ICCTG RCT#2 Study Protocol –Amendment #2

Summary of Protocol Amendment #2

The goal of this proposed amendment is to incorporate long-term follow-up on responders into the overall study design. Although the analysis of long-term data will be primarily descriptive, these data will provide baseline information on long-term response rates and provide an important addition to the study data.

In the current version of the protocol, patients who are deemed to be non-responders after the first phase of treatment (Phase 1) and follow-up are offered open-label BCG therapy at 7.5 months post-randomization. The second treatment and follow-up phase is referred to as Phase 2 of the study.

Currently, responders after the first 7.5 months of treatment and follow-up in Phase 1 are considered to have completed the study and are no longer followed. This amendment will incorporate select follow-up time points for responders corresponding in part to that for the non-responders participating in Phase 2. Therefore, the protocol amendment will refer to Phase 2 of the study in two parts: Phase 2 for non-responders and the new Phase 2R for responders.

1. Study Design and Objectives [Section 2 – Page 6]

This section outlines the primary objectives of RCT #2.

Current Text: The current text outlines four primary objectives of the trial, which do not include the objective of long-term follow-up on those patients considered to be responders at the completion of Phase 1 of the trial.

Additional Text to Read: "Primary Objective #5 – To obtain information on long-term response of those patients determined to be responders at the completion of Phase 1 of treatment."

2. Study Design and Objectives [Section 2 – Page 7]

This section outlines and illustrates the two phases of the study design (Phase 1 and Phase 2).

Current Text Reads: "The second phase 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."

Current Text Illustration Reads: "Phase 2-Non-Responders-Open Label BCG Treatment."

Change Text to Read: "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.

Change Text Illustration to Read: "Phase 2-Non-Responders-Open Label BCG Treatment" and "Phase 2R-Responders-Long-Term Response."

3. Study Plan [Section 4.2 Phase 2]

Revision made to Section 4.2 heading and content to reflect the defined two sections of Phase 2.

Current Text Heading Reads: "4.2 Phase 2"

Change Text Heading to Read: "4.2 - Phase 2 and Phase 2R"

Current Text Reads: "The second phase 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".

Change Text to Read: "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".

Additional Paragraph to Text to Read: Phase 2 R 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 a 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.

Change Text to Read: "For both Phase 2 and for Phase 2 R, 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 & phase 2R) of the study, and the analysis of these results will be primarily descriptive.

4. Appendix A [Suggested Subject Consent Form – Page 4 & Page 5]

Current Text: Current Text of Subject Consent Form "What Will Happen After You Finish Your Treatments?" does not include patient signed permission to participate in a long-term follow-up period (Phase 2R) if deemed a responder at the six month clinic visit (week 34) primary endpoint.

*Additional Paragraph to Text of Current Subject Consent Form "What Will Happen After You Finish Your Treatments?" to Read: "*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.

5. Appendix B [Visit Schedule Table]

Revision made to current visit schedule table to include additional visit schedule and events for Phase 2 R-Responders Long term Responders (see attached).