcotic analgesics during the last four weeks of post-treatment follow-up (week 31-34) will be considered equivalent to starting a new IC medication, and therefore, would cause the patient to be classified as a non-responder. In addition, any patient who ***requests*** narcotic analgesics for treatment of IC symptoms during the last four weeks of post-treatment follow-up will also be classified as a non-responder.

Therefore, patients will be considered to be "responders" for the primary endpoint if they fulfill both of the following two criteria:

1. Report "moderate" or "marked" improvement on the global assessment at 34 weeks.
2. Report no increase in pre-study IC medications, and no initiation of new IC medications, and no new or increased use of narcotic medications during the final 4 weeks of the follow-up phase.

The proportion of responders in each treatment arm will be compared in an intent-to-treat analysis to evaluate the overall effectiveness of BCG. Criteria #1 and #2 must both hold for a patient to be considered a responder at 34 weeks; all other patients will be considered "non-responders" and included in denominators for evaluation of response rates between treatment arms. Specifically, participants who withdraw from the study for

any reason (e.g. adverse event or participant choice) prior to the primary endpoint, will be considered treatment non-responders for the primary endpoint.

4.4.2 Secondary Endpoints

Secondary endpoints will include symptom indices, quality of life, and biomarkers. All of these will be assessed repeatedly during the treatment and follow-up period. The schedule of follow-up data collection is shown in the study procedures table. Analyses will include changes over time using longitudinal data models, and associations between these changes and overall patient response as defined above. The latter analyses will involve a component of validation of the symptom indices. Furthermore, changes in biomarkers will be correlated with changes in symptoms to evaluate possible mechanisms of effects. Details of these analyses are given in the Statistical Considerations section.

5 STUDY ORGANIZATIONS

The ICCTG Study organization includes nine main Clinical Centers recruiting for this study. All Clinical Centers will maintain their own computing hardware for direct data entry into the study database at the DCC. Throughout this document, the nine centers recruiting for this study will be referred to as *Clinical Sites*. The Clinical Sites that will enroll patients into the ICCTG Study are:

1. University of Pennsylvania Health System, Philadelphia, PA 19104
2. New England Medical Center, Boston, MA 02111
3. University of Rochester, Rochester, NY 14642
4. University of Maryland, Baltimore, MD 21201
5. University of Oklahoma, Oklahoma City, OK 73104
6. William Beaumont Hospital, Royal Oak, MI 48073
7. Henry Ford Hospital, Detroit, MI 48202
8. Queens University, Kingston, Ontario, Canada K7L2V7
9. Stanford University Medical Center, Stanford, CA 94305

6 PARTICIPANT CRITERIA

6.1 Participant Recruitment

Participant recruitment will be conducted through the urology clinic at each of the designated clinical sites. Participants may be self-referred or referred through their primary physician (either solicited or unsolicited by the urology clinic). Participants referred to the clinics with refractory symptoms of IC will be introduced to the ICCTG protocol and asked whether they are interested in participating in the study. Interested subjects will be asked to sign the informed consent form (See Appendix A Suggested Subject Consent Form), approved by the local Institutional Review Board (IRB). This form will provide consent for both the screening and the follow-up procedures.

6.2 Study Population and Number of Participants

The study population for this RCT #2 protocol will be drawn from participants with a diagnosis of IC, confirmed sometime in the past with the results from a cystoscopy/hydrodistention. It is expected that 260 participants will be accrued within a 14 month time period from the start of the study. (See Section 13.2).

Any IC participant presenting with symptoms of urinary frequency in conjunction with urinary pain/discomfort persisting for at least 24 weeks will be considered a candidate for enrollment into the study. Participants must satisfy the following eligibility criteria in order to be entered into this study.

6.2.1 Inclusion Criteria

1. At least 18 years of age.
2. Participant must sign and date the informed consent.
3. Participant must have received a minimum of 12 weeks of treatment with some standard form of therapy or combination of therapies for IC. The treatment must have occurred after diagnosis of IC and administered in response to the patient's IC symptoms. Potential previous therapies include: tricyclic antidepressants, hydroxyzine, other antihistamines, DMSO, pentosanpolysulfate, heparin, NSAIDS, and anticholinergics.
4. Participant (male or female) must agree to use a medically approved method of birth control.
5. Participant must report a urinary frequency of at least 11 times per 24-hour day, on average over the previous four weeks. This frequency criterion must be met at each of the two baseline-screening visits as reported by the participant.
6. Participant must report a pain/discomfort score of 4 or greater on a 0 - 9 Likert scale. This pain/discomfort criterion must be met at each of the two baseline-screening visits.
7. These reported urinary symptoms of frequency and pain/discomfort must have been present for at least the previous 24 weeks prior to the first baseline screening visit.
8. Participants must report in the baseline voiding diary at least one voided volume greater than or equal to 75cc in a 24 hour period.

6.2.2 Exclusion Criteria

Any participant satisfying one of the following criteria will **not** be eligible to participate in the ICCTG Study:

1. Active tuberculosis that requires ongoing therapy
2. Immunocompromised patients and/or known positive HIV test results.
3. Known allergy to or intolerance of BCG, or any of its components as reported by the participant or derived from their medical records.
4. Previously treated with intravesical BCG.

5. Unable to void spontaneously.
6. Any imminent change in residence, which could compromise compliance.
7. Unlikely to be compliant due to unmanaged medical or psychological problem including dementia, aphasia or other deficits of cognition or speech/language function that will interfere with her/his ability to complete study.
8. Substance abuse or dependency problem within the past 2 years for which patient received no treatment.
9. Severe debilitating concurrent medical conditions including severe coronary artery disease, azotemia, moderate to severe hepatic insufficiency, systemic cancer requiring treatment, or similar severe conditions.
10. Previous treatment with Cytoxan®/cyclophosphamide.
11. A history of pelvic radiation treatment, bladder calculus, tuberculous cystitis, neurologic disease affecting bladder function, bladder cancer or cancer in situ, or urethral cancer. Any other neoplastic process currently requiring systemic, non-prophylactic treatment.
12. Previous augmentation cystoplasty, cystectomy or cystolysis, neurectomy (i.e. hypogastric nerve plexus ablation) or implanted peripheral nerve stimulator which has affected bladder function.
13. Currently has an active urethral calculus, ureteral calculus, urethral diverticulum.
14. A current history of visicoureteral reflux.

Exclusion criteria for men only:

1. Having a residual urine volume >150 cc by ultrasound or catheter.
2. Currently being treated for chronic bacterial prostatitis as documented by a positive urine culture.
3. History of prostate cancer.

Exclusion criteria for women only:

1. Currently pregnant or breastfeeding.

6.2.3 Deferral Criteria

There are several physical conditions for which a participant will be deferred from entry into the ICCTG Study. Once it is formally ascertained that the condition is not present or has subsided according to the time frame identified, the participant will be reconsidered for entry into the ICCTG Study. The following list identifies the conditions for deferment and the criteria that a participant must meet in order to be evaluated further for entry into the study:

1. If a participant has initiated any new medications for IC during the past 4 weeks, he/she will be deferred until he/she has been on the same dose for at least 4 weeks.
2. Within six weeks prior to study enrollment, if a participant has undergone bladder instrumentation such as urethral dilation, urodynamics, bladder cystoscopy or

bladder biopsy under general or regional anesthesia, he/she will be deferred until at least 6 weeks from the date of the procedure.

3. If a participant has undergone hydrodistention within six weeks prior to study enrollment, he/she will be deferred until at least 12 weeks from the date of the procedure.
4. If a participant has had a positive urine culture (100,000 col.ct) during the past 6 weeks, he/she will be deferred until the participant has been without the condition for at least 6 weeks.
5. Participating in another intervention study or received an investigational drug or device within 4 weeks prior to screening.
6. If a participant has active genital herpes or has had active genital herpes during the past 12 weeks, he/she will be deferred until the participant has been without the condition for at least 12 weeks.
7. If a participant has had any intravesical treatment (i.e. DMSO, Heparin, cystostat) other than BCG within 12 weeks prior to study enrollment, he/she will be deferred until at least 12 weeks after the last treatment received.
8. Participants treated with botulinum toxin injections for voiding dysfunction within 24 weeks prior to baseline will be deferred until 24 weeks after last treatment received.
9. History of incontinence surgery or any other bladder or urethral surgery within the past 24 weeks, which could interfere with bladder function.
10. Participants must have been off treatment with pentosan polysulfate (Elmiron®) for a minimum of four weeks prior to randomization.

Deferral criteria for women only:

1. If a participant has active vaginitis, she will be deferred until she is free of the condition.
2. If a participant has had any form of transvaginal surgery, hysterectomy, prolapse surgery, vaginal delivery or C-section, she will be deferred until at least 24 weeks from the date of the procedure.
3. Participants must have completed breastfeeding for 24 weeks prior to study enrollment.

Deferral criteria for men only:

1. Having had a TURP, TUIP, TUIBN, TUMT, TUNA, balloon dilation of the prostate, open prostatectomy or any other prostate treatment such as cryotherapy or thermal therapy, participant will be deferred until or at least 24 weeks from the date of the procedure.

7 Biomarkers Studies

One of the major frustrations associated with IC is the lack of objective markers to diagnose and monitor disease progression. Recently, several urinary markers have been

identified; however, there are minimal data available regarding their utility in diagnosing IC and monitoring changes in the disease. Therefore, a component of this trial of intravesical BCG for the treatment of IC will involve collecting and processing urine specimens at defined intervals to study alterations in urine IC markers as a result of BCG and/or placebo therapy, and then correlate any alterations with changes in symptom scores at each defined time point to determine whether response to treatment is predictable. In addition, the same urine specimens will be used to measure other physiologic markers associated with known effects of BCG therapy, and to determine whether physiologic evidence of drug activity correlates with a change in symptom scores.

Urine specimens will be collected at four specific time points: immediately before administration of the first treatment, before the administration of the 4^{th} treatment and six hours after the 4^{th} treatment, and at the 34 week time point. The first pre-treatment, 4^{th} pre-treatment, and 34 week specimens will be collected at the study sites, and cells removed by centrifugation. The cell pellet will be fixed using provided fixative and container for cytology. The urine will be separated into two sterile containers, one containing a stabilizing agent with a protease inhibitor tablet added for the chemokine/cytokine assays, and the other without preservative. (See Appendix E Urine Specimen Collection and Archive Protocol) The specimens obtained six hours after the 4^{th} treatment will be collected at home by the patient, who will be given a cup and instructions for urine collection (See Appendix F Patient Instructions). .

In order to investigate the potential impact of BCG on urine markers, the following markers will be considered for analysis:

1. Markers of IC: APF, HB-EGF, EGF, IL-6.
2. Markers of BCG activity: known markers for a Th1 or Th2 response, as well as control cytokines, IL-2, IL-8, IL-10, IFN-gamma, GMCSF, MCP-1 and IP-10.

In addition, urine cytology specimens will be evaluated for

1. DNA cytometry and fluorescence in situ hybridization.
2. Persistence of BCG (by PCR)

8 INVESTIGATIONAL MATERIAL

8.1 TICE® Bacillus Calmette-Guérin [BCG (NSC-116327)]

8.1.1 BCG Pharmaceutical Data:

Bacillus Calmette-Guérin is a freeze-dried lyophilized preparation of live mycobacteria containing $5\pm3 \times 10^8$ colony- forming units (CFU), per 50 mg (wet weight) of protein. This BCG is manufactured by Organon Teknika (Durham, NC) and is supplied in 2 mL glass vials. The package insert Appendix H.

8.1.2 BCG Storage and Stability:

Storage of the intact vials of TICE® BCG should be at refrigerated temperatures of 2-8 °C (36-46 °F). BCG contains live bacteria and should be protected from light. Do not freeze. BCG has limited stability after production. Check expiration date on vial. Use within two hours of reconstitution and discard any unused portion.

8.1.3 BCG Preparation of Agent:

Using aseptic methods, draw 1-mL of sterile, preservative-free saline into a small (3 mL) syringe and add to one vial of TICE® BCG to resuspend. Draw mixture into the syringe and gently expel into the vial until grossly observable particles are thoroughly dispersed to ensure thorough mixing. Dispense the BCG suspension into the tip end of a catheter-tip syringe that contains 49 mL preservative-free saline diluent bringing the total volume to 50 mL. To prevent clumping, exclude all air from the syringe. Gently rotate the syringe. The suspended TICE® BCG should be used immediately after preparation. Discard after two hours. See Appendix D for details on the **syringe masking procedure**.

8.1.4 BCG Dose:

The intravesical dose consists of one vial of 1 mL of TICE® BCG. This is then used to combine with 49 mL of preservative-free sterile saline. The intravesical dose will be 50 mL.

8.1.5 BCG Disposal and Clean-Up:

All containers, syringes, and needles that contain the vaccine should be disposed of in standard biohazard disposal containers immediately after use (Appendix G Handling of BCG Vaccine).

8.1.6 BCG Toxicity:

Adverse reactions are often localized to the bladder but may be accompanied by systemic manifestations. Systemic adverse effects such as malaise, fever, and chills often reflect hypersensitivity reactions that can be treated with antihistamines. The "flu-like" syndrome of 1-2 days' duration that frequently accompanies intravesical BCG administration often can be managed by standard symptomatic treatment. However, symptoms such as fever ≥38.5°C (101.3°F), or acute local reactions such as epididymitis, prostatitis, or orchitis, persisting longer than 48 hours, suggest active infection, and consideration should be given to multiple-drug antituberculosis therapy.

8.2 Sterile Preservative-free Saline – PLACEBO For BCG

8.2.1 Placebo Pharmaceutical Data:

Commercially available sterile preservative-free saline will be labeled and shipped by Organon Teknika (Durham, NC) and will be used as the placebo instillation and dissolution of vaccine. Each mL contains sodium chloride, 9 mg USP. No antimicrobial agent is added. Osmolarity is 0.308 mOsmol/mL (calc.). It is sterile and nonpyrogenic.

8.2.2 Placebo Storage and Stability:

It is recommended that it be stored at room temperature (25°C). Avoid excessive heat. Use prior to expiration date on container.

8.2.3 Placebo Dose:

Intravesical dose will be 50 mL. See Appendix D for details on the labeling and syringe masking procedure.

8.2.4 Placebo Toxicity:

There is no known toxicity for the intravesical instillation of this dose of sterile preservative-free saline.

9 CONCOMITANT MEDICATIONS

Participants will be monitored at each clinic and phone visit as to their use of OTC and prescription medications. All concomitant medication(s), prescription or over-the-counter (OTC), must be reported on the appropriate case report form (CRF). Intermittent or as needed (PRN) use of any medication during the study must be noted. Such medications will be recorded on the Concomitant Medication Form.

9.1 Exclusionary Medications:

During the course of the study, participants **MAY NOT** inititate or otherwise consume any of the following medications or treatments:

- Isoniazid*
- Rifampin
- Other antituberculosis therapies (e.g. Ethambutol, Pyrazinamide)
- Anticoagulant therapy (e.g. Coumadin®) with the exception of low dose aspirin therapy.
- Steroids (low dose steroid nasal spray is permitted)

- Intravesical therapies (e.g. DMSO, Clorpactin, Heparin)
- Pentosanpolysulfate (Elmiron®)

**Isoniazid (INH) will only be given if the patient is withdrawn from the study, unblinded according to protocol (see section 11.4), and the determination is made that antituberculosis therapy is necessary.*

9.2 Allowable Medications:

9.2.1 Antibiotics

If, during the course of the study, patients must be treated with antibiotics, the patients will be allowed to defer treatment until the course of the antibiotics has been completed, not to exceed ten days between treatments. If the course of antibiotic treatment cannot be completed in this timeframe, the patient should be discontinued from the study. If a patient experiences a fever greater than 38.5ºC (101.3º F) for 12-24 hours, the investigator should consult with the Infectious Diseases consultant associated with the study site.

In the event that antibiotics are required for prophylaxis or treatment, penicillins, cephalosporins, and macrodantin are recommended. Other antibiotics may be used as clinically required, however, the following have been demonstrated to have activity against TICE® BCG and **should be avoided UNLESS absolutely necessary**: Quinolones (Cipro, Floxin, Noroxin, Levaquin), Doxycycline, and gentamycin.

9.2.2 Breakthrough Medications

Breakthrough medications allowed for exacerbation of IC symptoms are outlined in Section 4.3.1.

10 STUDY CONDUCT (See Appendix B Visit Schedule Phase I & Phase II)

Phase I of this study is outlined as follows:

- two Baseline Screening Visits (completed within 4 weeks of initial consent)
- ten-week treatment phase
- 24 week follow-up phase

Phase II of this study is outlined as follows:

- ten-week treatment/reinstillation of BCG for patients with negative response to Phase 1
- 24 week Post BCG reinstillation treatment follow-up phase

10.1 Patient Recruitment and Screening (B1and B2 Visits)

Potential patients may be recruited from referral of IC patients and from patients of record at the clinical study sites. (**Potential participants will sign written consent to participate *prior* to screening visit B1).** Potential participants will then be evaluated during two office visits. The screening period is expected to be completed in less than four weeks. A screening log should be maintained documenting all patients screened for participation in this study and noting reasons for non-enrollment or ineligibility.

10.1.1 Screening Visit B1

During the first baseline screening visit (Week -4) the study will be explained, and the general condition of each patient will be evaluated. The screening evaluations will include tests, examinations, and questionnaires to establish baseline clinical and experimental values. The procedures to be completed by the investigator and study coordinator during the first screening visit include:

Demographic information

Medical history

IC history

Baseline Symptom Form

If, after reviewing the historical results, the investigator decides that the patient remains potentially eligible for enrollment, the following will be done:

Urinalysis

Urine culture

Collect blood sample and send for:

Complete blood count (CBC) with electronic differential, RBC's, platelets

Serum pregnancy (female-child bearing potential)

Voiding Diary-Will be given for use during a 24 hour period preceding the next study visit.

Medication Diary with instructions to record all medications taken until the next scheduled visit.

10.1.2 Screening Visit B2

The second Baseline Screening should be completed at least one week after, but no more than four weeks after screening Visit Baseline1. During this visit, the patient will have an opportunity to ask questions and express concerns related to the study. The following information will be collected:

Baseline symptoms form

University of Wisconsin Symptom Survey

IC Symptom and Problem Index

SF-36 Health Status Questionnaire

MOS Sexual Functioning Scale

The following procedures will be completed by the investigator and study coordinator:

Collect and review Voiding Diary - (patient must record at least one void greater than or equal to 75 cc's)

Collect and review Medication Diary.

Review laboratory results - (If the CBC is outside the site's normal laboratory values range, the investigator will determine whether the abnormality presents a medical risk to the patient. If a clinically significant abnormality is noted, the investigator will determine whether the patient must undergo further evaluation prior to enrollment into the study.)

Assess current birth control methods.

If the patient remains eligible for enrollment, the following clinical examinations will be completed:

Physical examination

Pelvic examination (female patients only)

Digital rectal exam (male patients only)

10.2 Enrollment and Randomization Procedure

The inclusion and exclusion criteria will be reviewed with the patient, as well as checked against their symptom questionnaires, medication use, voiding diary and lab results from the previous visit. The average baseline symptoms score and the average voids per day over the 2 baseline screening visits will be calculated. If the patient is eligible for the study, the patient eligibility checklist will be entered into the computer database by the research coordinator and computer randomization will be performed. The patient will be scheduled for their first study treatment visit (scheduling should occur within two weeks of completion of Baseline two screening Visit and Randomization). The patient will be given instructions in preparation for the treatment (Appendix F Patient Instructions Pre-Treatment).

10.3 Treatment Phase One (Visits 1 – 6)

Treatment Visit I should begin within two weeks of Baseline 2 visit with randomization. All attempts should be made to ensure compliance with the visit schedule for treatment. During the treatment phase of the study, BCG or placebo solution will be instilled into the bladder (Appendix C Protocol for Administration of Study Agent). This procedure will be repeated once each treatment for a total of six treatments within a 10 week period of time from the date of randomization. The interval between treatments will be a minimum of 6 days and a maximum of three weeks. No more than 3 weeks may lapse between treatments. Therefore, treatment schedules must take into consideration the following:

1. Treatment visits will be scheduled according to patient's tolerability.
2. Some patients may not receive all six study treatments.
3. All intravesical treatments must be administered within a 10 week visit schedule.
4. Treatment regimen will require the interval between treatments to be a minimum of 6 days and a maximum of 3 weeks.

Information obtained during the instillations, as well as a record of treatment follow-up phone call, will be recorded. Patients will be instructed to report any adverse reactions without delay. Intercourse should be avoided during the period of 48 hours following each treatment instillation. Although sexual transmission of BCG has not been reported, it is required that a condom be used in the event of intercourse during this period.

10.3.1 Treatment Visit I

The study coordinator or investigator will review any clinical problems or events occurring since last study contact and update the concomitant medications record with any changes in medication use.

Safety Assessment: Female patients will be asked the date of their last menstrual period. An assessment of current birth control methods will be performed and recorded in the patient's chart and Case Report Form (CRF), if appropriate. For women of child-bearing potential, if pregnancy is suspected, a repeat β-HCG pregnancy test will be performed. If a repeat pregnancy test is performed and the results are positive, treatment should be discontinued immediately and the patient should be discontinued from the study and the Clinical Center Stop Point or "STOP" CRF should be filled out.

Prior to administering the first study treatment, a urine specimen for biomarkers study and a urine specimen for analysis will be obtained via catheterization of the patient. An analysis of the urine specimen will be completed *before* administration of the study treatment.

When it has been determined that treatment may proceed, the Pharmacy should be notified to prepare and deliver the test solution. The patient will then be prepared for the

treatment procedure. The patient's temperature will be recorded *before* the instillation of the test solution.

When test solution has been received from the Pharmacy, the time of preparation should be checked on the label and a determination made that the product was prepared no more than two hours ago. If the product was prepared more than two hours ago, it should be returned to the Pharmacy and fresh product obtained. Instillation of study product will be performed as described in Protocol for the Administration of Study Agent (Appendix C).

Prior to dismissal, the patient will be given instructions regarding the next study visit and will be advised of the two follow-up telephone calls as described in Section 10.3.1.1. An information sheet (Appendix F Patient Instructions Post-Treatment) will be reviewed with the patient describing signs and symptoms of complications or side effects, which should be reported, and providing 24-hour contact information. The patient will be asked to take an oral temperature at bedtime on the night of treatment and again at bedtime on the following night.

10.3.1.1 Treatment Follow-up Phone Calls

The study coordinator or investigator will contact the patient by telephone on each of the two days following treatment delivery. At this time, the patient will be questioned about any side effects or adverse experiences, any medications stopped or started, and asked to report their bedtime temperature reading. Results will be recorded on the Telephone Contact During Treatment "PHNTP" CRF. If a patient cannot be reached, a message should be left, if possible, requesting that the patient call the study site.

10.3.1.2 Treatment Visits 2 - 6

The conduct and procedures for Visits 2-6 are the same as for Visit 1, with the exception of urine specimen for biomarkers study. A urine specimen for biomarkers study is not collected at treatment visits 2,3,5,6.

A pre-treatment catheterized urine specimen is collected at treatment visit four for biomarkers study. In addition, the patient will be instructed to collect a second urine specimen 6 hours after treatment visit four for the biomarkers study. (Appendix F-Patient Instructions Urine Collection After 4th Treatment Visit).

Each treatment visit is followed by two days of telephone follow-up. At the end of the patients last treatment visit (the 6th instillation) the patient is given a Voiding Diary to complete in the week preceding Week 18 post-treatment clinic visit.

10.4 Post Treatment Follow-up Period (Weeks 14-34)

Treatment follow-up phone visits will be scheduled at week 14, 22, and 30. Treatment follow-up clinic visits will be scheduled at week 18, 26, and 34. All attempts should be made to ensure compliance with all scheduled follow-up visits. However, a one week

visit window (plus/minus one week) will be allowed in the post treatment follow-up period.

Since the first scheduled post-treatment visit will occur at week 14, post-randomization, the investigator has the option of scheduling an interim visit (either phone or clinic visit) before week 14, if it is determined by the investigator that a visit is needed to assess the patient who has completed their treatment schedule prior to week 10 (end of treatment phase).

10.4.1 Phone Visit Assessments at Post-Treatment Week 14, 22, 30

The investigator or study coordinator will interview the patient to determine:

Adverse experiences
Concomitant medication use

If there have been any adverse experiences since last study visit, an Adverse Event Form must be completed.

Patients will be reminded to fill out and bring to next clinic visit, the one day voiding diary record.

An assessment of current birth control methods will be done. For women of child-bearing potential, if pregnancy is suspected, a repeat serum ß-HCG pregnancy test will be ordered. If a repeat pregnancy test is performed and the results are positive, the patient should be discontinued from the study and the clinical Center Stop Point or "STOP" CRF should be filled out.

10.4.2 Clinic Visit Assessments at Post Treatment Week 18, and 26

The Medication and Voiding Diaries are collected and reviewed by the study coordinator. The patient is asked to complete the following self-assessment forms:

Follow-up Symptoms
Rand SF-36 Questionnaire
IC Symptom and Problem Index
University of Wisconsin Symptom Survey
MOS Sexual Functioning Scale

When these forms are completed, the investigator or study coordinator will interview the patient and collect the following:

Adverse experiences
Concomitant medication use

If there have been any adverse experiences since last study visit, an Adverse Event Form must be completed.

A Voiding Diary is dispensed at this visit and instructions given to complete it during the 24 hours preceding the next study visit.

An assessment of current birth control methods will be completed. For women of child-bearing potential, if pregnancy is suspected, a repeat ß-HCG pregnancy test will be performed. If a repeat pregnancy test is performed and the results are positive, the patient should be discontinued from the study and the Clinical Center Stop Point or "STOP" CRF should be filled out.

10.4.3 Clinic Visit Response Assessment - Week 34 Final Post-Treatment Follow-up

The Medication Diary and Voiding Diary will be collected and reviewed by the study coordinator. The patient is asked to complete the following self-assessment forms:

Follow-up Symptoms
Rand SF-36
IC Symptom and Problem Index
University of Wisconsin Symptom Survey
MOS Sexual Functioning Scale

When these forms are completed, the investigator or study coordinator will interview the patient and collect the following:

Adverse experiences
Concomitant medication use

If there have been any adverse experiences since last study visit, an Adverse Event CRF must be completed.

The patient then will be prepared for the clinical procedures and the following repeat procedures performed:

Physical examination
Urinalysis
Urine culture
Urine specimen for biomarkers study
CBC with electronic differential, RBC's, platelets
Serum ß-HCG (women of child-bearing potential only) and an assessment of current birth control methods will be performed.
All patient information and laboratory reports will be reviewed by the Principal Investigator and the Study Coordinator within one week of the final post-treatment visit to determine patients response.

10.5 Reinstillation of BCG – Treatment Phase 2

Those patients determined to be **non-responders** at Week 34 (See Section 4.4.1)**,** will be offered a six treatment course of open-label BCG instillation (**Second Treatment Phase).** The study treatment visit schedule as maintained in Phase One will be continued throughout Phase Two. The Post-treatment follow-up visits in Phase Two will be phone visits. The final visit of Phase Two will be a clinic visit.

Those patients determined to be **responders** at Week 34 (See Section 4.4.1), **will not** be permitted to receive open-label BCG instillation therapies during this period.

10.6 End of Study

When a patient has ended participation in the trial, a Clinical Center Stop Point or "STOP" CRF should be completed documenting the date on which study participation ended and identifying the reason for end of study.

11 ADVERSE EVENTS AND PARTICIPANT WITHDRAWALS

The Investigator(s) will be required to provide appropriate information concerning any findings that suggest significant hazards, contraindications, adverse events, or precautions pertinent to the safety of the drug under investigation.

11.1 Types of Adverse Events

An adverse event is any unfavorable and unintended sign, symptom, or disease temporarily associated with the use of a medicinal product, whether or not considered related to the medicinal product (38)**.**
The term "adverse event" could include, but not be limited to, any of the following events, which develop or increase in severity during the course of the study:

- Any signs or symptoms whether thought to be related or unrelated to the condition under study;
- Any clinically significant laboratory abnormality;
- Any abnormality detected during physical examination.

These data will be recorded on the appropriate CRFs, regardless of whether they are thought to be associated with the study or the drug under investigation. (Associated with the use of the drug means that there is a reasonable possibility that the event may have been caused by the drug).

- Any event reported by the participant, other than those expected and described in the treatment brochure, will be immediately reported to the treating urologist.

- Signs and symptoms will be graded by the Research Coordinator as mild, moderate, or severe as referenced by Common Toxicity Criteria (CTC) Standard (39).
- Adverse events will be addressed at each participant visit and as reported by the participant, a detailed description of the adverse event will be recorded on the Adverse Event CRF. Adverse Event CRFs will be reviewed and summarized quarterly or on an as needed basis.

11.1.1 Serious Adverse Events

A serious adverse event (SAE) is any adverse event occurring during the course of a clinical investigation, whether or not determined to be related to exposure to the test article, that is fatal or life-threatening, is persistent or significantly disabling/incapacitating, requires in-patient hospitalization or prolongs hospitalization, or is a congenital anomaly. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered an SAE when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition (40).

11.2 Reporting Obligations

Serious adverse events, whether or not unexpected or considered to be associated with the study, must be communicated to (see list below) immediately upon discovery of the event either by telephone, or fax.

The Research Coordinator will evaluate the potential SAE in consultation with the corresponding clinical site Principal Investigator. The reporting of serious adverse events in this study will involve recording any and all SAEs on the Serious Adverse Event form. Within one working day the following people or groups need to be notified via phone call. In addition, a fax of the SAE form, and mailed hard copy of the SAE will be sent to the following:

- Clinical Site Principal Investigator
- Respective Clinical Site IRB office
- Data Coordinating Center

The DCC will keep records of all SAE reports and report them to the NIDDK and the External Advisory Committee, Organon Teknika, and all clinical site Principal Investigators. The NIDDK will notify the FDA. The details of the reporting of the serious adverse events will be provided in the Study Manual of Procedures. The Investigator must promptly inform the IRB or Ethics Committee of any serious, unexpected adverse event that is considered possibly related to the study. **Serious adverse experiences (deaths) need to be reported for a period of 30 days following cessation of study medication.**

11.3 Follow-Up of Adverse Events

All serious adverse events must be followed with appropriate medical management until resolved.

11.4 Unmasking (Unblinding) of Treatment

At the end of Baseline Visit 2, participants will be randomly assigned to one of the two treatment groups according to the randomization schedule generated by the DCC prior to study initiation. Neither the Principal Investigator nor the clinical site personnel (with the exception of the site pharmacist) will know the treatment group to which any participant is randomized. If there is a serious adverse event, which is thought by the clinical site staff to be possibly or probably related to the coded medication, the clinical site staff, when necessary for the safety of the participant, will unmask treatment group assignment upon conferring with the clinical site's Principal Investigator. In this event, the clinical site staff must promptly contact the DCC with an explanation of the need for unmasking the treatment group assignment. The Principal Investigator must also submit a detailed report to the DCC within three working days of the initial DCC contact. Unmasking of treatment assignment is anticipated to be an uncommon occurrence and is highly discouraged.

11.5 Management of Associated Adverse Events and Discontinuation of Treatment

The administration of the test product may be discontinued at the patient's request or by the investigator, based on clinical judgment. If the patient is withdrawn from the study and participation terminated, a Clinical Center Stop Point "STOP" CRF must be completed and all required assessments performed as indicated in Section 10.6.

Patients will be instructed to report any adverse event experienced after treatment without delay. In addition, the patients will be contacted by the study coordinator during each of the two days following each instillation. If a patient has a serious adverse event or toxicity which has been judged to possibly or probably be associated with BCG, the investigator should consult with the Infectious Diseases physician affiliated with the study site. Patients reporting febrile reactions may be managed according to the method of Lamm and co-workers (41).

If, during the course of the study, patients must be treated with antibiotics, the patients will be allowed to defer treatment until the course of the antibiotics has been completed, not to exceed ten days between treatments. If the course of antibiotic treatment cannot be completed in this timeframe, the patient should be discontinued from the study. If a patient experiences a fever greater than 38.5ºC (101.3ºF) for 12-24 hours, the investigator should consult with the Infectious Diseases consultant associated with the study site.

If it is felt that the febrile reaction is potentially associated with BCG, the blind will be broken for that patient and, if the patient was assigned to the BCG-treated group, a determination will be made as to whether antituberculosis therapy should be prescribed.

Acute, severe illnesses potentially associated with BCG-treatment should be aggressively treated with isoniazid (300 mg), rifampin (600 mg), and ethambutol (1,200 mg) daily for six months and further BCG treatments discontinued. Sepsis, the most severe complication, may be treated with isoniazid (300 mg), rifampin (600 mg), and ethambutol (1,200 mg), and cycloserine (500 mg) twice daily. At the discretion of the principal investigator, prednisone (40 mg) may be prescribed intravenously and acutely. For acute severe illness, consultation with an Infectious Disease Specialist is required.

11.6 Premature Termination

In the event that a patient terminates from the study prior to week 34 or week 68, every effort should be made to obtain follow-up efficacy and safety data which should include the following:

- Concomitant medications
- Physical examination
- Urinalysis
- Urine culture
- CBC with electronic differential, RBC's, Platelets
- Voiding diary collected
- Follow-up symptoms
- IC symptom and Problem Index
- RAND SF-36
- MOS Sexual Functioning Scale
- University of Wisconsin Symptom Survey
- Adverse experiences
- Serum ß-HCG (women of child-bearing potential only) and assessment of current birth control methods

The Clinical Center Stop Point or "STOP" CRF should also be filled out for these patients, indicating the reason for termination.

12 ADMINISTRATIVE SECTION

12.1 Institutional Review Board

It is the responsibility of the Principal Investigator to provide the appropriate Institutional Review Board (IRB) with all pertinent material, including a copy of the informed consent. Approval of the protocol and the informed consent form must be obtained and forwarded to the sponsor prior to screening or enrolling any subjects. The Investigator also maintains the responsibility of initiating protocol re-approval, notification of protocol and/or consent form changes, notification of adverse reactions, and termination of the study according to the appropriate IRB requirements. A suggested consent form is included in Appendix A.

12.2 Laboratory Accreditation

The Principal Investigator must maintain documentation of adequate licensure or accreditation for all clinical laboratory facilities used for study samples analysis. In addition, the clinical laboratory's normal values for test results must be forwarded to the DCC prior to study initiation. This documentation should cover the entire period the protocol is active.

12.3 Sponsor Monitoring/On-site Monitoring

The progress of the study will be carefully monitored by an experienced site-monitoring firm, for compliance with applicable government regulations and protocol. These individuals will have access to all records necessary to ensure integrity of the data and the regulatory documents at the clinical sites.

12.4 Compliance with Agencies

The sponsor will ensure this study is performed in compliance with applicable regulations associated with the Food and Drug Administration (FDA), the International Conference on Harmonization (ICH) (42)Guidelines and the Declaration of Helsinki. The sponsor will also keep a 1572 (Statement of Investigator), and current CVs of all Principal Investigators and Co-Investigators on file.

12.5 Record Retention

The DCC must maintain all study records for a period of time in accordance with their internal SOPs and applicable regulations. The study site must retain source records, including original Patient Consent Forms, until either the sponsor or DCC notifies them in writing.

12.6 Direct Access to Source Documents

Investigators will maintain, on-site, in an orderly fashion, and make available to the sponsor or the sponsor's representative, the following documents: the signed study protocol, amendments, informed consent documents, investigator brochure, approval letters from the IRB, drug accountability forms, CRFs, all primary source documentation, and all letters of correspondence.

12.7 Data Management and Analysis

The Data Coordinating Center (DCC) will coordinate all ICCTG activities pertaining to:

1. Design, development, production, testing and distribution of case report forms (CRFs) over the internet to the client workstations at each clinical center;
2. Collection, entry, verification, validation and query resolution of data; and
3. Quality assurance monitoring and reporting.

Data management issues, especially those concerning data quality and integrity in multicenter trials, as discussed extensively in Meinert (43) DeMets (44) Neaton (45) Bailey (46), and McFadden (47), will be addressed within the Manual of Procedures (MOP) and emphasized during the Research Coordinator (RC) training prior to protocol initiation.

The DCC will develop and maintain a computerized Data Management System (DMS) for this ICCTG Protocol, that will be deployed on client workstations within each of the Clinical Centers. Case report forms (CRFs) will be available to be printed locally at the clinical centers from Portable Data Files (PDF). Originals of these forms will be retained by the clinical sites. Double data entry will be performed at the Clinical Centers, utilizing the DMS tools available on the clients' workstations. In particular, for the Baseline Visit 2, there will be a manual back-up system for implementing randomization of participants, in the event the DMS system is not functional at the moment that a new randomization is required.

Validation checks will be performed at the centralized database to verify data accuracy and identify missing, unclear, illogical, or problematic responses. Queries will be generated to resolve discrepancies. Confidentiality will be strictly adhered to by assigning a unique participant identifier that will not identify the subject by name. The Manual of Procedures will define these processes in detail.

Details describing the transfer of urine specimens between the clinical sites and the ICCTG associated laboratories are presented in the Appendix E.

13 STATISTICAL CONSIDERATIONS

13.1 Study Design

The proposed study design is a two-arm, double-blind, randomized clinical trial (RCT) to evaluate the effect of intravesical BCG, compared to intravesical saline placebo on IC symptoms. The primary analysis on which sample size requirements are based is the comparison of response rates for the composite primary outcome as defined in Section 4.4.1. For this comparison, we desire adequate numbers of participants to detect a difference in response rates between 30% and 50% (difference of 20%).

The primary endpoint for which the comparative efficacy of BCG and saline will be evaluated is a composite endpoint with two components: a) the patient-reported global assessment of response and b) the use of specified breakthrough medications for IC symptoms during the last four weeks of the follow-up period. The global evaluation of improvement for the primary endpoint will occur at week 34 or withdrawal, whichever comes first, relative to IC symptoms at baseline, via the question:

> "As compared to when you started the study, how would you rate your Interstitial Cystitis (IC) symptoms now?"

A seven point scale, centered at zero, will be used, with categories as follows: -3) markedly worse; -2) moderately worse; -1) slightly worse; 0) no change; +1 slightly improved; +2) moderately improved; and +3) markedly improved. Participants who answer either +2) moderately improved or +3) markedly improved on the global evaluation are considered to have evidence of "clinical improvement", and will be classified as a "responder" for the global assessment portion of the primary endpoint.

The second component of the primary endpoint relates to changes (increase or addition) in the use of IC treatment medications from the level at which the patient was stabilized at the beginning of the study, and the use of "breakthrough" medications. Increased usage of pre-study IC medications, or the initiation of new IC medications, during the last four weeks of post-treatment follow-up (weeks 31 - 34 post-randomization), will cause the patient to be classified as a "non-responder." Use of *breakthrough* medications as described in Section 4.3.1 will be allowed during this time **with the exception of narcotic analgesics.**

Therefore, patients will be considered to be "responders" overall for the primary endpoint if they fulfill both of the following two criteria:

1. Report "moderate" or "marked" improvement on the patient-reported global assessment at 34 weeks.
2. Report no increase in pre-study IC medications, and no initiation of new IC medications, and no new or increased use of narcotic medications during the final 4 weeks (weeks 31-34) of the post-treatment follow-up phase.

The proportion of "responders" in each treatment arm will be compared in an intent-to-treat analysis to evaluate the overall effectiveness of BCG. Criteria #1 and #2 must both hold for a patient to be considered a responder at 34 weeks; all other patients will be considered "non-responders", and will be included in denominators for evaluation of response rates between treatment arms. Specifically, participants who withdraw from the study for any reason (e.g. adverse event or participant choice) prior to the primary endpoint determination at 34 weeks, will be considered treatment "non-responders."

13.2 Sample Size Calculations

The baseline response rate for the intravesical saline placebo of 30% is based on previous IC studies, and other studies suggesting that this is a typical placebo rate for symptom-related outcomes. Assuming 80% power to detect the specified difference between groups at a two-sided $\alpha = 0.05$ level of significance using the Fisher's exact test, a total of 260 participants (130 per arm) are required. This proposed sample size includes adjustments for clustering within clinical sites (20% increase), and interim monitoring (5% increase). Total required sample sizes for alternative response rate differences are shown in the table below.

Sample Size Calculations for 2-arm Study

Response Rate			Sample Size Per Arm		Total Sample Size
Placebo	Treatment	Δ	Before Adjustments	After Adjustments	
20%	40%	20%	91	115	230
25%	45%		98	124	248
30%	**50%**		**103**	**130**	**260**
35%	55%		106	134	268
20%	45%	25%	62	78	156
25%	50%		66	83	166
30%	55%		68	86	172
35%	60%		69	87	174
20%	50%	30%	44	56	112
25%	55%		47	59	118
30%	60%		48	60	120
35%	65%		48	61	122
20%	55%	35%	34	43	86
25%	60%		35	44	88
30%	65%		36	46	92
35%	70%		36	46	92

13.3 Randomization and Stratification

The nine treating Clinical Centers comprise the nine Clinical Sites. To ensure balance across treatment groups within each Clinical Site, a stratified randomization will be used. Within each of the nine strata, subjects will be randomly allocated in equal proportions to the two treatment arms using a permuted block randomization procedure with variable block sizes. In order to maintain blinding, each subject will be assigned a unique treatment identifier number. The treatment assignment code, corresponding to each treatment identifier number, will be known only to the University of Pennsylvania Medical Center Investigational Drug Service and the Data Coordinating Center Quality Assurance Director, until the completion of treatment and data collection on all participants.

13.4 Intent-to-Treat Analyses and Missing Data

An *intent-to-treat* analysis, in which all available data on all randomized participants are included, will be used for the primary comparison of treatments. All attempts will be made to keep missing data to a minimum, and participants who withdraw from treatment, will be encouraged to continue on study in order to provide complete follow-up information. However, it is expected that up to 15% of the randomized participants may withdraw prior to the final assessment of response at 34 weeks. These participants will be included in the denominator for evaluation of the response rate defined for the primary endpoint. The characteristics at the time of randomization for those participants without complete follow-up will be examined; however, there will be limited statistical power to detect any but major differences between these participants and those with complete follow-up. In addition, in order to assess the potential biases introduced by differential withdrawal among treatment arms, a comparison of withdrawal rates and time to withdrawal will be included as an ancillary analysis to the primary endpoint comparison.

13.5 Statistical Analyses

In addition to the analyses described subsequently, descriptive statistics will be used during the course of the project as part of data management procedures for monitoring data quality. A brief overview of some of the statistical methods that may be used at the time of analysis, both for descriptive purposes and in more comprehensive analysis of the primary research questions, is summarized in the following sections. It is recognized that these methods may be revised and additional ones considered as the details of the specific analyses are developed.

Descriptive Analyses

Standard descriptive statistics will be used to describe baseline characteristics and follow-up measures, both overall, and within each treatment group. Examination of baseline characteristics will include estimates of the distribution of age, race, and other demographic characteristics, baseline severity based upon pain/discomfort, urgency and frequency, and Clinical Site. These factors will be examined, both separately for each of

the nine Clinical Sites, and combined across centers. Summary statistics such as means, medians, and ranges will be produced for all measured variables. Frequencies will be computed for all categorical and ordinal variables. Graphical methods including stem-and-leaf diagrams and boxplots will be used to examine distributions, identify potential influential points, and guide in the choice of transformations if warranted. The balance of baseline measures across the two treatment groups will be compared using appropriate 2-sample tests, including Fisher's exact tests.

Analysis of Primary Outcome

The primary analysis comparing response rates will make use of the exact conditional test (ECT) version of Mantel-Haenszel methods to adjust for within-center clustering, as implemented within the Proc-StatXact software system (48). Secondary analyses of the primary endpoint will rely on logistic regression and generalized estimating equation (GEE) methods to evaluate whether observed differences, if any, are attributable to imbalances in prognostic factors such as baseline symptom severity (49). Standard regression diagnostics will be used to assess model adequacy and examine potential outlying or influential data points. In addition, time to response will be compared among groups using standard methods for failure-time data, including Kaplan-Meier curves, logrank tests, and Cox proportional hazards modeling (50).

Secondary Analyses

A number of secondary analyses will be conducted, both to evaluate the secondary symptom-related outcomes, and to supplement the primary endpoint comparison. Secondary outcomes include pain and urgency measured on the Likert scales, urinary frequency and volume measures obtained from the voiding diary, the IC Symptom and Problem Index, the University of Wisconsin Symptom Survey, the Health Status Questionnaire (MOS SF-36), and the MOS Sexual Functioning Scale. Other outcomes to be used in the final assessment include withdrawal rates.

Profiles of symptom changes over time as collected from the symptom questionnaires and voiding logs will be compared among treatment groups using methods for longitudinal data analysis (51). These methods will include random effects regression models for continuous outcomes and GEE methods for categorical and ordinal outcomes (51). Both within and between-participant variability in these outcomes will be carefully assessed to provide pilot data for future clinical trials. For measures obtained only at baseline and one follow-up time point, change from baseline will be compared among groups using analysis of variance (ANOVA) and regression methods. When applicable, additional analyses of the symptom outcomes will include evaluation of time to response defined by specific changes in symptoms (e.g. 50% drop in symptom score). Associations between longitudinal changes in secondary outcomes and the overall participant assessment of improvement will be used to supplement the primary endpoint analysis and evaluate the validity of the symptom scales for assessing change.

Changes in the distribution of "worst" symptoms from baseline to 34 weeks; as recorded on the symptom ranking cards, will be evaluated using a marginal homogeneity test (48).

Withdrawal rates will be compared among arms using standard methods for failure-time data as described above (50).

Biomarker Studies

Urine specimens for biomarker studies will be collected before the first treatment, before and after the 4th treatment, and at the 34 week time point. Markers to be evaluated are outlined in Section 7. The primary goal of these studies is to evaluate changes in marker levels over time and evaluate the associations between these changes and both treatment and overall patient responses. Due to the large number of markers being evaluated, in order to protect against an inflation in Type I error rates due to multiple comparisons, the sample size and power calculations below utilize an overall Type I error of α=0.01. It is recognized that these evaluations are primarily exploratory, and that measures that demonstrate promise as laboratory markers may require further evaluation in another clinical trial setting.

Analyses on which sample size estimates are based will consist of two primary types. The first type will involve paired comparisons of changes from baseline to 34 weeks, within subgroups defined by treatment arm and/or response to therapy (as defined by the primary endpoint). These analyses will utilize a paired t-test. The required sample sizes to detect changes of a given magnitude, in units of standard deviations of the change (s.d.), are given in the table below. The second set of analyses will compare these changes between subgroups defined by treatment arm and/or response to therapy using a two-sample t-test. The required sample sizes to detect differences in the changes, also in units of s.d., are also in the table. These calculations assume 80% power with a two-sided α=0.01.

Size of Difference (in units of s.d.)	Required Sample Sizes				
	Paired t-test to Compare Changes Within a Group	Two-Sample t-test to Compare Two Groups			
		1:1 Ratio of Group Sizes		1:2 Ratio of Group Sizes	
1.0	15	50	(25 + 25)	57	19 + 38
0.9	18	60	(30 + 30)	69	23 + 46
0.8	21	76	(38 + 38)	84	28 + 56
0.7	27	98	(49 + 49)	111	37 + 74
0.6	36	130	(65 + 65)	147	49 + 98
0.5	50	186	(93 + 93)	210	70 + 140
0.4	76	> 260		> 260	
0.3	130	> 260		> 260	
0.2	> 260	> 260		> 260	
0.1	> 260	> 260		> 260	

Since the response rate is unknown and may vary among treatment groups, it is not possible a priori to evaluate the exact number of patients that will be available in each subgroup. However, the table above may provide guidance on approximate required sample sizes. For example, for the paired t-test, within each treatment group of 65 patients, we will have adequate power to detect changes of less than half of a standard deviation between groups. If the overall response rate is 50%, we would have adequate power to detect a change of approximately 0.65 s.d. among responders on a particular treatment arm or 0.8 s.d. if the response rate is 30%.

The calculations above for the two-sample t-test consider both a 1:1 and 1:2 ratio in group sizes to allow evaluation of sample sizes for comparisons among groups defined by treatment and response. To compare two treatments (n=65 per arm) we would have adequate power to detect a 0.6 s.d. difference in the change. If groups are to be further subdivided by response, assuming a 50% response rate, we would have adequate power to detect a 0.8 s.d. difference in the changes between responders and non-responders within a treatment group (approximately 34 per group). For a response rate of 33%, a total of 57 patients (19 responders and 38 non-responders) would be required to detect a 1.0 s.d. difference in the changes.

The table below provides data on these changes in terms of the actual units for measures of HBEGF, IL-6, APF, and hyperdiploid fraction (HDF) from DNA cytometry. The values shown are based on pilot data provided by ICCTG investigators conducting marker studies comparing IC patients to controls. It should be noted that these data do not include estimates of changes over time under treatment and are only given to provide guidance on the size of differences that may be detectable given the sample sizes available in the current protocol. Similar calculations will be performed as pilot data on alternative markers become available.

Marker	Difference between IC Patients and Controls	s.d. in IC patients	Detectable difference	
			n = 65/group (0.88 s.d.)	n = 32/group (0.60 s.d.)
HBEGF (ng/mg creatinine)	16.0	5.0	4.4	3.0
IL-6 (pg/mg creatinine)	44.2	1.85	1.63	1.1
APF (%)	68.0	24.4	21.5	14.6
HDF	2.9	6.45	2.6	3.9

In addition to the two-sample tests above, changes in marker values over time will be compared with changes in symptom scores including the global assessment of response, pain/urgency scales, and scores on the symptom indices. Depending on the nature of the symptom outcome, various regression models including linear regression, logistic regression, and regression models for ordinal outcomes will be used to evaluate the associations between marker changes and symptom changes controlling for treatment and other relevant baseline measures. The statistical methods for these analyses are described in the previous section.

13.5.1 Data Safety and Monitoring and Interim Analyses

In addition to the final data analysis and standard monitoring for adverse events and data quality, one interim analysis will be conducted for the primary safety and efficacy data after approximately one half (n = 130) of the participants have been accrued and followed for 34 weeks. Given the projected accrual rates, it is expected that this will occur approximately fifteen months into the conduct of this study. The results of these analyses will be presented to the External Advisory Committee. The goal of this analysis is to identify major differences among treatment arms that might lead to early study closure for ethical reasons. The endpoints to be considered at the interim time point include the primary response endpoint, toxicity and adverse events, and withdrawal rates. For the primary endpoint, the Lan and DeMets (52) analog to an O'Brien-Fleming boundary (53) will be used to calculate the nominal significance level to which interim p-values are compared. Only an "upper" boundary, which allows for closure in the case of evidence of a treatment difference, will be used at this interim analysis. Assuming this analysis is conducted using 34-week data on 130 participants, corresponding to an information time of 50%, the boundary significance level to which the observed p-value will be compared is 0.0031. As described above, sample sizes have been adjusted to account for this interim monitoring.

13.5.2 Final Analysis

Details of the final analysis of the data will be provided in the Data Analysis and Monitoring Plan (DAMP).

13.6 Statistical Computing

The appropriate ASCII and SAS data files will be extracted from the Oracle database for use in statistical analysis. Primary analyses, including graphical methods, will be implemented using various commercially available statistical packages including SAS (54-61) and S-plus (62). The Proc-StatXact for SAS Users software (48) will be used to compute the exact tests of discrete measures between groups. All software is currently available through the networked computing environment within the DCC.

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APPENDICES

APPENDIX A: Consent Form

APPENDIX B: Visit Schedule Phase I and Phase II

APPENDIX C: Protocol for Administration of Study Agent

APPENDIX D: Syringe Masking Procedure

APPENDIX E: Urine Specimen Collection and Archive Protocol

APPENDIX F: Patient Instructions

- Pre-Treatment
- Post-Treatment
- Procedure for Urine Collection After the 4th Treatment Visit

APPENDIX G: Handling of BCG Vaccine

APPENDIX H: TICE®BCG Package Insert (United States)

Appendix A

P.I. Name and Department
Telephone Numbers(s)
Co-P.I. Name(s)
Day Telephone Number(s)
24-Hour Emergency Number
IRB # of protocol

SUGGESTED SUBJECT CONSENT FORM

A Randomized, Multicenter Clinical Trial to Evaluate the Efficacy of Intravesical Bacillus Calmette Guerin (BCG), for the Treatment of Interstitial Cystitis (IC)

Interstitial Cystitis Clinical Trials Group (ICCTG)
Randomized Clinical Trial #2 (RCT #2) Protocol

You are being asked to participate in a research study because you have been diagnosed with Interstitial Cystitis and have been informed that you may be eligible for the investigational study known as: "A Randomized, Multicenter Clinical Trial to Evaluate the Efficacy of Intravesical Bacillus Calmette Guerin (BCG), for the Treatment of Interstitial Cystitis (IC)."

The Interstitial Cystitis Clinical Trials Group (ICCTG) has been established by the National Institute of Diabetes, Digestive and Kidney Diseases (NIDDK) of the National Institutes of Health (NIH) to identify and study treatments for people with symptoms of IC. It is hoped that such a study will eventually lead to improvement in the treatment of IC.
Approximately 260 participants with clinically diagnosed interstitial cystitis will be involved in this study at the following clinical centers: University of Maryland, Baltimore, Maryland; New England Medical Center, Boston, Massachusetts; Henry Ford Hospital, Detroit, Michigan; University of Oklahoma, Oklahoma City, Oklahoma; University of Pennsylvania, Philadelphia, Pennsylvania; University of Rochester, Rochester, New York; and William Beaumont Hospital, Royal Oak, Michigan; Queen's University, Kingston, Ontario, Canada; and Stanford University, Stanford, California.

While you are participating in this study, you must agree not to begin any other therapy for your IC. You may not participate in this study if you are currently enrolled in another clinical trial research project.

Introduction

The purpose of clinical research is to look at the nature of disease and attempt to develop improved methods of diagnosis and treatment. You have the right to know about the procedures that will be performed during the study. This information is meant to inform you of potential risks/benefits so you can decide with confidence whether to participate in this study. Please read this information carefully and ask as many questions as you like before deciding whether you want to take part.

What is the purpose of this study?

You are being asked to participate in a research study because you have been diagnosed with interstitial cystitis (IC). The purpose of this study is to investigate the effectiveness of intravesical BCG in treating the symptoms of IC. Intravesical BCG has been approved by the U.S. Food and Drug Administration (FDA) in the treatment of patients with superficial bladder cancer, but not for patients with IC. Thus, the use of intravesical BCG is considered investigational for this study. If you choose to participate, your involvement in the study will last at least 8 months, but could be as long as 20 months.
The medical term "intravesical" means within the urinary bladder. This study consists of the administration of a medical substance into your bladder that may have some therapeutic effect on your disease. This substance may also cause unwanted side effects.

What is BCG?

BCG is a live but weakened form of cow tuberculosis bacteria that has been used in millions of patients world wide as a vaccine intended to prevent tuberculosis. It is also used medically to successfully treat patients who have bladder cancer in which its exact mechanism of action is unknown. In the past few years, approximately one hundred patients have participated in clinical trials to study the effects of BCG in the treatment of interstitial cystitis.

Initial Evaluation

If you decide you are interested in participating in this study, you will begin with two screening periods. After each screening assessment, the study doctor will determine if you are eligible to be in the study. You will complete several questionnaires about your medical history, general health, sexual functioning, and interstitial cystitis symptoms. If the study doctor decides that you remain eligible to be in the study, the following tests will be performed: a urine culture (a test for bladder infection), a urine analysis (examining a sample of urine to detect blood, infection and other processes), a blood test for pregnancy if you are a woman capable of bearing children, and a physical examination. You will have blood drawn from your vein (approximately two teaspoonsful) for routine laboratory tests.

The study doctor will discuss with you your use of birth control, if you are capable of bearing children. In order to participate in the study, you must agree to use a medically approved method of birth control during your participation in this study and for one month afterward.

You will keep a - ONE DAY voiding (when you pass urine) diary for each of six study visits. These diaries will be kept for your screening visits, and then at visit week 18, visit week 26, and visit week 34. In this diary, you will record the time you urinate, the volume (amount), whether you awoke during your routine sleeping cycle, the time you awoke and the time you went to sleep, and the degree of discomfort you experience during the day.

Before each of your six intravesical treatments are given, a catheterized urine specimen will be obtained from you. This urine specimen will immediately be analyzed before your intravesical treatment is given. A regularly voided (clean catch) urine specimen will be collected from you at the week 34 final visit.

With your permission, a portion of the urine from the urine specimens obtained at treatment visit week one, treatment visit week four, and final visit week 34, will be shipped to laboratories associated with the ICCTG to be banked for a biologic study (referred to as a urine biomarkers study). This urine biomarkers study looks at how BCG may affect certain elements in the urine which may be of help in diagnosing and treating IC. After your 4th treatment visit, you will be asked to collect one of the urine samples at home. You will receive special instructions on the collection of this 4th treatment visit specimen. A total of four (4) urine specimens will be collected for the urine biomarkers study.

Treatments You Will Receive

If you are eligible for this study, you will be assigned by chance (like flipping a coin) to one of two treatment groups. One group will receive BCG mixed with sterile, dilute salt water placed in their bladders one time a week for six treatments. The other group will receive the same volume of a placebo (does not contain active medicine) placed in the bladder one time a week for six treatments. In this study the placebo is sterile, dilute salt water without BCG. Neither the study doctor, the study staff, or you will be able to tell which treatment is being given. However, this information is available in case of an emergency. You will go to your study doctor's clinical site for each treatment. A total of six treatments will be given on a weekly basis. Your temperature will be taken before the study medication is placed in your bladder.

A lubricated catheter will be passed through your urethra and into your bladder. Approximately 4 tablespoons of the study medication will be placed into your bladder through the catheter. This procedure is called instillation. The catheter will be removed. You will be required to remain at the clinical site for up to 2 hours, and during this time, you should try to hold the medication in your bladder. After two hours, you will be asked to urinate.

Special Precautions You Will Be Asked to Follow

The BCG treatment contains weakened, but possibly infectious bacteria. Although there has never been a documented case of transmission of BCG infection between humans, certain precautions should be taken for you and your household's protection. For the first one to two voids at home, AFTER a treatment, you will pour 1 cup of household bleach (such as Clorox®), or hydrogen peroxide into the toilet each time you urinate. Let the mixture stay in the toilet for 15-20 minutes before flushing. You should wash your hands and genital areas thoroughly after you urinate. Additionally, you should sit down while urinating to avoid splashing. You will be given post-treatment discharge instructions to follow at home.

To prevent the potential transmission of BCG infection to your partner, you are asked NOT to have sexual intercourse for at least 48 hours after each instillation treatment. Male patients will be asked to use a condom if they have sexual intercourse during this time of treatment.

In some patients the treatments may temporarily cause an increase in irritation to the urinary tract, which can make the instillation of BCG very uncomfortable. Your study physician may treat this by prescribing medication such as Pyridium®, Urisid®, Levsin®, Ditropan®, or narcotic analgesics, which are all FDA approved medications. The risks from these drugs will be discussed with you by your study doctor at the time they are prescribed.

The study coordinator will contact you by telephone on each of the two days following each of your treatment to ask you questions about your health.

What Will Happen After You Finish Your Treatments?

On the first, third, and fifth month after your treatment visits, a phone call will be conducted between you and the research coordinator. You will be asked questions about your health and any medications you are taking.

You will have three (3) return visits to the clinic after you finish your treatments. They occur once on the second, once on the fourth and once on the sixth month after your treatments to complete symptom questionnaires and to turn in your voiding diaries. You will start the voiding diaries one day prior to each of your clinic visits.

At the six month clinic visit (week 34), the following tests will be repeated: physical examination, urine culture, urine analysis, blood draws for routine laboratory tests, and pregnancy test (if you are a woman of childbearing capability), and a urine specimen collected for shipment to a biologic study laboratory. Additionally, the research coordinator will ask you questions about your health and any medications you are taking.

At the six month visit, if it is determined that you have not responded to the series of treatments you received, you will be offered a second series of six (6) intravesical

treatments with BCG which you may accept or refuse. No placebo will be used. These second series of treatments will occur on the same time schedule, as the first series of treatments and you will be followed for an additional six-month period of time.

At the six month visit, if it is determined that you have responded to the series of treatments you received, you will be asked for your permission to allow the study doctor to continue to follow your response for an additional 7.5 months. You will be asked to provide information to the study coordinator. This information will be obtained from three (3) telephone contacts with the study coordinator at the following time points: week 46, week 56, and week 68, and from forms that you will be asked to complete and mail to the study coordinator.

The forms you will be asked to fill out before the three (3) telephone contacts are the quality of life and IC symptom questionnaires, just like those that you filled out in the first part of the study. You will be asked to complete a 24-hour voiding diary before each of the three (3) telephone contacts. You will be asked to complete a four-week medication diary before the final telephone contact at week 68. At each telephone contact, the research coordinator will ask you to report on any serious adverse responses you may have experienced.

You will be asked to mail the completed questionnaires and all diaries to the study coordinator. There will be no charge to you for study forms, materials, phone contact, or postal fees.

No study treatments, no laboratory tests, no collection of specimens, and no medical examinations will be required in this part of the study.

Summary of Study Visits

	Procedures or Tests
Start of study	physical exam, medical history, urine culture, urine analysis, blood cell count, blood test for pregnancy, quality of life and life and symptom questionnaires and voiding diary.
Weekly treatment visits	administration of study medication,adverse events and concomitant medication questionnaires. Urine specimen for analysis (obtained by catheter). The first and fourth treatment week visit will require that part of the urine specimen be shipped to biologic study laboratories for biomarkers study.

Follow-up visits	quality of life and symptom questionnaires and voiding diary. The six month visit will include: a physical examination, blood cell count, blood pregnancy test, urine specimen (clean catch) for urine culture and urine analysis. Part of the urine specimen will be shipped to biologic study laboratories for biomarkers study.

The same Summary of Study Visits will be repeated for all non-responders who choose to undergo a second series of treatments.

What benefit will I receive from participating in this study?

You may or may not receive direct benefit from participating in this study. The purpose of this study is to determine the effectiveness of BCG in treating the symptoms of Interstitial Cystitis. Even though you may receive BCG, or a placebo, there is no assurance that you will receive any benefit from participating in this study. It is possible that your symptoms may even worsen while participating in this study. No representation can be made that your participation will be of certain benefit to you. Other patients who have Interstitial Cystitis may benefit from the knowledge gained from this research study.

What are the risks of participating in this study?

The drawing of blood from your arm may have side effects including faintness, inflammation of the vein, pain, bruising or bleeding at the needle-stick site. There is also a slight possibility of infection.

The risks of inserting a catheter into the bladder include discomfort on insertion, episodes of burning on urination after the catheter is removed, blood in the urine, and a small risk of urinary tract infection.

Most patients will experience burning on urination or frequency or urgency of urination after treatment with BCG, that usually resolves by the next day, but may last for several days following a treatment. If needed, medications such as Pyridium®, Urisid®, Levsin®, or narcotic analgesics will be prescribed to help manage these symptoms. Visible blood in the urine has been reported in about a quarter of the patients who receive BCG and almost always resolves on its own.

You may experience a slight fever and mild to moderate flu-like symptoms, such as chills or sweating, muscle aches and/or fatigue. These symptoms may last for several days after your treatments and are usually responsive to treatment with acetominophen (Tylenol) or related aspirin-like agents. Flu-like symptoms such as these, have been reported by about one-third of the patients who received intravesical BCG treatments.

Additional side effects reported in a minority of patients receiving BCG include, but are not limited to: joint pain, coughing, skin rash, nausea, vomiting, abdominal cramps, incontinence, and loss of appetite. Joint pain or swelling or rash could be evidence of an allergic reaction to the BCG organism that may require stopping further BCG treatments.

If you are male, you have a slight risk of inflammation or infection of the prostate, epididymis (the tube that carries sperm during ejaculation) and the testicles. This inflammation or infection may be painful and require additional treatment with antibiotics active against the BCG organism.

The risks of serious BCG complications is low (less than 5% in bladder cancer patients who have received intravesical BCG treatments), however,there have been rare reports of life-threatening illnesses which have led to death. These serious BCG complications include: hepatitis (inflammation of the liver), tuberculosis pneumonitis (tuberculosis infection of the lungs), contracture of the bladder (scarring of the bladder muscle which could in rare cases necessitate surgical removal of the bladder), blockage of the ureter (the tube that carries urine from the kidney to the bladder), tuberculosis infection of the kidneys, and sepsis (tuberculosis infection of the bloodstream). If such risks occur, you will require hospitalization and may require treatment for up to 3 to 6 months with antibiotics active against the BCG organism. Over the past 15 years, there have been 10 reported cases worldwide of BCG-related deaths in patients who received intravesical BCG treatments for bladder cancer.

In order to help your doctor monitor your individual response to the study treatments, it is required that you record your bedtime temperature for two nights after each treatment. If your temperature is more than 101.3 Farenheit (38.5º Centigrade) for longer than 12 to 24 hours, or if you have flu-like symptoms lasting more than 48 hours after your treatment, or if you experience severe episodes of muscle or joint aches, fatigue, or bloody urine, you are to contact your study doctor **immediately**. Telephone numbers have been provided at the beginning of this consent form for contacting the doctor during and after usual business hours.

Not all possible hazards or effects are known and, therefore, the exact dose of study medication to be used and its effect on IC cannot be predicted. However, BCG has been carefully tested and studied in animals and humans and these studies indicate BCG may be of use in treating IC. To date, there have been no reported serious adverse events from BCG intravesical instillation treatments given to patients with IC.

Unforseen Risks

Since the study medication is investigational when taken alone or in combination with other medications, there may be other risks that are unknown. You should not take part in any other investigational study or take any other investigational medications during your participation in this study. This is to protect you from possible injury arising from extra tests, procedures, interactions of research drugs or similar hazards. All drugs have a potential risk of an allergic reaction, which if not treated promptly, could become life threatening.

Pregnancy/Birth Control

Administration of BCG may have adverse effects on a fetus, embryo or nursing infant. It is important that BCG is not taken during pregnancy or by nursing females. If you are female and of childbearing potential, you should be certain that you are not pregnant, and practice medically approved birth control methods throughout the study, until the six-month visit. For all women who are of childbearing potential, a blood test for pregnancy must be negative prior to entering the study and at the six month post-treatment follow-up period. A repeat blood pregnancy test will be done as required by your study doctor if pregnancy is suspected during your participation in the study. You should notify the study doctor as soon as possible if you suspect you are pregnant any time during the study. If you become pregnant during the study, you will not receive any remaining BCG instillations. If you decide to carry the pregnancy to term, the pregnancy should be monitored according to standard medical practice by your healthcare doctor. If you withdraw before the six month visit you will be asked to come in for a final assessment. Nursing mothers may not participate in this study.

Medically approved methods of birth control are: the consistent use of an oral contraceptive (birth control pill), a intrauterine device (IUD), hormone implants (Norplant ®), contraceptive injection (Depo-Provera®), and double barrier methods (diaphragm with spermicidal gel or condoms with contraceptive foam). Oral contraceptives as well as hormone implants and injections are considered effective if used and started at least one (1) month before you begin the study, continuing throughout the study and for one (1) month after the study ends (six-month visit). If you are unsure whether the method of birth control you use is acceptable to use while participating in this study, you should ask your study physician before beginning the study.

Alternatives

You have been informed that you may choose not to participate in this study. If you decide not to participate, you will receive the usual standard of medical care for your interstitial cystitis.

Withdrawal From the Study

Your study physician or the study sponsor may, at their discretion, remove you from this study without your consent, based on medical judgment regarding the safety or effectiveness of the treatment, or if you do not follow the study directions, or if you do not meet the study requirements or if the study is cancelled.

Your participation in this study is voluntary. You are free to withdraw from the study at any time without penalty, or without jeopardizing your medical care received from your doctor.

If you should withdraw voluntarily from the study, you will be asked questions about your experience with the study drug. You may also be asked to cooperate in having whatever tests and physical examinations the doctor considers necessary as follow-up assessments.

Confidentiality

Your records of this study will remain confidential, except as required by law. Your records of this study, and your medical records, may also be reviewed and copied by the Institutional Review Board (IRB) of (insert institutions name), representatives from the Study Sponsor, the National Institute of Diabetes, Digestive and Kidney Diseases (NIDDK) of the National Institutes of Health (NIH), as well as the Food and Drug Administration (FDA), to insure the accuracy of the research findings and your safety and welfare.

Your identity will remain confidential. Information from this study may be published without identifying individual patients.

New Findings

Any new important information which is discovered during the study, and which may influence your willingness to continue participation in the study, will be made available to you.

Costs

All procedures, examinations, and tests described above are specifically related to your participation in this study and are outside the standard of care for interstitial cystitis. As such, neither you nor your insurance carrier will be charged for the study medication, or

for these additional tests, procedures, examinations, office visits for the purpose of participating in this study. You will receive no money for your participation in this study.

Compensation

You voluntarily agree to participate in this study with an understanding of the possible effects or hazards that might occur in the course of this study as described in this consent form, and with the understanding that not all ill effects from the use of the drug are known. You have been informed that, should inadvertent injury or damage result from your participation in this investigational study, there are no designated funds provided for subsequent medical care or compensation from either your study doctor or (insert name of institution).

Contact Person

If at any time you have questions, concerns or comments about this study or suffer a research related injury, you should contact:

Principal Investigator_____ Telephone Number (Day Time)_____
(After Hours)_____

Subject Rights

If you wish further information regarding your rights as a research participant, you may contact your study doctors Institutional Review Board (IRB) (insert Institutions name and address) at Telephone Number_____

Permission for Banking of Urine for Biomarkers Study

Urine specimens obtained from you will be banked at laboratories associated with the ICCTG for a biologic study of urine biomarkers. These specimens will be banked indefinitely and are accessible only to Dr.(name of Investigator) and his/her collaborators for the purpose of comparing various urine components between IC patients treated with BCG and untreated IC patients and controls. Urine specimens you provide will have all personal identifiers removed. You may, at anytime, withdraw your urine specimens from banking by contacting Dr (name of Investigator) at (telephone number).

You do not have to provide urine specimens for banking and use in biomarkers study in order to participate in this study. You may choose to provide or choose not to provide urine specimens for banking and biomarkers study.

If you agree to provide urine specimens for banking at a laboratory for use in urine biomarkers study please indicate here with your signature and date:

Patient's Signature Authorizing Banking of Urine Specimens For use in Urine Biomarkers Study **Date**

Statement of Voluntary Participation

I have read the above information, have asked questions and have received answers about this study to my satisfaction. I understand what I have read and willingly give my consent to participate in this study: "A Randomized, Multicenter Clinical Trial to Evaluate the Efficacy of Intravesical Bacillus Calmette Guerin (BCG) for the Treatment of Interstitial Cystitis (IC)."

I will receive a signed copy of this consent form and will be informed of any new findings regarding this study which may influence my willingness to participate. I authorize the release of my medical records to the sponsor, agents of the sponsor, the NIH, NIDDK, the FDA, and the Institutional Review Board of (Institutions Name).

By signing this consent form, I have not given up any of the legal rights which I otherwise would have as a participant in a research study.

Patient's Name (Printed) **Patient's Signature** **Date**

If Patient Unable to Sign (Legally authorized representative signature) **(Relationship to Patient and Date)**

Witness Signature –Completed **Only** if patient or their legal representative is unable to read this consent form and an impartial witness present for the discussion **Date**

INVESTIGATOR/AUTHORIZED CONSENT PROVIDER'S STATEMENT

I have explained the meaning of the above consent form as well as offered an opportunity for any further discussion of the study with me. I will inform the participant in a timely manner of any changes in procedure, risks or benefits, or other information which may affect his/her willingness to continue participation in this study.

Name (please print) of Person Obtaining Consent

Signature of Person Obtaining the Consent **Date**

Name of Principal Investigator (please print) **Signature of Principal Investigator** **Date**

Interstitial Cystitis Clinical Trials Group

ICCTG Protocol #2 – Visit Schedule (Weeks)
Phase I – Randomized, Double-Blind Study

APPENDIX B

Event	Screening Visits		Treatment Phase 6 Treatments in 10 Weeks						Post-Treatment Follow-up Phase 24 Weeks (6 Months)						
	B1	B2	RX 1	RX 2	RX 3	RX 4	RX 5	RX 6	Phone Visit (optional)	Phone Visit	Clinic Visit	Phone Visit	Clinic Visit	Phone Visit	Clinic Visit
Week	-4	-1	1*	*	*	*	*	*	10, 11, or 12	14	18	22	26	30	34
Visit Number	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**
Consent Form	X														
Clinic Visit	X	X	X	X	X	X	X	X			X		X		X
Treatment Follow-Up Phone Call									☎	☎		☎		☎	
Day 1 Follow-up (PHNTP)			☎	☎	☎	☎	☎	☎							
Day 2 Follow-up (PHNTP)			☎	☎	☎	☎	☎	☎							
Patient Contact Information (PTCONT)	X														
Medical History (MED)	X														
Voiding Diary (VOID)		X[3]									X[3]		X[3]		X[3]
Demographics (DEMO)	X														
Eligibility Confirmation (ELIG)	X	X													
Randomization (RAND)		X													
Patient's Daily Medication Diary (PTDIARY)	X[3]	X[3]	X[3]	X[3]	X[3]	X[3]	X[3]	X[3]			X[3]				X[3]
Medication Diary Record (CMED)		X	X	X	X	X	X	X			X				X
Instillation/Dosing Information (DOSE)			X	X	X	X	X	X							
Adverse Event/Serious Adverse Event (AE)			X	X	X	X	X	X	X	X	X	X	X	X	X
Contraceptive Use (DOSE and STVISIT)			X	X	X	X	X	X	X	X	X	X	X	X	X
Unmasking Record (UNMASK)[4]															
Treatment Stop Point I (TSTOPI)[4]								X							
Study Stop Point I (SSTOPI)[4]															X
Patient Transfer (TRANS)[4]															
Study Close-out (STCL)[4]															X
Patient Close-out (PTCL)[4]															X
SYMPTOM QUESTIONNAIRES:															
Baseline Symptoms (BSYM1&2)	X	X													
Follow-up Symptoms (FUSYM)								X			X		X		X
IC Symptom & Problem Index (SYMPROB)		X						X			X		X		X
Health Status Questionnaire (SF36)		X						X			X		X		X
MOS Sexual Functioning Scale (MOS)		X						X			X		X		X

* The six treatments are to be given within a ten-week period. The first instillation must occur as soon as possible after randomization, but no later than two weeks after randomization. No instillations will be given after Week 10. No more than three weeks and no less than six days may elapse between instillations. 2=At baseline and PRN. 3=Diaries to be handed out at B1 are collected at B2. Diaries collected at subsequent clinic visits will be given to the patient at the previous clinic visit. 4=When indicated. 5=Urine biomarker samples will be collected during catheterization on treatment visits 1 and 4 just before treatment. Voided samples will be collected 6 hours after the fourth treatment and at the 6-month post-treatment visit.

Interstitial Cystitis Clinical Trials Group

ICCTG Protocol #2 – Visit Schedule (Weeks)
Phase I – Randomized, Double-Blind Study

APPENDIX B

Event	Screening Visits		Treatment Phase 6 Treatments in 10 Weeks						Post-Treatment Follow-up Phase 24 Weeks (6 Months)						
	B1	B2	RX 1	RX 2	RX 3	RX 4	RX 5	RX 6	Phone Visit (optional)	Phone Visit	Clinic Visit	Phone Visit	Clinic Visit	Phone Visit	Clinic Visit
Week	-4	-1	1*	*	*	*	*	*	10, 11, or 12	14	18	22	26	30	34
Visit Number	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**
U. of Wis. Symptom Survey (UNIVWIS)		X						X			X		X		X
LABS & PROCEDURES															
Urine Screening: Culture[2] (URINE)	X														X
Urine Screening: UA (DOSE/URINE)	X		X	X	X	X	X	X							X
Physical Exam (EXAM)		X													X
Serum ß-HCG Pregnancy Test[2] (LAB)	X														X
Pelvic/DRE (EXAM)		X													
Blood: CBC (LAB)[4]	X														X
Urine Sample Tracking (for Banking/Biomarkers) Urine Tracking (UTRAC)[5] Participant Urine Tracking (PUTRAC)[5]			X			X X									X
Temperature (PHNTP)			X	X	X	X	X	X							

* The six treatments are to be given within a ten-week period. The first instillation must occur as soon as possible after randomization, but no later than two weeks after randomization. No instillations will be given after Week 10. No more than three weeks and no less than six days may elapse between instillations. 2=At baseline and PRN. 3=Diaries to be handed out at B1 are collected at B2. Diaries collected at subsequent clinic visits will be given to the patient at the previous clinic visit. 4=When indicated. 5=Urine biomarker samples will be collected during catheterization on treatment visits 1 and 4 just before treatment. Voided samples will be collected 6 hours after the fourth treatment and at the 6-month post-treatment visit.

Interstitial Cystitis Clinical Trials Group

ICCTG Protocol #2 – Visit Schedule (Weeks)
Phase II – Open-Label Study

APPENDIX B

Event	Treatment Phase 6 Treatments in 10 Weeks						Post-Treatment Follow-up Phase 24 Weeks (6 Months)						
	RX 1	RX 2	RX 3	RX 4	RX 5	RX 6	Phone Visit (optional)	Phone Visit	Phone Visit	Phone Visit	Phone Visit	Phone Visit	Clinic Visit
Week	**35***	*	*	*	*	*	44, 45 or 46	48	52	56	60	64	68
Visit Number	16	17	18	19	20	21	22	23	24	25	26	27	28
Clinic Visit	X	X	X	X	X	X							X
Treatment Follow-Up Phone Call							☎	☎	☎	☎	☎	☎	
Day 1 Follow-up (PHNTP)	☎	☎	☎	☎	☎	☎							
Day 2 Follow-up (PHNTP)	☎	☎	☎	☎	☎	☎							
Voiding Diary (VOID)													X[3]
Patient's Daily Medication Diary (PTDIARY)	X[3]	X[3]	X[3]	X[3]	X[3]	X[3]			X[3]				
Concomitant Medication (CMED)	X	X	X	X	X	X			X				X
Instillation Dosing Information (DOSE)	X	X	X	X	X	X							
Adverse Event/Serious Adverse Event (AE)	X	X	X	X	X	X	X	X	X	X	X	X	X
Contraceptive Use (DOSE/STVISIT)	X	X	X	X	X	X	X	X	X	X	X	X	X
Unmasking Record (UNMASK)[4]													
Treatment Stop Point II (TSTOPII)[4]						X							
Study Stop Point II (SSTOPII)[4]													X
Patient Transfer (TRANS)[4]													
Study Close-out (STCL)[4]													X
SYMPTOM QUESTIONNAIRES:													
Follow-up Symptoms (FUSYM)													X
IC Symptom & Problem Index (SYMPROB)													X
Health Status Questionnaire (SF36)													X
MOS Sexual Functioning Scale (MOS)													X
U. of Wis. Symptom Survey (UNIVWIS)													X
LABS & PROCEDURES													
Urine Screening: Culture (URINE)[4]													X
Urine Screening: UA (DOSE/URINE)	X	X	X	X	X	X							X
Physical Exam (EXAM)													X
Serum ß-HCG Pregnancy Test[2] (LAB)													X
Blood: CBC (LAB)[4]													X
Temperature (PHNTP)	X	X	X	X	X	X							

* The six treatments are to be given within a ten-week period. The first instillation must occur as soon as possible after randomization, but no later than two weeks after randomization. No instillations will be given after Week 10. No more than three weeks and no less than six days may elapse between instillations. 2=At baseline and PRN. 3=Diaries to be handed out at B1 are collected at B2. Diaries collected at subsequent clinic visits will be given to the patient at the previous clinic visit. 4=When indicated. 5=Urine biomarker samples will be collected during catheterization on treatment visits 1 and 4 just before treatment. Voided samples will be collected 6 hours after the fourth treatment and at the 6-month post-treatment visit.

Interstitial Cystitis Clinical Trials Group

ICCTG Protocol #2 – Visit Schedule (Weeks)

Phase II R – Responders Long-Term Response

Appendix B

Event	Post Treatment Follow Up Phase (7.5 Months)		
	Phone Visit (Clinic Optional)	Phone Visit (Clinic Optional)	Phone Visit (Clinic Optional)
Week	**46**	**56**	**68**
Visit Number	**22**	**25**	**28**
Voiding Diary (VOID) (24 hour)	X[1]	X[1]	X[1]
Patient's Daily Medication Diary (PTDIARY)			X[2]
Concomitant Medication (CMED)			X
Serious Adverse Event (SAE)	X	X	X
Study Stop Point II R (SSTOPIIR)			X[3]
Study Close-out (STCL)			X[3]
SYMPTOM QUESTIONNAIRES:			
Follow-up Symptoms (FUSYM)	X	X	X
IC Symptom & Problem Index (SYMPROB)	X	X	X
U. of Wis. Symptom Survey (UNIVWIS)	X	X	X

X[1] = Voiding Diaries handed out at week 34.

X[2] = Patient Daily Med Diary handed out at Week 34. Patient instructed to begin filling out at week 65.

X[3] = When indicated.

APPENDIX C

PROTOCOL FOR THE ADMINISTRATION OF BCG

I. Pre-Instillation

A. Initial Visit for First Instillation:

1. Upon presentation to office, the pharmacy is contacted to reconstitute and prepare solution.
2. Position patient in lithotomy and prepare skin and genitalia in a standard manner with antiseptic solution.
3. Prepare for catheterization (lubrication, etc.).
4. Perform urethral catheterization.
5. Dipstick urine for nitrites.
6. If nitrites are absent, proceed with instillation.
   (GO TO NEXT SECTION: **Instillation of Solution**).
7. If nitrites are present on dipstick analysis, perform microscopic examination of urine. If microscopic examination reveals bacteria, consider empiric antibiotic therapy for bacterial UTI. Perform urine culture and postpone instillation pending results of urine culture. In 24-48 hours, the urine culture results will be available. If the urine culture is negative, proceed with instillation. If the urine culture is positive, complete antibiotic therapy and proceed with instillation after UTI is appropriately treated.

B. Subsequent Visits for Repeat Instillations:

1. Query patient regarding adverse effects including gross hematuria, etc.
2. Record patient temperature.
3. In the absence of adverse effects, proceed as per section I.A.1.
4. If adverse effects from prior therapy are ongoing, obtain voided urine specimen, assess adverse effects and manage adverse effects appropriately as per protocol and, when appropriate, at the discretion of the Principal Investigator at the site.

II. Instillation of Solution

1. The solution is reconstituted and prepared in the pharmacy, placed in a standard blinded syringe, bagged appropriately and maintained at room temperature.
2. Upon transport to the clinic, the syringe is removed from pharmacy bag.
3. The syringe is attached to the previously placed indwelling urethral catheter.
4. The solution is instilled slowly over 1-2 minutes. The time of day that the instillation is performed is recorded.
5. If the syringe is completely (successfully) emptied into the bladder, the syringe, catheter and catheterization kit with gloves and other materials are removed together as one unit.

   If the syringe cannot be completely emptied into the bladder (due to pain, severe urgency, etc., upon instillation) then the catheter and attached syringe are removed as one unit. In order to maintain strict blinding conditions, a third party (i.e. uninvolved in the study) will empty the

APPENDIX C

PROTOCOL FOR THE ADMINISTRATION OF BCG (cont'd.)

remaining solution within the syringe into a measuring container. This volume is recorded as per study protocol. The container, solution, and other materials are then disposed of as per section II.6.

6: The instillation materials are disposed of in a Biohazard container or by alternative suitable measures as determined by local/hospital regulations.

7: The subjects genitalia are washed with antiseptic solution.

8: The subject is repositioned in a comfortable manner as to maximize retention of solution. The subject may be provided with diversionary activities during dwell time while in the clinic. Antispasmodics and other agents may be administered as per protocol to maximize the subjects comfort and dwell time up to 2 hours.

III Post-Instillation

1. The solution is held intravesically for 2 hours. If the solution is unable to be held for 2 hours, the subject is allowed to void and the total dwell time is recorded as per study protocol.
2. The subject is instructed to void completely into a receptacle (toilet or "hat"). One cup (8 oz.) of bleach or equivalent is spilled into the receptacle after voiding is completed. In the absence of a "hat", the bathroom (toilet area in the clinic) is functionally closed for 15 minutes. After 15 minutes, the mixture is either flushed down the toilet or the "hat" is disposed of appropriately.

   If the subject is unable to void at two hours from instillation, a repeat urethral catheterization is performed to empty the bladder.

3. The subject is given standardized instructions regarding the instillation and arrangements are finalized for the next clinic visit and follow-up phone call for the next day.

APPENDIX D

SYRINGE MASKING PROCEDURE

The study medication will be masked and maintained in a sterile environment until instillation. Briefly, the pharmacist will prepare the study medication appropriate for the study subject using the usual precautions and methodology approved by that institution. The final BCG suspension or saline placebo will be delivered for instillation in a masked 60 cc Luer-lock tip syringe as follows: The site pharmacist will be provided with two-part tear-off labels which will be used to affix to the syringe and to append to the CRF. The pharmacist will complete the labels appropriately after he/she has prepared the test solution instillation. The larger completed label will be affixed to the syringe before providing to the investigator or study coordinator. The smaller completed label will be appended to the appropriate CRF. The syringe mask (see draft example) will be labeled to indicate the intended recipient (by Study Number), the name or initials of the preparer, as well as the date and time of preparation. The study medications will not be instilled if more than two hours have elapsed since the time of preparation. With the sterile Luer tip cover remaining on the syringe, the backing of the mask will be peeled away and the mask pressed around the barrel of the syringe with the projections extending beyond the Luer end. The projections will then be pressed to mask the beveled portion of the syringe up to the base of the Luer-lock fitting. The sterile Luer tip cover will be removed and maintained in a sterile condition while the study medication is drawn into the syringe through an appropriate sterile needle. The needle will be removed for disposal using appropriate precautions. The sterile Luer-lock tip cover will be replaced on the syringe for transport. The syringe will be delivered with an opaque Luer-to-Catheter tip adaptor (catalog #2219: Addto, Inc., 816 North Kostner Avenue, Chicago, Illinois 60851). The instilling physician will remove the Luer-lock tip cover and immediately affix the adaptor. The adapter will be inserted into the instillation catheter and the instillation will proceed in the usual fashion.

APPENDIX E

Urine Specimen Collection and Archive Protocol

1. Urine will be collected into a sterile urine cup at 4 time points during RCT #2 (before administration of the first treatment, before and 6 hours after the 4th treatment, and at the 34 week post-treatment time point). The first two specimens will be collected by bladder catheterization; the last two will be collected by the clean catch method. Specimens should be labeled with the patient's identifier number and date of collection.

2. The 1st pre-treatment, 4th pre-treatment and 34 week specimens will be collected at the study sites and processed as soon as possible after collection. Urine will be centrifuged at 1000g for 10 minutes in 50 ml conical polypropylene tubes (VWR #21008-242) and the supernatant aspirated.

Fifteen (15) ml of urine supernatant will be immediately put into a sterile cup containing a stabilizing agent for the chemokine/cytokine assays. Urine is then put into a 15 ml sterile polypropylene centrifuge tube (21008-216) and a protease inhibitor tablet is then added to the tube.

Fifteen (15) ml of untreated urine supernatant will be put into a 15ml sterile polypropylene centrifuge tube (21008-216) and saved for other assays.

Urine in both of these tubes will then be aliquotted into 2ml polypropylene tubes (Continental Lab Products, San Diego, CA #3472). Each 2 ml tube will be labeled with patient's identifier number, date of collection, and whether stabilizer is present. Tubes will be frozen at –70C. Remaining urine will be discarded.

Urine cell pellets from the centrifuged urine will be re-suspended in 0.5 to 1ml of PBS. While vortexing at low speed, 2 volumes of 95% ethanol will be added to the cells, and the cell suspension then divided into two 2 ml tubes (250 µl in one tube, 1.25 – 2.75 ml (remaining) in the other tube, and stored at –20C.

Once per month all accumulated specimens collected during these time points will be sent on dry ice by overnight mail to the following ICCTG urine banking laboratories (See Manual of Procedures for shipping addresses). One half of the aliquotted treated and untreated specimens will be sent to the University of Pennsylvania, Philadelphia, PA; one half of the aliquotted treated specimens will be sent to University of Iowa , Iowa City, Iowa. The other one half of the aliquotted untreated specimens and the small cell pellet specimens will be sent to the University of Maryland. All large cell pellet specimens will be sent to the University of Rochester, Rochester N.Y., on wet ice pack.

3. A clean catch urine specimen will be collected by the patient at home, 6 hours after the 4th treatment. For the 4th post-treatment specimen collection, the patient will be given a cup in which to collect the specimen, a specimen tube containing a stabilizing agent, and instructions for specimen collection. (See Appendix F Patient Instructions). The patient will then return the urine specimen to the clinical site. The clinical site will process the specimen, (See Manual of Procedures for Specimen Processing Procedure) and ship it to the University of Iowa on dry ice.

4. The necessary tubes and other supplies for urine collection, processing and shipping will be provided to each clinical center.

APPENDIX F

PATIENT PRE-TREATMENT INSTRUCTIONS

Now that you are about to begin your treatment, we would ask you to:

1. Not drink anything for **four** hours prior to treatment.

2. Bring something to occupy yourself such as books, tapes, etc. Some people like to bring their own special pillow for comfort.

3. You may bring another person along to keep you company after your treatment.

4. At each visit you will be asked if you have changed any of your medications, or had any illness or side effects since your last treatment. Please have this information with you.

5. Please bring the "Post-Treatment Discharge Instructions" you received at your prior treatment visit with you to your next treatment visit.

If you have any questions or concerns, please feel free to contact us at _____

APPENDIX F

PATIENT POST-TREATMENT DISCHARGE INSTRUCTIONS

PATIENT IDENTIFICATION (SUBJECT # AND INITIALS):_____

VISIT #:_____

SITE #:_____

DATE OF VISIT:_____

1. Resume normal activity according to how you are feeling.
2. During the six hours after treatment, pour 1 cup of bleach (such as Clorox®) into the toilet each time you urinate and let the mixture stand in the toilet 15-20 minutes before flushing. You must sit down while urinating to avoid splashing.
3. Wash your hands and genital area thoroughly after you urinate.
4. Drink plenty of fluids.
5. Take and record your temperature (by mouth) once at bedtime on the night of your treatment and again the following night. Record your temperature on page two of these instructions.
6. You will be called by phone on each of the two days after your treatment. You will be asked to report your temperature and answer questions about your health.
7. Contact your study doctor (phone number) **immediately** if you experience a high fever (101.3ºF) or flu-like symptoms that lasts longer than 2 days, or if you feel generally unwell after 2 days.
8. Go to the nearest hospital emergency room if you experience:
    - Severe skin rash
    - High amounts of blood in your urine
    - Severe pain when passing urine
    - Contractions of your bladder muscle
    - If you cannot pass urine
    - For male patients. If your testicles become painful and swollen
9. Please bring this paper with you if you should need to visit a hospital near your home that is different from the study doctor's clinic.

Study Coordinator Signature:_____Date:_____

I have read and understand the above discharge instructions. I have no further questions regarding these instructions.

Patient Signature:_____Date:_____

NOTE: The site should keep the original copy and provide the patient with a copy of these instructions. These instructions will be used as the patient's source document.

APPENDIX F

PATIENT POST-TREATMENT DISCHARGE INSTRUCTIONS

PATIENT IDENTIFICATION (SUBJECT # AND INITIALS):_____

VISIT #:_____

SITE #:_____

DATE OF VISIT:_____

Day 1 following my treatment visit:

The time the study coordinator will call for my temperature reading, any new medication I am taking or have stopped taking, and any changes in my health:

DATE: _____

TIME: _____

Temperature as indicated on the oral thermometer:_____

DATE:_____

TIME:_____

Day 2 following my treatment visit:

The time the study coordinator will call for my temperature reading, any new medication I am taking or have stopped taking, and any changes in my health:

DATE: _____

TIME: _____

Temperature as indicated on the oral thermometer:_____ DATE_____
TIME_____

PLEASE REMEMBER TO BRING THE DISCHARGE INSTRUCTION SHEETS TO YOUR NEXT SCHEDULED VISIT.

Study Coordinator Signature:_____Date:_____

I have read and understand the above discharge instructions. I have no further questions regarding these instructions.

Patient Signature:_____Date:_____

NOTE: The site should keep the original copy and provide the patient with a copy of these instructions. These instructions will be used as the patient's source document.

APPENDIX F

PROCEDURE FOR URINE COLLECTION
AFTER THE 4TH BCG VISIT TREATMENT

PATIENT INSTRUCTIONS

You will be given the following material for collecting this urine sample:

- A small cup in which to collect the specimen
- A small specimen tube which contains a stabilizing agent (preservative)
- A packaged antiseptic wipe
- A plastic disposable eyedropper for transferring a sample of urine into the specimen tube
- A plastic zip-lock bag to contain the urine sample with a paper towel inside.

This urine sample is to be collected approximately 6 to 8 hours AFTER you receive your 4th BCG treatment.

Cleanse your genital area with the antiseptic wipe (female patients wipe the labial area, male patients wipe the head of the penis).

Void into the small cup. Once you void at least 30 cc of urine, use the plastic eyedropper to remove about 12 cc of urine from the small cup. Add the 12cc of urine to the urine specimen tube that contains the stabilizing agent.

Next, place the cap on the tube securely and invert gently several times.

The remainder of the urine can be discarded in the toilet.

Put the urine specimen tube into the zip-lock bag, and store it at refrigerator temperature either in the Styrofoam box provided or in a cooler. A cold pack or ice must be kept in the container with the specimen at all times.

It is important that you bring the specimen back to your study site as soon as possible (within two weeks). Do not freeze this urine specimen.
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Interstitial Cystitis Clinical Trials Group (ICCTG)

APPENDIX G

RCT #2

HANDLING OF BCG VACCINE

HEALTHCARE WORKER SAFETY

BCG is an active biological and care should be taken while handling and reconstituting. These instructions apply equally to all types of BCG.

PPD SKIN TESTING

PPD negative healthcare personnel who routinely handle BCG should keep a record of yearly PPD skin testing.

BCG ACCIDENT INSTRUCTIONS

Eye Splash: Flush affected eyes) with copious amounts of water for at least 15 minutes while holding the eyelids) open; then seek evaluation by a physician.

Skin Exposure/Self-Inoculation: In case of skin contact with the drug, exposure of open sores, or finger laceration, thoroughly wash affected area with soap and water and clean wound with alcohol.

In case of suspected, accidental self-inoculation, PPD skin testing is advised at the time of the accident and six weeks later in order to detect skin test conversion. Asymptomatic skin test conversion is equivalent to BCG vaccination and does not require anti-tuberculous medication.

Skin test conversion should, however, be evaluated by a physician.

NOTE: If finger stick or laceration should develop granulomatous lesion of the skin, treatment may be given with isoniazid (300 mg/day) and continued for two weeks after wound has healed.

BCG SPILLS

The following recommendations should be followed for proper clean-up of BCG spills. Use a germicide that passes the A.O.A.C. Tuberculocidal Activity Test (e.g., Sporicidin or household bleach).

Place several layers of disposable towels over spills. Soak towel with germicide solution and allow soaked toweling to sit for at least 10 minutes. Carefully gather all waste materials into a biohazard bag, autoclave or expose to sterilizing conditions, and dispose of properly.

NOTE: Report all accidents during the handling of BCC to supervisory personnel.

DISPOSAL AND HANDLING OF TICE© BCG RECONSTITUTING MATERIALS

After completing BCC preparation, wipe down the drug preparation field (safety cabinet) with 70% isopropyl alcohol solution or household bleach using a disposable towel.

Contaminated needles and syringes should be disposed of intact. Place in puncture-proof container. All used materials, including waste BCG drug, should be placed in labeled biohazard containers and disposed of in accordance with Federal and State requirements applicable to biohazardous materials.

NOTE: Expired BCC should never be used in the clinic. Unopened ampules should be disposed of in accordance with Federal and State requirements applicable to biohazardous materials.

DISPOSAL AND HANDLING OF INSTILLATION MATERIALS

All contaminated materials used in the BCG instillation including the catheter should be placed in biohazard disposable bags, autoclaved or exposed to sterilizing conditions, and disposed of properly.

Linens and gowns used during an instillation should be placed in isolation bags and handled by the laundry service in routine fashion.

Permanent fixtures, furniture, or other items in the treatment room and bathroom should be scrubbed down with disinfectant in the routine fashion of the urology clinic.

See Package Insert for complete details.

For Product Information
800-842-3220

Provided as a service by
ORGANON, INC.

Manufactured by:
Organon Teknika Corporation
Durham, NC 27704

Distributed by:
Organon. Inc.
West Orange. NJ 07052

95-1101-BC 8 91

APPENDIX H

Pharma Group | **Confidential** | **07.533/C**

Organon Teknika N.V.
Turnhout Belgium

R&D
Pharmaceuticals.

8263.95.0262

ORGANON TEKNIKA

Identification

DMS nr	**8263.95.0262**	Doc.Type	SPECS	Proj.nr	
TekName		Alt.nr	**07.533/C**	Rev.nr	2
Title	**Package insert BCG LIVE USA**				
Part nrs					
Date created	990623	Supersedes	07.533/B	Dar/DCO	991059
Relevant DMRs					
Keyword(s)					

Author

Department	Name	Date	Signature
R&D Pharmaceuticals		.....	
		.....	

Approval

Function	Name	Date	Signature
RA Officer	S. Kruger-Peters	.....	
Marketing	P. Sloterdijk	.....	
		.....	
		.....	
		.....	
		.....	

To be returned to : E. Catsburg (C117) , before final approval.

Final authorization

Department	Name	Date	Signature
Development Pharmaceuticals	D. Zollinger	.....	

Mailing List

Shadow files y RA&L

DRAFT 10 4/20/99

BCG LIVE

TICE®BCG

WARNING

TICE®BCG contains live, attenuated mycobacteria. Because of the potential risk for transmission, it should be prepared, handled, and disposed of as a biohazard material (see **Precautions** and **Dosage administration**).

BCG infections have been reported in health care workers, primarily from exposures resulting from accidental needle sticks or skin lacerations during the preparation of BCG for administration. Nosocomial infections have been reported in patients receiving parenteral drugs that were prepared in areas in which BCG was reconstituted. BCG is capable of dissemination when administered by the intravesical route, and serious infections, including fatal infections, have been reported in patients receiving intravesical BCG (see **WARNINGS**, **PRECAUTIONS** and **ADVERSE REACTIONS**).

DESCRIPTION

TICE®BCG for intravesical use, is an attenuated, live culture preparation of the Bacillus of Calmette and Guerin (BCG) strain of *Mycobacterium bovis*.[1] The TICE® strain was developed at the University of Illinois from a strain originated at the Pasteur Institute.

The medium in which the BCG organism is grown for preparation of the freeze-dried cake is composed of the following ingredients: glycerin, asparagine, citric acid, potassium phosphate, magnesium sulfate, and iron ammonium citrate. The final preparation prior to freeze drying also contains lactose. The freeze-dried BCG preparation is delivered in glass vials, each containing 1 to 8 x 10^8 colony forming units (CFU) of TICE®BCG which is equivalent to approximately 50 mg wet weight. Determination of *in-vitro* potency is achieved through colony counts derived from a serial dilution assay. A single dose consists of 1 reconstituted vial (See Dosage and Administration).

For intravesical use the entire vial is reconstituted with sterile saline. TICE®BCG is viable upon reconstitution.

No preservatives have been added.

CLINICAL PHARMACOLOGY

TICE®BCG induces a granulomatous reaction at the local site of administration. Intravesical TICE®BCG has been used as a therapy for, and prophylaxis against, recurrent tumors in patients with carcinoma *in situ* (CIS) of the urinary bladder, and to prevent recurrence of Stage TaT1 papillary tumors of the bladder at high risk of recurrence. The precise mechanism of action is unknown.

CLINICAL STUDIES

To evaluate the efficacy of intravesical administration of TICE®BCG in the treatment of carcinoma *in situ,* patients were identified who had been treated with TICE®BCG under six different Investigational New Drug (IND) applications in which the most important shared aspect was the use of an induction plus maintenance schedule. Patients received TICE®BCG (50 mg; 1 - 8 x 10^8 CFU) intravesically, once weekly for at least 6 weeks and once monthly thereafter for up to 12 months. A longer maintenance was given in some cases. The study population consisted of 153 patients, 132 males, 19 females, and 2 unidentified as to gender. Thirty patients lacking baseline documentation of CIS and four patients lost to follow-up were not evaluable for treatment response. Therefore, 119 patients were available for efficacy evaluation. The mean age was 69 years (range: 38-97 years). There were two categories of clinical response: (1) Complete Histological Response (CR), defined as complete resolution of carcinoma *in situ* documented by cystoscopy and cytology, with or without biopsy; and (2) Complete Clinical Response Without Cytology (CRNC), defined as an apparent complete disappearance of tumor upon cystoscopy. The results of a 1987 analysis of the evaluable patients are shown in Table 1.

TABLE 1: THE RESPONSE OF PATIENTS WITH CIS BLADDER CANCER IN SIX IND STUDIES

	Entered	**Evaluable**	**CR**	**CRNC**	**Overall Response**
No. (%)Of Patients	153	119 (78%)	54 (46%)	36 (30%)	90 (76%)

A 1989 update of these data is presented in Table 2. The median duration of follow-up was 47 months.

TABLE 2: FOLLOWUP RESPONSE OF PATIENTS WITH CIS BLADDER CANCER IN SIX IND STUDIES

1989 STATUS OF 90 RESPONDERS (CR OR CRNC)

Response	1987/CR n = 54	1987/CRNC n = 36	1987 Response n = 90	Percent
CR	30	15	45	50
CRNC	0	0	0	0
Unrelated Deaths	6	6	12	13
Failure	18	15	33	37

There was no significant difference in response rates between patients with or without prior intravesical chemotherapy. The median duration of response, calculated from the Kaplan-Meier curve as median time to recurrence, is estimated at 4 years or greater. The incidence of cystectomy for 90 patients who achieved a complete response (CR or CRNC) was 11%. The median time to cystectomy in patients who achieved a complete response (CR or CRNC) exceeded 74 months.

The efficacy of intravesical TICE®BCG in preventing the recurrence of a TaT1 bladder cancer after complete transurethral resection of all papillary tumors was evaluated in two open-label randomized phase III clinical trials. Initial diagnosis of patients included in the studies was determined by cystoscopic biopsies. One was conducted by the Southwestern Oncology Group (SWOG) in patients at high risk of recurrence. High risk was defined as two occurrences of tumor within 56 weeks, any stage T1 tumor, or three or more tumors presenting simultaneously. The second study was conducted at the Nijmegen University Hospital; Nijmegen, The Netherlands. In this study patients were not selected for high risk of recurrence. In both studies treatment was initiated between 1 and 2 weeks after TUR.

In the SWOG trial (study 8795) patients were randomized to TICE®BCG or mitomycin C (MMC). Both drugs were given intravesically weekly for 6 weeks, at 8 and 12 weeks, and then monthly for a total treatment duration of 1 year. Cystoscopy and urinary cytology were performed every 3 months for 2 years. Patients with progressive disease or residual or recurrent disease at or after the 6 month follow-up were removed from the study and were classified as treatment failures.

A total of 469 patients was entered into the study: 237 to the TICE®BCG arm and 232 to the MMC arm. Twenty-two patients were subsequently found to be ineligible, and 66 patients had concurrent CIS, and were analyzed separately. Four patients were lost to follow-up, leaving 191 evaluable patients in the TICE®BCG arm and 186 in the MMC arm. Of the patients, 84% were male and 16% were female. The average age of these patients was 65 years old.

The Kaplan-Meier estimates of 2 year disease-free survival are shown in Table 3. The difference in disease-free survival time between the two groups was statistically significant by the log rank test (p=0.03). The 95% confidence interval of the difference in 2 year disease-free survival was 12% ± 10%. No statistically significant differences between the groups were noted in time to tumor progression, tumor invasion, or overall survival.

TABLE 3: RESULTS OF SWOG STUDY 8795

	TICE®BCG Arm N = 191	**MMC Arm N = 186**
Estimated Disease-Free Survival at 2 years	57%	45%
95% Confidence Interval (CI)	(50%, 65%)	(38%, 53%)

In the Nijmegen study, the efficacy of three treatments was compared: TICE substrain BCG, *Rijksinstituut voor Volksgezondheid en Milieuhygiene* substrain BCG (BCG-RIVM), and MMC.

TICE®BCG and BCG-RIVM were given intravesically weekly for 6 weeks. In contrast to the SWOG study, maintenance BCG was not given. Mitomycin C was given intravesically weekly for 4 weeks and then monthly for a total duration of treatment of 6 months. Cystoscopy and urinary cytology were performed every 3 months until recurrence.

A total of 469 patients was enrolled and randomized. Thirty-two patients were not evaluable, 17 were ineligible, 15 were withdrawn before treatment, and 50 had concurrent CIS and were analyzed separately, leaving 387 evaluable patients: 117 in the TICE®BCG arm, 134 in the BCG-RIVM arm, and 136 in the MMC arm. Twenty-eight patients (24%) in the TICE®BCG arm, 32 patients (24%) in the BCG-RIVM arm and 24 patients (18%) in the MMC arm had TaG1 tumors. The median duration of follow-up was 22 months (range 3-54 months).

The Kaplan-Meier estimates of 2 year disease-free survival are shown in Table 4. The differences in disease-free survival among the three arms were not statistically significant by the log-rank test (p=0.08).

TABLE 4: RESULTS OF NIJMEGEN STUDY

	TICE®BCG Arm N = 117	**BCG-RIVM Arm N = 134**	**MMC Arm N = 136**
Estimated Disease-Free Survival at 2 years	53%	62%	64%
95% Confidence Interval (CI)	(44%, 64%)	(53%, 72%)	(55%, 74%)

In both the SWOG 8795 study and the Nijmegen study, acute toxicity was more common, and usually more severe, with TICE®BCG than with MMC (see ADVERSE REACTIONS).

INDICATIONS AND USAGE

TICE®BCG is indicated for the treatment and prophylaxis of carcinoma *in situ* (CIS) of the urinary bladder, and for the prophylaxis of primary or recurrent stage Ta and/or T1 papillary tumors following transurethral resection (TUR). TICE®BCG is not recommended for stage TaG1 papillary tumors, unless they are judged to be at high risk of tumor recurrence.

TICE®BCG is not indicated for papillary tumors of stages higher than T1.

CONTRAINDICATIONS

TICE®BCG should not be used in immunosuppressed patients or persons with congenital or acquired immune deficiencies, whether due to concurrent disease (e.g., AIDS, leukemia, lymphoma), cancer therapy (e.g., cytotoxic drugs, radiation), or immunosuppressive therapy (e.g. corticosteroids).

Treatment should be postponed until resolution of a concurrent febrile illness, urinary tract infection, or gross hematuria. Seven to 14 days should elapse before BCG is administered following biopsy, TUR, or traumatic catheterization.

TICE®BCG should not be administered to persons with active tuberculosis. Active tuberculosis should be ruled out in individuals who are PPD positive before starting treatment with TICE®BCG.

WARNINGS

BCG LIVE (TICE®BCG) is not a vaccine for the prevention of cancer. BCG Vaccine, U.S.P., not TICE®BCG (BCG LIVE), should be used for the prevention of tuberculosis. For vaccination use, refer to BCG Vaccine U.S.P. prescribing information.

TICE®BCG is an infectious agent. Physicians using this product should be familiar with the literature on the prevention and treatment of BCG-related complications, and should be prepared in such emergencies to contact an infectious disease specialist with experience in treating the infectious complications of intravesical BCG. The treatment of the infectious complications of BCG requires long-term, multiple-drug antibiotic therapy. Special culture media are required for mycobacteria, and physicians administering intravesical BCG or those caring for these patients should have these media readily available.

Instillation of TICE®BCG with an actively bleeding mucosa may promote systemic BCG infection. Treatment should be postponed for at least one week following transurethral resection, biopsy, traumatic catheterization, or gross hematuria.

Deaths have been reported as a result of systemic BCG infection and sepsis.[2,3] Patients should be monitored for the presence of symptoms and signs of toxicity after each intravesical treatment. Febrile episodes with flu-like symptoms lasting more than 72 hours, fever $\geq$ 103^{o} F, systemic manifestations increasing in intensity with repeated instillations, or persistent abnormalities of liver function tests suggest systemic BCG infection and may require antituberculous therapy. Local symptoms (prostatitis, epididymitis, orchitis) lasting more than 2-3 days may also suggest active infection (See Management of Serious BCG Complications subsection of Warnings).

The use of TICE®BCG may cause tuberculin sensitivity. Since this is a valuable aid in the diagnosis of tuberculosis, it is advisable to determine the tuberculin reactivity by PPD skin testing before treatment.

Intravesical instillations of BCG should be postponed during treatment with antibiotics, since antimicrobial therapy may interfere with the effectiveness of TICE®BCG (see PRECAUTIONS). TICE®BCG should not be used in individuals with concurrent infections.

Small bladder capacity has been associated with increased risk of severe local reactions and should be considered in deciding to use TICE®BCG therapy.

Management of Serious BCG Complications

Acute, localized irritative toxicities of TICE®BCG may be accompanied by systemic manifestations, consistent with a "flu-like" syndrome. Systemic adverse effects of 1-2 days' duration such as malaise, fever, and chills often reflect hypersensitivity reactions. However, **symptoms such as fever of $\geq$ 38.5° C (101.3° F), or acute localized inflammation such as epididymitis, prostatitis, or orchitis persisting longer than 2-3 days suggest active infection, and evaluation for serious infectious complication should be considered**.

In patients who develop persistent fever or experience an acute febrile illness consistent with BCG infection, two or more antimycobacterial agents should be administered while diagnostic evaluation, including cultures, is conducted. **BCG treatment should be discontinued**. Negative cultures do not necessarily rule out infection. Physicians using this product should be familiar with the literature on prevention, diagnosis, and treatment of BCG-related complications and, when appropriate, should consult an infectious disease specialist or other physician with experience in the diagnosis and treatment of mycobacterial infections.

TICE®BCG is sensitive to the most commonly used antituberculous agents (isoniazid, rifampin and ethambutol). **TICE®BCG is not sensitive to pyrazinamide**.

PRECAUTIONS

General

TICE® BCG contains live mycobacteria and should be prepared and handled using aseptic technique (See Preparation of Agent subsection of Dosage and Administration). BCG infections have been reported in health care workers preparing BCG for administration. Needle stick injuries should be avoided during the handling and mixing of TICE®BCG. Nosocomial infections have been reported in patients receiving parenteral drugs which were prepared in areas in which BCG was prepared.[4]

BCG is capable of dissemination when administered by intravesical route and serious reactions, including fatal infections, have been reported in patients receiving intravesical BCG.[3] Care should be taken not to traumatize the urinary tract or to introduce contaminants into the urinary system. Seven to 14 days should elapse before TICE® BCG is administered following TUR, biopsy, or traumatic catheterization.

TICE®BCG should be administered with caution to persons in groups at high risk for HIV infection.

Laboratory Tests

The use of TICE®BCG may cause tuberculin sensitivity. It is advisable to determine the tuberculin reactivity of patients receiving TICE®BCG by PPD skin testing before treatment is initiated.

Information for Patients

TICE®BCG is retained in the bladder for 2 hours and then voided. Patients should void while seated in order to avoid splashing of urine. For the 6 hours after treatment, urine voided should be disinfected for 15 minutes with an equal volume of household bleach before flushing. Patients should be instructed to increase fluid intake in order to "flush" the bladder in the hours following BCG treatment. Patients may experience burning with the first void after treatment.

Patients should be attentive to side effects, such as fever, chills, malaise, flu-like symptoms, or increased fatigue. If the patient experiences severe urinary side effects, such as burning or pain on urination, urgency, frequency of urination, blood in urine, or other symptoms such as joint pain, cough, or skin rash, the physician should be notified.

Drug Interaction

Drug combinations containing immunosuppressants and/or bone marrow depressants and/or radiation interfere with the development of the immune response and should not be used in combination with TICE®BCG. Antimicrobial therapy for other infections may interfere with the effectiveness of TICE®BCG. There are no data to suggest that the acute, local urinary tract toxicity common with BCG is due to mycobacterial infection and antituberculosis drugs (e.g. isoniazid) should not be used to prevent or treat the local, irritative toxicities of TICE®BCG.

Carcinogenesis, Mutagenesis, Impairment of Fertility

TICE®BCG has not been evaluated for its carcinogenic, mutagenic potentials or impairment of fertility.

Pregnancy

Teratogenic Effects - Pregnancy Category C
Animal reproduction studies have not been conducted with TICE®BCG. It is also not known whether TICE®BCG can cause fetal harm when administered to a pregnant woman or can affect reproductive capacity. TICE®BCG should not be given to a pregnant woman except when clearly needed. Women should be advised not to become pregnant while on therapy.

Nursing Mothers

It is not known whether TICE®BCG is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions from TICE®BCG in nursing infants, it is advisable to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use

Safety and effectiveness of TICE®BCG for the treatment of superficial bladder cancer in pediatric patients have not been established.

Geriatric Use

Of the total number of subjects in clinical studies of TICE®BCG, the average age was 66 years old. No overall difference in safety or effectiveness was observed between older and younger subjects. Other reported clinical experience has not identified differences in response between elderly and younger patients, but greater sensitivity of some older individual to BCG cannot be ruled out.

ADVERSE REACTIONS

Symptoms of bladder irritability, related to the inflammatory response induced, are reported in approximately 60% of patients receiving TICE®BCG. The symptoms typically begin 4-6 hours after instillation and last 24-72 hours. The irritative side effects are usually seen following the third instillation, and tend to increase in severity after each administration.

The irritative bladder adverse effects can usually be managed symptomatically with products such as pyridium, propantheline bromide, oxybutynin chloride and acetaminophen. The mechanism of action of the irritative side effects has not been firmly established, but is most consistent with an immunological mechanism.[3] There is no evidence that dose reduction or antituberculous drug therapy can prevent or lessen the irritative toxicity of TICE®BCG.

"Flu-like" symptoms (malaise, fever, and chills) which may accompany the localized, irritative toxicities often reflect hypersensitivity reactions which can be treated symptomatically. Antihistamines have also been used.[5]

Adverse reactions to TICE®BCG tend to be progressive in frequency and severity with subsequent instillation. Delay or postponement of subsequent treatment may or may not reduce the severity of a reaction during subsequent instillation.

Although uncommon, serious infectious complications of intravesical BCG have been reported.[2,3,6] The most serious infectious complication of BCG is disseminated sepsis with associated mortality. In addition, *M. bovis* infections have been reported in lung, liver, bone, bone marrow, kidney, regional lymph nodes, and prostate in patients who have received intravesical BCG. Some male genitourinary tract infections (orchitis/epididymitis) have been resistant to multiple drug antituberculous therapy and required orchiectomy.

If a patient develops persistent fever or experiences an acute febrile illness consistent with BCG infection, BCG treatment should be discontinued and the patient immediately evaluated and treated for systemic infection (See Warnings).

The local and systemic adverse reactions reported in a review of 674 patients with superficial bladder cancer, including 153 patients with carcinoma in situ, are summarized in Table 5.

TABLE 5: SUMMARY OF ADVERSE EFFECTS SEEN IN 674 PATIENTS WITH SUPERFICIAL BLADDER CANCER, INCLUDING 153 WITH CARCINOMA IN SITU

Adverse Event	N	Percent of Patients Overall (Grade ≥3)	Adverse Event	N	Percent of Patients Overall (Grade ≥3)
Dysuria	401	60% (11%)	Arthritis/Myalgia	18	3% (<1%)
Urinary	272	40% (7%)	Headache/Dizziness	16	2% (0)
Frequency	224	33% (9%)	Urinary Incontinence	16	2% (0)
Flu-Like	175	26% (7%)	Anorexia/Weight Loss	15	2% (<1%)
Syndrome	134	20% (8%)	Urinary Debris	15	2% (<1%)
Hematuria	50	7% (0)	Allergy	14	2% (<1%)
Fever	40	6% (2%)	Cardiac (Unclassified)	13	2% (1%)
Malaise/Fatigue	39	6% (1%)	Genital	12	2% (<1%)
Cystitis	30	5% (1%)	Inflammation/Abscess		
Urgency	27	4% (1%)	Respiratory	11	2% (<1%)
Nocturia	22	3% (1%)	(Unclassified)	10	2% (1%)
Cramps/Pain	20	3% (<1%)	Urinary Tract Infection	10	2% (1%)
Rigors			Abdominal Pain		
Nausea/Vomiting					

The following adverse events were reported in ≤1% of patients: anemia, BCG sepsis, coagulopathy, contracted bladder, diarrhea, epididymitis/prostatitis, hepatic granuloma, hepatitis, leukopenia, neurologic (unclassified), orchitis, pneumonitis, pyuria, rash, thrombocytopenia, urethritis, and urinary obstruction.

In SWOG study 8795, toxicity evaluations were available on a total of 222 TICE®BCG-treated patients and 220 MMC-treated patients. Direct bladder toxicity (cramps, dysuria, frequency, urgency, hematuria, hemorrhagic cystitis, or incontinence) was seen more often with TICE®BCG, with 356 events compared to 234 events for MMC. Grade ≤ 2 toxicity was seen significantly more frequently following TICE®BCG treatment (p=0.003). No life-threatening toxicity was seen in either arm. Systemic toxicity with TICE®BCG was markedly increased compared to that of MMC, with 181 events for TICE®BCG compared to 80 for MMC. The frequency of toxicity was increased in all grades, particularly for grades 2 and 3. The most common complaints were malaise, fatigue and lethargy, fever, and abdominal pain. Thirty-two TICE®BCG patients were reported to have been treated with isoniazid. Five TICE®BCG patients had liver enzyme elevation, including two with grade 3 elevations. Eighteen of the 222 (8.1%) TICE®BCG patients failed to complete the prescribed protocol compared to 6.2% in the MMC group. Table 6 summarizes the most common adverse reactions reported in this trial.[7]

TABLE 6: MOST COMMON ADVERSE REACTIONS IN SWOG STUDY 8795*

	Study Arm			
	TICE®BCG (N = 222)		MMC (N = 220)	
Adverse Event	**All Grades**	**Grade ≥3**	**All Grades**	**Grade ≥3**
Dysuria	115 (52%)	6 (3%)	77 (35%)	5 (2%)
Urgency/Frequency	112 (50%)	5 (2%)	63 (29%)	7 (3%)
Hematuria	85 (38%)	6 (3%)	56 (25%)	5 (2%)
Flu-Like Symptoms	54 (24%)	1 (<1%)	29 (13%)	0
Fever	37 (17%)	1 (<1%)	7 (3%)	0
Pain (Not Specified)	37 (17%)	4 (2%)	22 (10%)	1 (<1%)
Hemorrhagic Cystitis	19 (9%)	3 (1%)	10 (5%)	0
Chills	19 (9%)	0	2 (1%)	0
Bladder Cramps	18 (8%)	0	9 (4%)	0
Nausea	16 (7%)	0	12 (5%)	0
Incontinence	8 (4%)	0	3 (1%)	0
Myalgia/Arthralgia	7 (3%)	0	0	0
Diaphoresis	7 (3%)	0	1 (<1%)	0
Rash	6 (3%)	1 (<1%)	16 (7%)	2 (1%)

* The adverse reaction profile of TICE®BCG was similar in the Nijmegen study.[8]

OVERDOSAGE

Overdosage occurs if more than one vial of TICE®BCG is administered per instillation. If overdosage occurs, the patient should be closely monitored for signs of active local or systemic BCG infection. For acute local or systemic reactions suggesting active infection, an infectious disease specialist experienced in BCG complications should be consulted.

DOSAGE AND ADMINISTRATION

The dose for the intravesical treatment of carcinoma *in situ* and for the prophylaxis of recurrent papillary tumors consists of one vial of TICE®BCG suspended in 50 ml preservative-free saline.

Do not inject subcutaneously or intravenously.

Preparation of Agent

The preparation of the TICE®BCG suspension should be done using aseptic technique. To avoid cross-contamination, parenteral drugs should not be prepared in areas where BCG has been prepared. A separate area for the preparation of the TICE®BCG suspension is recommended. All equipment, supplies and receptacles in contact with TICE®BCG should be handled and disposed of as biohazardous. The pharmacist or individual responsible for mixing the agent should wear gloves, and take precautions to avoid contact of BCG with broken skin. If preparation cannot be performed in a biocontainment hood, then a mask and gown should be worn to avoid inhalation of BCG organisms and inadvertent exposure to broken skin.

Draw 1 ml of sterile, preservative-free saline (0.9% Sodium Chloride Injection USP.) at 4 - 25° C, into a small syringe (e.g., 3 ml) and add to one vial of TICE®BCG to resuspend. Gently swirl the vial until a homogenous suspension is obtained. Avoid forceful agitation which may cause clumping of the mycobacteria.

Dispense the cloudy TICE®BCG suspension into the top end of a catheter-tip syringe which contains 49 ml of saline diluent, bringing the total volume to 50 ml. To mix, gently rotate the syringe. The suspended TICE®BCG should be used immediately after preparation. Discard after two hours.

Note: DO NOT filter the contents of the TICE®BCG vial. Precautions should be taken to avoid exposing the TICE®BCG to direct sunlight. Bacteriostatic solutions must be avoided. In addition, use only sterile preservative-free saline, 0.9% Sodium Chloride Injection USP, as diluent *and perform all mixing operations in sterile glass or thermoformed plastic containers and syringes.*

Treatment and Schedule

Allow 7-14 days to elapse after bladder biopsy before TICE®BCG is administered. Patients should not drink fluids for 4 hours before treatment and should empty their bladder prior to TICE®BCG administration. The reconstituted TICE®BCG is instilled into the bladder by gravity flow via the catheter. **DO NOT** depress plunger and force the flow of the TICE®BCG. The TICE®BCG is retained in the bladder 2 hours and then voided. Patients unable to retain the suspension for 2 hours should be allowed to void sooner, if necessary.

While the BCG is retained in the bladder, the patient ideally should be repositioned from left side to right side and also should lie upon the back and the abdomen, changing these positions every 15 minutes to maximize bladder surface exposure to the agent.

A standard treatment schedule consists of one intravesical instillation per week for 6 weeks. This schedule may be repeated once if tumor remission has not been achieved and if the clinical circumstances warrant. Thereafter, intravesical TICE®BCG administration should continue at approximately monthly intervals for at least 6 - 12 months. There are no data to support the interchangeability of BCG LIVE products.

HOW SUPPLIED

TICE®BCG is supplied in a box of one vial of TICE®BCG. Each vial contains 1 to 8 x 10^8 CFU, which is equivalent to approximately 50 mg (wet weight), as lyophilized (freeze-dried) powder, NDC 0052-0602-02.

STORAGE

The intact vials of TICE®BCG should be stored refrigerated, at temperatures of 2 - 8° C (36 - 46° F).

This agent contains live bacteria and should be protected from direct sunlight. The product should not be used after the expiration date printed on the label.

Rx Only

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Note : this text has been approved by the FDA.