

AMENDMENTS TO THE ICCTG STUDY PROTOCOL

The ICCTG (Interstitial Cystitis Clinical Trials Group) Multicenter Clinical Trial Protocol #1 is being amended in response to concern among investigators regarding the ability of participants to tolerate the maximum dose of the study medication, oral hydroxyzine. In an effort to allow flexibility in dose escalation to the maximum 50 mg dose, the protocol is being revised to accommodate a period for patient re-titration from 25 mg to 50 mg. This re-titration period will be permitted once during the dose escalation phase (initial three weeks) of the study.

These amendments include several minor changes to the ICCTG RCT Protocol #1, as well as the above described treatment procedure changes.

PROTOCOL EDITIONS

The ICCTG Randomized Clinical Trial Protocol #1 was developed by the ICCTG, and will be maintained by the Data Coordinating Center (DCC) at the University of Pennsylvania over the course of the study through issuance of protocol amendments and revisions. The first edition of the protocol (dated March 12, 1999) is being amended following a conference call of study investigators held on April 12, 1999. The revised edition of the ICCTG RCT Protocol #1 (dated 4/12/99) will be referred to as the Second Edition. Highlighted sections indicate revised or added text. The text box indicates the location of the changed text. Refer to the numbered edition of the enclosed protocol to locate the amendments within the protocol.

AMENDMENT #1A “PATIENT” CHANGED TO “PARTICIPANT”

Throughout the protocol, where appropriate, the term “patient” has been changed to “participant.” This change will not be reflected in the Case Report Forms.

AMENDMENT #1B “SIDE EFFECT” CHANGED TO “ADVERSE EXPERIENCE”

Throughout the protocol the term “side effect” will be changed to “adverse experience.”

AMENDMENT #2 SECTION 5.5 - DEFERRAL CRITERIA #10

If a participant has had any form of transvaginal surgery, hysterectomy, prolapse, vaginal delivery or C- Section, she will be deferred until at least 24 weeks from the date of the procedure.

Text of Amendment: P. 16. Replace lines # 452 – 454 with above text.

AMENDMENT #3 **SECTION 8 - TREATMENT PROCEDURES**

- The blister card for week 3 will have three rows labeled “Dose 1”, “Dose 2” and “Dose 3”. For participants successfully completing week 2 on “Dose 2”, they will be instructed to progress to “Dose 3” IN ADDITION to “Dose 2”. That is, participants will be instructed during week 3 to take 2 green capsules per day at bedtime, the capsule in the “Dose 2” column AND the capsule in the “Dose 3” column. This will be clearly labeled on the week 3 blister pack. If for any reason, the participant cannot tolerate “Dose 3”, s/he will be instructed to call the Research Coordinator, and get approval to switch back to “Dose 2” for 2 days then re-attempt “Dose 3” for the remainder of Week 3. This process will be monitored closely by the Research Coordinator so that the participant may comfortably be established on the dose that they can tolerate for the maintenance phase of the study.

Text of Amendment: Page 18. Replace lines # 555 – 565 with above text.

AMENDMENT #4 **SECTION 8 - TREATMENT PROCEDURES**

Participants will be instructed to take one or two green capsules each day, at bedtime. As a result, there will be one unused capsule left over for each day of week 2, and one or two unused capsules left over for each day of week 3.

Text of Amendment: Page 19. Replace lines # 570 – 572 with above text.

Throughout the protocol, where applicable, the term “one green capsule” has been changed to “one or two green capsules.”

AMENDMENT #5 **SECTION 8 - TREATMENT PROCEDURES**

Prior to the clinic visit at the end of three weeks of follow-up, the Research Coordinator will contact the participant to determine the maximum tolerable dose (either dose 1, 2 or 3) for the green capsules. Depending on this response, the drug distribution center will ship one sealed bottle of green capsules (at the selected dose) to the clinical center by overnight mail on time for the 3 week follow-up visit. An additional sealed bottle will be dispensed to the participant during clinic visits at weeks 10 and 17. The supply of green capsules in each sealed bottle is designed to be adequate for taking one or two green capsules each day, at bedtime, for the following 7-8 weeks until the next clinic visit.

If during this drug maintenance phase, participants determine that the sedative adverse experience is unpleasant, participants may request to de-escalate their drug dose one time only. This decision can only be made in consultation with and approval from the study Principal Investigator and Research Coordinator. The

participant and Research Coordinator will then determine if and when the participant can escalate the drug dose to the original level. These changes will be documented by the participant in his/her Daily Medication Log, and by the Research Coordinator in the participant study file.

Text of Amendment: P. 19. Add highlighted paragraph above after line

AMENDMENT #6 **SECTION 8.3.1 – DOSING SCHEDULE AND JUSTIFICATION**

In addition, the entire dose of hydroxyzine will be given as one or two capsules before bedtime to minimize sedative effects during waking hours the following day.

Text of Amendment: P. 20. Replace lines 642 – 644 with above text.

AMENDMENT #7 **SECTION 9.1 – EXCLUDED MEDICATIONS**

In addition, participants will be excluded from enrollment in this clinical trial, if at baseline screening visit 2, they report chronic use (more than 3 out of 7 days per week) of sedating histamine-1 receptor antagonists (only those drugs containing diphenhydramine, bromphenarimine, or chlorpheniramine).

Text of Amendment: P. 22. Replace lines 723 – 726 with above text.

AMENDMENT #8 **SECTION 10.1.1 BASELINE SCREENING PERIOD: FIRST BASELINE VISIT**

In addition, the participant will be asked to maintain a daily medication diary for each week that elapses between clinic visits. These diaries will be returned and replaced with additional diaries at every clinic visit.

Text of Amendment: P. 24. Add the above text after line #781.

AMENDMENT #9 **SECTION 10.2.2 URINE SAMPLE**

Elevated levels of three markers of bladder mast cell activity have been found in IC urine specimens: methylhistamine, tryptase and IL-6. Methylhistamine is the major metabolite of histamine which is released by activated mast cells. Although histamine levels were only slightly increased in spot urine specimens from IC patients, methylhistamine levels were shown to be greatly elevated, suggesting that they may serve as an important marker of disease activity.

Tryptase is a proteolytic enzyme also released by activated mast cells; unlike methylhistamine which can be excreted intact into the urine, urine tryptase is thought to be specific for urinary tract pathology, and elevations in urine tryptase in IC patient specimens were therefore taken as evidence of increased urinary tract mast cell activity. However, the measurement of tryptase by itself is not as sensitive of a marker for IC as is methylhistamine, making it desirable to measure both substances. IL-6 is a cytokine which has also been shown to be elevated in the urine of IC patients, and which can be elevated in the absence of detectable mast cell degranulation. The measurement of all 3 substances should therefore provide a very sensitive indication of bladder mast cell activity.

Another marker for IC has been described which appears to be very specific and sensitive for the disease itself - a urine "antiproliferative factor" or "APF". This factor is a low molecular weight peptide that inhibits the proliferation of primary normal human bladder epithelial cells in vitro. Because the bladder epithelium is abnormally attenuated in this disease, it is thought that the APF may be causally related to the disease process. Levels of this factor by IC patients have recently been shown to be decreased following bladder hydrodistension, a treatment currently used for IC and beneficial in some patients, making it another potential indicator of disease activity.

Because the primary parameters to be measured for this study are subjective in nature, potential objective measurements of disease activity were thought to be desirable. It is thought that the first 3 markers (methylhistamine, tryptase, and IL-6) may serve as objective indicators of whether the antihistamine in this study has an effect on bladder mast cell activity, and the fourth marker (APF) may serve as an objective indicator of whether the antihistamine and/or Elmiron have a measurable effect on another aspect of the disease process.

Text of Amendment: P. 26. Insert above text at line # 874.
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AMENDMENT # 10 SECTION 12.1 – TYPES OF ADVERSE EVENTS

The following drug reactions may have been reported:

Text of Amendment: P. 29. Replace line #958 with the above text.
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AMENDMENT #11 SECTION 12.2 – 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 judgement, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. (1)

Text of Amendment: P. 29. Replace lines # 972 – 980 with above text.

AMENDMENT #12 **SECTION 12.3 – FOLLOW-UP OF ADVERSE EVENTS**

For adverse events, a reinitiation of treatment may be allowed if considered both safe and ethical.

Text of Amendment: P. 30. Delete above text at line #1002.

AMENDMENT #13 **SECTION 13.6 – DIRECT ACCESS TO SOURCE DOCUMENTS**

Investigators will maintain, on-site, in an orderly fashion, for a period of no less than 7 years, 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.

Text of Amendment: P. 31. Replace lines # 1048 – 1052 with above text.

AMENDMENT #14 **APPENDIX E – PATIENT CONSENT FORM**

A typographical error was noticed in the Suggested Subject Consent Form template. In the section entitled Pentosan polysulfate sodium (Elmiron®), the report of liver function abnormalities as side effects was erroneously reported as 10%. The correct value is 1 – 4 %.

See Appendix E – Suggested Subject Consent Form.

AMENDMENT #15 **“INR” CHANGED TO “PT”**

Throughout the protocol, where appropriate, the laboratory value “INR” will be changed to “PT”. This change will be reflected in the Case Report Form [LAB],

but will not result in a change to the schedule of patient laboratory tests. This change is effective September 10, 1999.

Text of Amendment:	P. 14, Line # 394. Replace INR with PT. P. 27, Line # 918. Replace INR with PT.
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AMENDMENT #16 “Change Exclusion and Deferral Criteria as they apply to the study medications Elmiron® and hydroxyzine.”

A.) **EXCLUSION CRITERIA #6** (as currently listed in the study protocol.)

Having been previously treated with at least 100 mg TID of Elmiron®, or greater than 10 mg of hydroxyzine per day for greater than 12 consecutive weeks.

B.) **DEFERRAL CRITERIA #6** (as currently listed in the study protocol.)

If a participant has received treatment with Elmiron® or hydroxyzine, he/she will be deferred until the participant has been off drug for a minimum of 12 weeks prior to study entry.

Text of Amendment:	P. 14. Line 376-7. Delete Exclusion Criteria as listed above. P. 16. Line 441-3. Change Deferral Criteria listed above to 4 weeks.
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criteria pertaining to prior Elmiron® and hydroxyzine use in order to prevent biasing the trial results toward a negative finding by including participants who may have been “treatment failures.” However, even though the clinical centers have encountered an unexpectedly high proportion of IC patients reporting previous exposure to study medications, the previous exposure, especially to Elmiron®, is believed to have been extremely variable. Furthermore, the duration of previous use of Elmiron® is likely to have been erratic and potentially of a non-therapeutic interval (<6 months). Finally, the response status of potential study participants at the end of their previous usage of Elmiron® is unknown.

As a result, the ICCTG Steering Committee believes that exclusion criteria #6 should be removed, and that IC patients who meet the 4-week deferral criteria should be permitted to be screened into RCT#1. They re-confirmed the critical importance of investigating these study medications within the framework of an objective non-industry sponsored RCT under a rigorous protocol. Finally, they agreed that the validity of the trial would not be jeopardized by this protocol change.

AMENDMENT # 17

Present Exclusion Criteria # 15, *For All Participants*: A participant satisfying one of the following criteria will not be eligible to participate in the study:

- Reports a urinary void with a maximum volume >350 cc, as measured by a 24 hour voiding diary.

Text of Amendment:	P. 14. Line 387-388. Delete Exclusion Criteria #15 as listed above.
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AMENDMENT # 18

Present Exclusion Criteria # 28, *For Men Only*: A participant satisfying one of the following criteria will not be eligible to participate in the study:

- Having had a TURP, TUIP, TUIBN, TUMT, TUNA, balloon dilation of the prostate, open prostatectomy or any other prostate surgery or treatment such as cryotherapy or thermal therapy.

CHANGE TO DEFERRAL CRITERIA, *For Men Only*:

If a participant has had TURP, TUIP, TUIBN, TUMT, TUNA, balloon dilation of the prostate, open prostatectomy or any other prostate surgery or treatment such as cryotherapy or thermal therapy, he will be deferred until at least 6 months from the date of the procedure.

Text of Amendment:	P. 15. Line 409-411. Delete Exclusion Criteria # 28 as listed above. Insert Change To Deferral Criteria: P. 16. Line 455.
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