Clinical Protocol

Title:	**A Multicenter, Randomized, Placebo-Controlled, Double-Blind, Phase 3 Trial of Single-Dose Intravesical EOquin® as a Surgical Adjuvant Instilled in the Early Postoperative Period in Patients Undergoing Transurethral Resection for Noninvasive Bladder Cancer**
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1. LIST OF ABBREVIATIONS

AE	adverse event
ALT	amino alanine transferase
AST	aspartate aminotransferase
BUN	blood urea nitrogen
CBC	complete blood count
CFR	Code of Federal Regulations
CR	complete response
CIS	Carcinoma in situ
CRF	case report form
CRA	Clinical Research Associate
CTCAE	Common Toxicity Criteria Adverse Events
CV	curriculum vitae
dL	deciliter
ECOG	Eastern Cooperative Oncology Group
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HIPAA	Health Insurance Portability and Accountability Act
ICH	International Conference on Harmonization
ID	identification
IEC	Independent Ethics Committee
IRB	Institutional Review Board
ISUP	International Society of Urological Pathology
LDH	lactate dehydrogenase
mg	milligram
mL	milliliter
NCI	National Cancer Institute
SAE	serious adverse event
SEC	Securities and Exchange Commission
TUR	Transurethral resection
TUR-BT	Transurethral resection bladder tumor
US	United States of America
WHO	World Health Organization

2. SYNOPSIS

Title	A Multicenter, Randomized, Placebo-Controlled, Double-Blind Phase 3 Trial of Single-Dose Intravesical EOquin® as a Surgical Adjuvant Instilled in the Early Postoperative Period in Patients Undergoing Transurethral Resection for Noninvasive Bladder Cancer
Phase	This is a Phase 3 Clinical Study.
Investigational Product	EOquin® /Placebo for intravesical instillation
Dose	4mg in 40 mL
Route of Administration	Intravesical
Primary Objective	To evaluate the recurrence rate at 2 years in randomized patients with tumor histology Ta, G1-G2 who receive TUR-BT plus EOquin versus those who receive TUR-BT plus placebo.
Secondary Objectives	• To evaluate time to first recurrence in patients with tumor histology Ta, G1-G2 who receive TUR-BT plus EOquin® versus those who receive TUR-BT plus placebo. • To evaluate progression to higher stage or grade, number of recurrences per patient, disease free interval, disease free survival and overall survival. • To assess the safety of EOquin® instilled into the bladder in the early postoperative period. • To assess functional bladder capacity in a 150 subject subset of randomized patients.
Patient Population	Approximately 800 adult patients with ≤ 4 noninvasive bladder tumors, ≤ 3.5 cm in diameter all of which must have been fully resected at TUR.
Study Centers	Approximately 100 centers in North America and Europe
Study Design	This is a multicenter, randomized, placebo-controlled, double-blind, study. Following TUR-BT, eligible patients will be randomized to receive either intravesical EOquin® or matching placebo instilled within 6 hours of surgery. Patients will be seen for a postoperative follow-up exam 21±10 days after the TUR. At this time, the pathology report will be reviewed. If the histology of the patient's tumor is Ta, G1-G2 (low grade [WHO/ISUP classification]), then the patient will receive no further treatment and will be observed cystoscopically every three months through year two for tumor recurrence and progression. If the histology of the patient's tumor is other than Ta, G1-G2 (low grade [WHO/ISUP classification]), then the patient will receive further treatment in accordance with current treatment guidelines, following which the patient will be followed up cystoscopically every three months through year two for tumor recurrence and progression.
Study Duration	All patients will be followed for two years.
Study drug Administration Schedule	EOquin®/ Placebo will be given by intravesical administration one time within 6 hours of TUR-BT.
Efficacy Assessments	Cystoscopy every 3 months through year two.
Safety Assessments	Periodic physical examinations, safety laboratories and monitoring of adverse events will be performed. Functional bladder capacity will be performed at preselected US sites in a subset of 150 patients.
Adverse Event Reporting	All SAEs and all genitourinary AEs will be recorded for the patient's

Period	entire participation in the study. All other adverse events will be recorded for the first 6 months following randomization.

3. BACKGROUND

3.1 Noninvasive Bladder Cancer

Bladder cancer is the seventh most common cancer worldwide, accounting for approximately 280,000 new cases in the EU and over 60,000 new cases in the US. Bladder cancer ranks as the fourth most common malignancy in men and the tenth most common neoplasm in women. In the United States, over 13,000 deaths from bladder cancer are anticipated in 2006. [1] The median age at diagnosis is 65 years of age, which explains why treatment is frequently complicated by the presence of significant comorbidities.

The clinical spectrum of bladder cancer can be divided into three broad categories that differ in prognosis and management. The first category consists of noninvasive tumors, for which treatment is directed at reducing recurrences and preventing progression to a more advanced stage. The second category is comprised of the invasive lesions. The goal of therapy for this group of neoplasms is to determine whether the bladder can be spared without compromising survival. For the third category, metastatic disease, treatment is aimed at attempting to prolong life. Numerous chemo- and immunotherapies have shown activity in this disease. The issue for the clinician is how best to use these agents so as to achieve the most satisfactory outcome.

More than two-thirds of newly diagnosed cases of bladder cancer are transitional cell carcinomas with an exophytic papillary appearance. Approximately 70% of these tumors are confined to the epithelium (Ta), while approximately 30% reach the lamina propria (T1). [2] The natural history of these tumors is characterized by a tendency to recur at the same or different location in the bladder. Approximately one-half to two-thirds of these patients will experience a recurrence within 5 years. Thus these tumors require frequent follow up and retreatment, resulting in significant expense and morbidity for the patient. Statistics indicate that bladder cancer is the fifth most expensive tumor to treat. [3] Thus, it has become a goal of treatment to identify strategies to reduce the frequency of recurrence of these tumors.

One approach to preventing recurrence of these tumors involves the instillation of a chemotherapeutic agent into the bladder immediately after TUR. The purpose of such an instillation is to not only eradicate tumor cells missed by the TUR, but also to prevent floating tumor cells from implanting on traumatized bladder epithelium. To determine the effect of immediate instillation of chemotherapy, Sylvester *et al*. performed a meta-analysis of 7 randomized trials with recurrence information on 1476 patients. [4] Recurrence was compared in patients receiving TUR and 1 postoperative instillation of chemotherapy (epirubicin, mitomycin C, thiotepa or pirarubicin) and patients receiving TUR alone. Overall recurrence was reported for 629 of 1476 patients (42.6%). In the TUR alone group recurrence was reported for 362 of 748 patients (48.4%) whereas in the TUR plus one dose of chemotherapy group recurrence was reported in 267 of 728 patients (36.7%). These data represent a decrease of 64% in the odds of recurrence for patients receiving 1 chemotherapy instillation (OR 0.61, 95% CI from 0.49 to 0.75 $p < 0.0001$). Additionally, this meta-analysis concluded that one immediate intravesical instillation of chemotherapy significantly decreases the risk of recurrence after TUR in patients with stage Ta, T1 single and multiple bladder cancer". The study reported by Solsana *et al* reported the positive effect of TUR plus single immediate mitomycin C instillation (treatment group) vs. TUR plus observation (control group) in patients with low risk superficial bladder cancer.[5] The benefit was notable in patients with early recurrences defined as "recurrence within 2 years of follow up". Early recurrence was reported for 22 of 64 patients (34.3%) control group vs. for 9 of 57 patients (15.8%) in the treatment group. Moreover, the early recurrences were concentrated during the first 12 months, 13 of 22 patients (59%) in control group vs. 2 of 9 patients (22.2%) in the treatment group. Late recurrences (follow up more than 2 years) were similar in both groups. Late recurrence was reported for 13 of 57 patients (22.8%) in the treatment group and for 14 of 64 patients (21.8%) in the control group. No significant difference was reported for progression (increase in stage and or grade from baseline) in either group.

Given the apparent efficacy of this strategy, new drugs need to be evaluated in an effort to improve upon these results. EOquin®, an analog of mitomycin C, has been shown in

studies performed in Europe to have significant activity against bladder cancer. The current study is being performed to assess the effect on recurrence of a single dose of EOquin® instilled in the early post-operative period to patients with noninvasive (Ta) bladder cancer.

3.2 EOquin®

EOquin® (apaziquone for intravesical instillation) is a bioreductive alkylating indoloquinone that needs to be enzymatically activated *in* vivo in order to cause cell death. Both its pattern of activation and its activity in tumor cell lines exhibit marked differences from mitomycin C, the prototype of this class.

EOquin® is supplied as a sterile, nonpyrogenic, lyophilized product in a clear glass vial. It contains 4 mg of apaziquone, mannitol and sodium bicarbonate. The diluent contains a solution of sodium bicarbonate, propylene glycol and disodium EDTA in sterile water. Two ampoules of diluent are to be used for each vial of EOquin®.

3.3 Preclinical and Clinical Studies with EOquin®

3.3.1 Preclinical Studies

In vitro assays with panels of tumor lines showed a preferential cytotoxicity of EOquin® in most solid tumors as opposed to leukemia lines. The drug appeared significantly more potent than mitomycin C.

In intravenous and intraperitoneal toxicology studies, the drug was safely administered to mice and rats exposing them to a much higher plasma concentrations than can be achieved by intravesical instillation.

3.4 Clinical Studies with EOquin®

3.4.1 Intravesical Studies

There have been three studies of EOquin® administered by the intravesical route.

The first study was an intrapatient dose escalation study performed in patients with recurrent superficial (Ta-T1, G1-G2) bladder cancer in which all but one "marker" lesion had been removed at TUR. EOquin® was given weekly for 6 weeks beginning two weeks after TUR. The doses to be studied were 0.5, 1, 2, 4, 8 and 16 mg in 40 mL. Four patients received all dose levels up to the maximum dose of 16 mg. Two of the six patients treated experienced local toxicity (grade 3 dysuria) at the 8 mg dose but tolerated their last instillation at the reduced dose of 4 mg. Thus, 4 mg per instillation was determined to be the maximal tolerated dose. Six more patients were enrolled and treated with the fixed dose of 4 mg in 40mL. Four of these six patients experienced a complete response of their marker lesions. The drug was well tolerated at this dose with the majority of the side effects referable to the bladder and of mild to moderate severity. Pharmacokinetic testing failed to reveal the presence of EOquin® in the plasma of any patients with the limit of detection at 20 ng/mL.

Consequently, a Phase 2 study was initiated. This was a multi-center, non-randomized, open-label study conducted in patients with primary or recurrent, multiple (2-10) superficial (Ta-T1, G1-G2) bladder cancers for which all but one "marker" lesion had been removed at TUR. More than half of the patients enrolled had undergone prior TUR-BT plus intravesical immuno- and/or chemotherapy. EOquin® was given weekly for 6 weeks beginning two weeks after TUR. Tumor response was assessed two to four weeks following the last instillation of EOquin®. Thirty one patients (67%) experienced a complete response. There was no progression to a higher stage or grade. Treatment was well tolerated by the majority of patients. One patient discontinued treatment because of hematuria. The most common adverse events were hematuria, dysuria and urinary frequency. There were few systemic side effects. Most AEs were mild to moderate in severity and the only grade 3 AEs were referable to the bladder.

A safety and tolerability study of a single dose of EOquin® 4 mg/40mL administered within 6 hours of TUR-BT in patients with stage Ta-T1, grade G1-G2 non invasive bladder cancer has completed accrual of 20 patients. All twenty patients dosed tolerated EOquin® instillation and retention in the bladder for 1 hour. There was no evidence of

impaired wound healing on follow up cystoscopy performed at day 85 on the first 7 patients dosed. PK studies were performed in 6 patients. Blood samples were collected before instillation and at 5, 15, 30, 45, 60 minutes after instillation. Neither the parent drug (EO9) nor its metabolite EO5a was detected in plasma samples with a limit of detection for EO9 at 5ng/mL and EO5a at 10ng/mL.

3.4.2 Intravenous Studies

There have been eight studies (5 Phase I and 3 Phase II) of apaziquone administered by the intravenous route.

In Phase 1 studies, a total of 32 patients with solid tumors were given apaziquone at doses ranging from 2.7 mg/m^2 to 27 mg/m^2. The plasma half-life of apaziquone was 1-19 minutes. Dose limiting toxicity was reversible proteinuria, which first appeared at 18 mg/m^2. Limited efficacy was attributed to the drug's short half-life. [6]

In Phase 2 the drug was studied in 91 patients with breast, colorectal, gastric, and pancreatic cancers. The dose was 12 mg/m^2 given weekly as a 5-minute infusion. Proteinuria was the most common AE, occurring in 71% of patients. Other AEs reported by more than 10% of patients included nausea (48%), asthenia (44%), vomiting (33%), anemia (26%), headache (18%), elevations of hepatic enzymes (17%), injection site phlebitis (16%), myalgia (15%) and fever (11%). Again, attributed to the drug's short half-life, no significant anti-tumor activity was detected.

In addition a Phase 2 study was performed in 39 patients at a dose ranging from 12 mg/m^2/weekly to 22 mg/m^2 every 3 weeks in patients with non-small-cell lung cancer. As expected, the same type of AEs were reported, but with a higher incidence and severity compared to the studies performed at 12 mg/m^2. Again, attributed to the drug's short half-life, no significant anti-tumor activity was detected.

3.5 Summary of Risks and Benefits

3.5.1 Potential Risks

EOquin® is an investigational product, and its safety profile has not been firmly established. In studies performed to date, it appears to be well tolerated with most side effects limited to the bladder.

The physician is urged to use clinical judgment regarding the appropriateness of intravesical instillation in the immediate post-TUR period. Patients with an extensive resection, possible bladder perforation or significant postoperative bleeding should not receive EOquin®.

As with all alkylating agents, care must be taken in the handling of EOquin®. EOquin® should be prepared following each institution's standard operating procedure for preparation of cytotoxic drugs. Full protective equipment must be worn by persons handling EOquin®, and spills must be addressed using the institution's standard operating procedures for such accidents. If there is inadvertent contact with the patient's skin, the area should be washed immediately with warm soapy water.

3.5.2 Potential Benefits

EOquin® is an investigational product, and its efficacy in randomized clinical trials has not been established. Based on the Phase I and Phase II studies it is possible that the administration of EOquin® in this study may delay the time to recurrence in noninvasive bladder cancer.

3.6 Justification of the Dose, Schedule and Route of Administration of EOquin®

As noted above in section 3.1, single instillations of drugs such as mitomycin C and epirubicin have been shown to reduce recurrences of superficial bladder cancers when administered in the immediate post-TUR period. The sooner the drug can be instilled, the better, but for practical purposes, most studies have defined this immediate instillation as occurring within 6 hours of the TUR. Therefore, the current study also specifies administration within six hours of completion of the TUR. The dose of EOquin®, 4 mg

in 40 mL, was established in a dose-escalation study as demonstrating anti-tumor activity while being safe and well tolerated.

3.7 Population to be Studied

This study will enroll approximately 800 adult patients with noninvasive bladder cancer. Eligible patients will have 4 or fewer tumors, none of which exceeds 3.5 cm in diameter.

4. OBJECTIVE

4.1 Primary Objective

To evaluate the recurrence rate of bladder cancer at 2 years in randomized patients with tumor histology Ta, G1-G2 who receive TUR-BT plus EOquin versus those who receive TUR-BT plus placebo.

4.2 Secondary Objective

- To evaluate time to first recurrence in patients with tumor histology Ta, G1-G2 who receive TUR-BT plus EOquin® versus those who receive TUR-BT plus placebo.

- To evaluate progression to higher stage or grade, number of recurrences per patient, disease free interval, disease free survival and overall survival.

- To assess the safety of EOquin® instilled into the bladder in the early postoperative period.

- To assess functional bladder capacity in a 150 subject subset of randomized patients.

5. STUDY DESIGN

5.1 Overview

This is a multi-center, randomized, double-blind, placebo-controlled trial. All patients must sign a consent form prior to undertaking any study-related procedures. Screening procedures must be performed prior to and within 14 days of randomization. After screening procedures are performed, appropriate patients will undergo a TUR-BT. Following TUR of all visible tumors, patients meeting all of the inclusion/exclusion criteria will be randomized to receive either Placebo or EOquin® instilled into the bladder within 6 hours of the end of the TUR procedure. EOquin® / Placebo will be retained for 60 minutes, following which it will be drained from the bladder. If there are no complications, the patient will be discharged. The patient will be seen for a postoperative follow-up exam 21±10 days after the TUR. At this time, the pathology report will be reviewed. If the histology of the patient's tumor is confirmed Ta, G1-G2 (low grade [WHO/ISUP classification]), then the patient will receive no further treatment and will be observed cystoscopically every three months through year two for tumor recurrence. If the histology of the patient's tumor is other than Ta, G1 or G2 (low grade [WHO/ISUP classification]), then the patient will be free to receive further treatment in accordance with current treatment guidelines, and will be followed up cystoscopically every three months through year two for tumor recurrence. All patients will be followed for two years.

5.2 Dose, Route of Administration and Schedule of Study Drug

5.2.1 Dose and Route of Administration of Study Drug

Randomized patients will receive either matching Placebo or EOquin® 4 mg reconstituted with 40 mL of diluent. The 40 mL of reconstituted study drug is to be instilled into the bladder via an indwelling, Foley catheter, where it is to be retained for 60 minutes. For details of study drug preparation please see **Section 8**.

5.2.2 Schedule of Study Drug Administration

Study drug is to be administered once within 6 hours of the completion of the TUR.

5.3 Study Duration and Follow-up

All patients will be followed for two years.

5.4 Enrollment

Patients who meet all of the inclusion criteria and none of the exclusion criteria may be considered for randomization. Following confirmation of the number and size of the bladder tumors at TUR, the patient will be randomized to receive either placebo or EOquin®.

5.5 Blinding Procedures

This is a randomized, double blind, placebo-controlled study. An independent central pathology laboratory blinded to the treatment assignments will perform the histologic eligibility and histologic outcome assessments.

5.6 Termination of the Study

The study will continue until all randomized patients have completed 2 years of follow up. The Sponsor retains the right to terminate the study at any time.

6. PATIENT SELECTION AND WITHDRAWAL

6.1 Inclusion Criteria

All of the following questions must be answered "Yes" in order for the patient to participate in the study.

1. Has the patient given written informed consent?
2. Is the patient at least 18 years old?
3. Does the patient have transitional cell carcinoma of the bladder with clinically apparent stage Ta, grade G1-G2?
4. If the patient is a female of childbearing potential, is she using an acceptable/effective method of contraception?
5. If the patient is a female of childbearing potential, has she had a negative serum pregnancy test within the past 14 days?
6. Is the patient willing and able to abide by the protocol?

6.2 Exclusion Criteria

All of the following questions must be answered "No" in order for the patient to participate in the study.

1. Does the patient have more than 4 bladder tumors?
2. Does any single bladder tumor exceed 3.5 cm in diameter?
3. Does the patient have a single, primary (no previous diagnosis of TCC) bladder tumor <0.5 cm?
4. Has the patient ever received EOquin®?
5. Does the patient have, or has the patient ever had, any bladder tumor known to be other than stage Ta or grade G1 or G2 (low grade [WHO/ISUP classification])?

6. Does the patient have, or has the patient ever had any bladder tumor with histology other than transitional cell carcinoma?

7. Does the patient have, or has the patient ever had, CIS?

8. Does the patient have an active urinary tract infection?

9. Does the patient have a bleeding disorder or a screening platelet count < 100 x 10^9/L?

10. Does the patient have any unstable medical condition that would make it unsafe for him/her to undergo TUR-BT under general or spinal anesthesia?

11. Does the patient have a screening hemoglobin < 10 mg/dL, a screening absolute neutrophil count < 1.5 x 10^9/L or a screening creatinine > 2 mg/dL?

12. Does the patient have a known immunodeficiency disorder?

13. Has the patient received any investigational treatment within the past 30 days?

14. Is the patient breast feeding?

15. Does the patient have a history of interstitial cystitis?

16. Does the patient have a history of allergy to red color food dye?

17. Has the patient had transitional cell carcinoma of the bladder within the past 4 months?

6.3 Patient Withdrawal from Treatment

Since this is a single dose study, the only way to withdraw from treatment is to shorten the period of time during which the study drug is retained in the bladder. If during the retention a patient suffers a severe adverse experience that, in the judgment of the Principal Investigator or the Medical Monitor, is caused by, or made worse by the study

drug, the drug should not be retained in the bladder for the full 60 minutes. In the event of such an occurrence, the Sponsor should be notified.

6.4 Patient Withdrawal from Study

Following the single dose of study drug, patients may be discontinued from the study for any of the following reasons:

1. The patient withdraws consent.
2. The patient refuses follow-up cystoscopy.
3. The patient is lost to follow-up.
4. Investigator's or Sponsor's decision

7. STUDY VISIT PROCEDURES

7.1 Screening Identification Number

Patients will be assigned a screening identification number (screening numbers) for screening purposes. Screening numbers will be assigned by the site after a patient has signed the Informed Consent Document. The screening ID number will be site's three-digit ID number, followed by three unique digits increasing sequentially from 001. For example, the first patient screened at site 20 would be assigned a screening ID number of 020-001.

The investigational site personnel must maintain a log of screened patients.

7.2 Screening and Pre-Study Assessments

Prior to the performance of any protocol-specific procedures, written informed consent must be obtained. The following assessments should be performed in order to determine whether the patient is eligible for this study. All screening procedures must be performed prior to and within 14 days of randomization.

A complete medical history, including review of systems, bladder cancer history and history of previous treatment for bladder cancer, must be obtained. Copies of relevant pathology reports and operative reports should be obtained. Past and current history of smoking should be recorded.

Physical examination; rectal and pelvic examinations should be performed when clinically indicated.

Weight, vital signs (temperature, blood pressure, pulse).

Screening labs: CBC, chemistry panel, urine cytology, and pregnancy test for females of childbearing potential.

Urinalysis

7.3 Randomization

Patients will be randomized 1:1 to either EOquin® or placebo. The randomization plan will use a permuted block design and will not be stratified by prognostic factors. However, patients will be randomized within center with a block size of four. Patient

numbers will be assigned sequentially at each site. The study drug will be shipped to the sites in blocks of four to ensure balance at each site. The study drug will be labeled with the randomization number which will consist of the four-digits that starts from 1001 and increases sequentially. For Polish sites the randomization numbers will start from 4501 and increase sequentially. After performing all screening procedures (except TUR), the patient's screening CRFs will be completed and faxed to the Medical Monitor. Within 24 hours of receipt, the medical monitor or designee will approve or reject the patient for study entry. Study drug should not be prepared until the number, size and appearance of all bladder tumors are confirmed at TUR. If following TUR the patient does not receive study drug, the Medical Monitor should be notified immediately via e-mail or fax.

7.4 On-Study Procedures and Evaluations

The following tests will be conducted according to the Schedule of Events **(See Section 19 and 20).**

7.4.1 Physical Examination

Brief physical examination includes auscultation of the heart and lungs, and examination of the abdomen. Examination of other systems, including rectal and pelvic examination, should be performed if clinically indicated. Physical examinations should be completed by a physician or other health professional licensed to perform such examinations.

Documentation will be made in the patient's records for all examinations and assessments.

7.4.2 Vital Signs

Temperature, blood pressure, and pulse should be recorded at each visit.

7.4.3 Laboratory Evaluations

CBC with differential and platelet count, chemistry panel (including electrolytes, BUN, creatinine, total bilirubin, alkaline phosphatase, LDH, ALT and AST), and urinalysis will be performed as indicated on the Schedule of Events (**Section 19 and 20)**. Urine cytology will be performed at screening and at 6-month intervals during follow up.

Urinalysis will be performed in the office using urine dipsticks provided by the sponsor. If dipstick is positive for leukocyte esterase and/or nitrite, then urine specimen should be sent to central lab.

A central laboratory will be used to process clinical specimens.

7.4.4 Functional Bladder Capacity

Functional bladder capacity will be assessed at screening, at year 1 and at year 2 in a subset of 150 patients. This testing will be performed only at preselected US sites and will consist of 3-day voiding diaries and assessment of voided volume and post-void residual. The details of this assessment are listed in **Section 19.**

7.4.5 TUR-BT

TUR-BT will be performed according to each site's standard operating procedure. All visible tumors should be removed by using electrocautery to a depth that will allow the pathologist to accurately stage the tumor. An operative report should include number, size and location of the tumors removed. The seven bladder regions are: dome, left and right lateral walls, anterior and posterior walls, trigone and bladder neck. All histology specimens will be read by a blinded, central laboratory that specializes in urologic pathology. Depending upon each institution's standard operating procedures, the specimens may also be read by the local pathologist. In such cases, all clinical decisions will be made based on the local pathologist's report. All pathology reports must include the tumor stage and grade for each lesion removed.

7.4.6 Instillation of Study Drug

After adequate hemostasis has been obtained, the study drug should be slowly instilled into the bladder using a catheter-tip syringe or syringe with catheter tip adapter attached to an indwelling Foley catheter.

7.4.7 First follow-up visit Post TUR-BT

All patients will have a follow-up office visit 21± 10 days following their TUR-BT. Vital signs (temperature, blood pressure, and pulse) will be recorded. A brief physical, CBC,

chemistry panel and urine analysis will be done. All AEs and concomitant medications will be recorded on appropriate CRFs.

7.4.8 Cystoscopy

7.4.8.1 Ta, G1-G2 patients

Cystoscopy will be performed every three months ± 10 days, from the date of the TUR-BT through year two. An operative report should contain the number, size and location of the recurrent tumors, if any. Suspicious lesions should be biopsied, and recurrences reported on the appropriate CRF. All histology specimens will be read by a blinded, central laboratory that specializes in urologic pathology. Depending upon each institution's standard operating procedures, the specimens may also be read by the local pathologist. In such cases, all clinical decisions will be made based on the local pathologist's report. All pathology reports must include the tumor stage and grade for each lesion removed.

7.4.8.2 Higher grade/stage patients

Cystoscopy will be performed every three months ± 20 days, from the date of the start of the additional therapy through year two. Suspicious lesions should be biopsied, and recurrences reported on the appropriate CRF. An operative report should contain the number, size and location of the recurrent tumors, if any. All histology specimens will be read by a blinded, central laboratory that specializes in urologic pathology. Depending upon each institution's standard operating procedures, the specimens may also be read by the local pathologist. In such cases, all clinical decisions will be made based on the local pathologist's report. All pathology reports must include the tumor stage and grade for each lesion removed. All subsequent treatments (chemo- and immunotherapy) administered for bladder cancer will be recorded.

7.4.9 Urine cytology

Urine cytology will be obtained at screening for all patients. Follow-up urine cytology will be obtained at 6 months intervals. Urine cytology will be read by a central laboratory (Bostwick Laboratories).

7.4.10 Adverse Events (AEs) and Concomitant Medications

Only those AEs that occur following randomization should be recorded on the Adverse Event CRF. All SAEs and all genitourinary AEs will be recorded for the patient's entire participation in the study. All other adverse events will be recorded for the first 6 months following randomization. **See Section 11 for additional details regarding the recording of AEs.**

All subsequent intravesical chemo- and immunotherapies used must be recorded. Other concomitant medications should be recorded from randomization (visit 1) through month 6 (visit 4). Medications used for SAEs and genitourinary AEs and will be recorded for the duration of the study (2 years).

7.5 Follow-up of Recurrent Disease

On any surveillance cystoscopy, if the patient is found to have a recurrence with histology other than Ta, G1-G2 and requires additional therapy, the follow-up surveillance cystoscopy window is 3 months ± 20 days from the start of the additional therapy.

8. STUDY DRUG

8.1 Composition of EOquin®

EOquin® (apaziquone for intravesical instillation) is a sterile, non-pyrogenic, lyophilized product supplied in clear glass vials. It contains 4 mg apaziquone, mannitol and sodium bicarbonate. After reconstitution, EOquin® has a reddish appearance similar to that of cranberry juice.

8.2 Composition of Matching Placebo

Matching placebo containing FD&C red dye #40, sodium chloride and mannitol is supplied in identical appearing vials. Reconstitution and instillation procedures for placebo are the same as for EOquin®.

8.3 Composition of Diluent

8.3.1 Diluent for EOquin®

The diluent for EOquin contains a solution of sodium bicarbonate, propylene glycol and disodium EDTA in sterile water

8.3.2 Diluent for Placebo

The diluent for placebo contains 9 mg/mL sodium chloride

8.4 Dose of Study Drug

4mg of EOquin in 40 mL of diluent will be administered intravesically via an indwelling Foley catheter and retained for one hour.

8.5 Shipping of the Study Drug

Study drug is shipped on cool packs in insulated containers.

8.6 Storage of Study Drug

Study drug kits are to be refrigerated (approximately 2-8°C) in a secure area. Study drug should be protected from direct light.

Because patient specific supplies will be provided to sites, diluent and sterile water for injection will be stored with the study drug in the refrigerator at approximately 2-8°C.

8.7 Supply and labeling of Study Drug and Diluent

8.7.1 For Randomization Numbers: 1001 – 1336

Study drug will be provided by the Sponsor as patient specific boxes containing study drug, 2 ampoules of diluent (10 mL each) and a 20 mL vial of sterile water for injection. Each box will be labeled (white label) with the patient's randomization number. Each vial of the study drug will be labeled as below:

PATIENT RANDOMIZATION #

Store in refrigerator – Protect from light - Sterile

EOquin® or Placebo for intravesical administration

See Protocol SPI 611 for reconstitution directions

Caution: New Drug Limited by U.S. Federal Law to Investigational Use

Spectrum Pharmaceuticals, Inc., 157 Technology Dr., Irvine, CA 92618

The Diluent will be labeled as below:

PATIENT RANDOMIZATION #

May be refrigerated or stored at room temperature – Sterile

Diluent for EOquin® or Placebo

See Protocol SPI 611 for reconstitution directions

Caution: New Drug Limited by U.S. Federal Law to Investigational Use

Spectrum Pharmaceuticals, Inc., 157 Technology Dr., Irvine, CA 92618

8.7.2 For Randomization Numbers: 1337 – 1900

Study drug will be provided by the Sponsor as patient specific boxes containing study drug and diluent. Each box will be labeled (yellow label) with the patient's randomization number. Each vial of the study drug will be labeled as below:

PATIENT RANDOMIZATION #

Store in refrigerator – Protect from light - Sterile

EOquin® or Placebo for intravesical administration

See Protocol SPI 611 for reconstitution directions

Caution: New Drug Limited by U.S. Federal Law to Investigational Use

Spectrum Pharmaceuticals, Inc., 157 Technology Dr., Irvine, CA 92618

The Diluent vial will be labeled as below:

PATIENT RANDOMIZATION #

May be refrigerated or stored at room temperature – Sterile

Diluent for EOquin® or Placebo

See Protocol SPI 611 for reconstitution directions

Caution: New Drug Limited by U.S. Federal Law to Investigational Use

Spectrum Pharmaceuticals, Inc., 157 Technology Dr., Irvine, CA 92618

8.7.3 For Randomization Numbers: 4501-4580

Study drug will be provided by the Sponsor as patient specific boxes containing study drug and diluent. Each box will be labeled (yellow label) with the patient's randomization number. Each vial of the study drug will be labeled as below:

Study Ref: SPI-611 EudraCT No: 2009-015404-26

1 vial containing 4 mg EOquin® (apaziquone) or Placebo (10 mL vial).

Sterile lyophilized powder for reconstitution for intravesical instillation.

For clinical trial use only. Store at 2-8°C.

Batch No: Expiry Date: _ _/_ _ _ _

Sponsor: Spectrum Pharmaceuticals, Inc., 157 Technology Dr., Irvine, CA 92618, USA

Tel: 001 949 743-9246

The Diluent vial will be labeled as below:

Study Ref: SPI-611	EudraCT No: 2009-015404-26
1 vial containing 45 mL Diluent for EOquin® (apaziquone) or Placebo (50 mL vial).	
Sterile liquid for intravesical instillation.	
For clinical trial use only.	Store at 2-8°C.
Batch No:	Expiry Date: _ _/_ _ _ _
Sponsor: Spectrum Pharmaceuticals, Inc., 157 Technology Dr., Irvine, CA 92618, USA	
Tel: 001 949 743-9246	

8.8 Preparation of Study Drug for Randomization Numbers: 1001 - 1336

Equipment needed: one vial of study drug, two 10 mL ampoules of Diluent, sterile water for injection, one 50 or 60 mL Luer-lok syringe, catheter tip adapter, 18 gauge needle, protective clothing. **Study drug for instillation should be prepared on the day of surgery after the patient's TUR**. The prepared instillate is stable for 8 hours at room temperature.

1. Wearing appropriate protective clothing, draw up approximately 5 mL of the diluent and inject it into the vial of study drug.

2. Gently agitate the vial of study drug until no undissolved particles remain.

3. Using the 50 or 60 mL syringe, withdraw the dissolved study drug from its vial. (Note: if vacuum remains in the vial, injecting air into the vial first will ease the removal of study drug.

4. Using the same 50 or 60 mL syringe, draw up the remaining 5 mL of diluent from the already opened ampoule and 10 mL from the second ampoule.

5. Mix by inverting the syringe at least 10 times.

6. Using the same syringe, draw up 20 mL of **sterile water** for injection.

7. The final volume of instillate in the syringe should be 40 mL

8. Again, invert the syringe at least 10 times to insure adequate mixing.

Reconstituted study drug is stable at room temperature for up to eight hours. If the reconstituted product is not to be used within eight hours, it should be discarded.

8.9 Preparation of Study Drug for Randomization Numbers 1337 – 1900 & 4501-4580

Equipment needed: one vial of study drug, one vial of diluent containing 45 mL of diluent, one 50 or 60 mL Luer-lok syringe, catheter tip adapter (supplied), 18 gauge needle, protective clothing. **Study drug for instillation should be prepared on the day of surgery after the patient's TUR**. The prepared instillate is stable for 8 hours at room temperature.

1. Wear protective clothing

2. Draw up 40 mL of diluent in the syringe (approximately 5 mL will remain in the vial)

3. Inject approximately 5-10 mL of diluent into the study drug vial

4. Gently agitate the vial and attached syringe until no undissolved particles are visible (Do not detach the syringe and the study drug vial)

5. Withdraw all dissolved study drug into the syringe

6. Withdraw the syringe from the study drug vial

7. Cover the needle with needle cover

8. Invert the syringe at least 10 times to ensure adequate mixing

9. Carefully expel all trapped air in the syringe

10. The final volume in the syringe should be 40 mL

Reconstituted study drug is stable at room temperature for up to eight hours. If the reconstituted product is not used within eight hours, it should be discarded.

8.10 Criteria for Mixing Study Drug

If study drug is reconstituted and not used it may be difficult to resupply the used kit in a reasonable time. Therefore patient eligibility should be confirmed **prior** to drug reconstitution. Please make sure that all of the following criteria are met prior to drug reconstitution:

- Patient has no more than 4 tumors
- No single tumor is greater than 3.5 cm
- Visual appearance consistent with a Ta, low grade histology
- No evidence of bladder perforation
- Complete hemostasis is obtained

8.11 Administration of Study Drug

Study drug is to be instilled into the bladder via an indwelling Foley catheter within 6 hours of TUR-BT. For this purpose, a catheter tip adapter has been supplied. Remove the 18-gauge needle from the syringe and attach the adapter. After hemostasis is obtained, the bladder should be emptied and the catheter-tip adapter attached to the Foley catheter. Slowly inject the previously reconstituted study drug taking care not to introduce air into the bladder. Clamp the Foley catheter for 60 minutes.

8.12 Disposal of Study Drug

At the end of the 60-minute period of retention, study drug should be carefully drained into a suitable container and disposed of according to the institution's policies for disposal of hazardous waste.

8.13 Product Accountability

The Investigator and the investigational pharmacist must maintain accurate accounting of investigational product. During the study, the following information must be recorded:

- Date of receipt, quantity and identification of the product received from the Sponsor
- ID number of the patient to whom the product is dispensed
- The date(s) and quantity of the product dispensed
- Dates and quantity of product returned, lost or accidentally or deliberately destroyed

Accountability Records will be provided by the Sponsor. They must be kept current and must be readily available for inspection.

The Investigator should not return clinical study materials to the Sponsor unless specifically instructed to do so by the Sponsor. All used vials of Study drug and diluent should be destroyed as per the institution's policy.

All expired vials of study drug and diluent should be retained. The CRA will periodically conduct an accountability of the expired vials and authorize their destruction. If the participating pharmacy is prohibited by institutional policy from retaining expired vials, the investigational pharmacist will then be responsible for documenting the destruction of the vials.

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9. COMCOMITANT AND PROHIBITED MEDICATIONS

9.1 Concomitant Medications

For all patients, subsequent intravesical therapies (chemo and immunotherapy) will be recorded. Patients may use non-prescription analgesics or antipyretics to manage side effects associated with TUR-BT and administration of study drug. The Investigator may also prescribe standard postoperative medications.

9.2 Prohibited Medications

Prior to recurrence, patients with tumor histology of Ta, G1-G2 may not receive other medications to treat bladder cancer.

10. EFFICACY ASSESSMENTS

The primary efficacy assessment will be the recurrence rate at 2 years in patients with Ta, G1-G2 histology receiving one immediate instillation of EOquin® or placebo following TURBT. These patients will be assessed cystoscopically at three-month intervals calculated from the time of randomization. For patients with higher grade and stage tumors, recurrence will be assessed cystoscopically at 3-month intervals calculated from the time of start of their additional chemo- or immunotherapy. The date of the biopsy procedure at which the bladder tumor was confirmed histologically will be used as the date of recurrence. Tumor stage and grade will be assessed by a blinded central laboratory that specializes in urologic pathology. Urine cytology will not be considered as histologic confirmation of recurrence. Patients who recur will continue to be followed for two years after randomization.

11. SAFETY ASSESSMENTS

11.1 Definitions

11.1.1 Definition: Adverse Event

An adverse event (AE) is any unfavorable and unintended sign, symptom, or disease experienced by a study participant while in a clinical study, whether or not considered related to the investigational product. Examples include: reactions or side effects, a pre-existing condition that worsens in severity or frequency, a concurrent illness, an injury, or a clinically significant laboratory abnormality.

11.1.2 Definition: Serious Adverse Event

A serious adverse event is an AE that meets at least one of the following criteria:

- Is fatal
- Is life-threatening (A life-threatening AE is an AE that places the patient at immediate risk of death from the reaction as it occurred. It does not include a reaction that, had it occurred in a more severe form, might have caused death.)
- Requires inpatient hospitalization or prolongs an existing hospitalization (excluding emergency room visits)
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect in the offspring of an exposed patient
- Other important medical events that may not result in death, be life-threatening or require hospitalization may be considered SAEs when, based upon appropriate medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias, or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

The onset date of an SAE is defined as the date on which it met the criteria for an SAE; e.g., the date of admission to a hospital. The end date is the date on which it no longer met the criteria for an SAE, e.g., the date that the patient was discharged from a hospital.

11.1.3 Definition: Relationship to Investigational Product

In this study, the investigational product is EOquin™ / Placebo. The relationship of an adverse event to the investigational product should be classified by the Investigator using the following guidelines:

Definite: Experience follows a reasonable temporal association and could not have been explained by the patients underlying condition or is confirmed with a positive re-challenge.

Probable: Experience follows a reasonable temporal association, is confirmed by improvement upon discontinuation of investigational product, and is not reasonably explained by the patient's clinical state.

Possible: Experience follows a reasonable temporal association, but may have been produced by the patient's clinical state or other factors.

Unlikely: Experience does not follow a clear temporal association, and is probably produced by the patient's clinical state or other factors.

Unrelated: No relationship between the experience and administration of the investigational product.

For this study, adverse events that are considered by the Investigator to have a Possible, Probable, or Definite relationship to the investigational product are considered to be related to the investigational product.

11.1.4 Definition: Severity of Adverse Events

The severity of an AE should be defined according to the National Cancer Institute (NCI) Common Toxicity Criteria Adverse Events (CTC AE) Version 3.0 which will be provided to the sites. AEs that are **not** listed in the NCI Common Toxicity Criteria should be evaluated using the following guidelines:

1 = Mild AE: Awareness of symptom, but easily tolerated; usually transient requiring no special treatment; does not interfere with usual status or activities

2 = Moderate AE: May be ameliorated by simple therapeutic measures; may interfere with usual activities

3 = Severe AE: Incapacitating, inability to perform usual activities

4 = Life threatening or disabling AE

5 = Fatal AE

11.2 Adverse Event Reporting Period

Only those AEs that occur following randomization should be recorded on the Adverse Event CRF. All genitourinary AEs will be recorded for the patient's entire participation in the study. All other adverse events will be recorded for the first 6 months following randomization. All SAEs will be recorded for the patient's entire participation in the study.

11.3 Recording Adverse Events

Adverse events should only be recorded by an investigator or by a health-care provider qualified by training and experience. Patients should be asked in an open-ended manner about the occurrence of AEs. All AEs, regardless of whether or not ascribed to the investigational product, should be recorded in the CRF.

It is generally not necessary to record both a diagnosis and its associated symptoms and laboratory abnormalities. For example, if "acute renal failure" is recorded as an AE, "creatinine 5 mg/dL" need not be recorded.

If an AE necessitates a procedure, the description of the event (e.g., appendicitis) rather than the procedure (appendectomy) should be listed as the AE. However, if a procedure is performed for a reason other than an AE, the name of the procedure should be used as the name of the event.

If an AE was caused by the patient's bladder cancer,that fact should be clear from the name of the event, e.g., "hematuria due to bladder tumor."

11.4 Reporting Serious Adverse Events

11.4.1 Reporting Serious Adverse Events to the Sponsor

The Investigator must notify the Sponsor of any event that meets one of the criteria for an SAE within one working day of learning of the event. This notification should be made to:

Monica Rossi, MD
Director, Clinical Research
Spectrum Pharmaceuticals, Inc.
157 Technology Drive
Irvine, CA 92618
Office Phone: (949) 743-9284
Cell Phone: (760) 420-7683
SAE Fax: (949) 788-6711

Following receipt of this notification, the Sponsor, with input from the Investigator, will complete an SAE Report.

Each SAE should be followed until resolution, or until such time as the Investigator determines its cause or determines that it has become stable. Information pertaining to follow-up of SAEs should be immediately reported to the Sponsor.

11.4.2 Reporting Serious Adverse Events to the IRB/IEC

It is the Investigator's responsibility to report serious adverse events to the Institutional Review Board (IRB) or Independent Ethics Committee (IEC) according to the requirements of the IRB/IEC.

12. STATISTICAL DESIGN AND ANALYSIS

This section contains an overview of the statistical design and analysis plan for this study. A detailed description of the statistical design and analyses is contained in the Statistical Analysis Plan.

12.1 General Considerations

To evaluate the anti-tumor effect of EOquin® the efficacy analysis will compare the proportion of patients that recur on or before year 2 for patients randomized to the TUR-BT plus EOquin® group and for patients who are randomized to the TUR-BT plus placebo group.

To evaluate the safety profile of EOquin®, the safety analysis will be based on all patients randomized to the TUR-BT plus EOquin® group and on all patients who are randomized to the TUR-BT plus placebo group and have received an instillation of EOquin® or placebo, regardless of duration of retention, and who have had at least one safety assessment. Patients who have been randomized to the TUR-BT plus EOquin® group, but did not receive EOquin® will be excluded from the safety population.

12.2 Sample Size

The sample size was determined using the software nQuery Advisor 6.01 (Statistical Solutions Ltd., Cork, Ireland). This study has 1:1 randomization (TUR-BT plus EOquin® vs. TUR-BT plus placebo). All patients will be assigned to one of the two treatment arms. Based on a 2-sided test at the 5% significance level, a total of 562 patients randomized to TUR-BT plus EOquin® or TUR-BT plus placebo (281 per treatment group) will provide 80% power to detect a 12% reduction in the recurrence rate at year 2 for patients treated with TUR-BT plus EOquin® from an assumed 48% recurrence rate at year 2 for patients treated with TUR-BT plus placebo.

The randomizing physician must visually estimate the stage and grade of the bladder tumors removed prior to randomization and ensure they appear to be Ta, G1 or Ta, G2. Since randomized study treatment must be administered within 6 hours of

TUR-BT, patients must be randomized prior to definite staging and grading of the tumor by the pathologist. We estimate the randomizing physician will be incorrect in their visual assessment of tumor stage and grade approximately 28% of the time. Therefore, up to 800 patients will be enrolled in order to achieve the target enrollment of 562 Ta, G1 or Ta, G2 patients randomized to TUR-BT plus EOquin® or TUR-BT plus placebo.

12.3 Analysis of Efficacy Endpoints

12.3.1 Primary endpoint

The primary efficacy analyses will be conducted on all Ta G1-G2 patients. The primary efficacy parameter is recurrence rate at year 2. The recurrence rate is defined as the proportion of patients with histologically confirmed recurrence of the bladder tumor at any time after randomization and on or before year 2. The date of the procedure at which the bladder tumor was confirmed histologically will be used as the date of recurrence. Additional efficacy analyses of the primary end point will be conducted on the intent-to-treat population, i.e., all randomized patients

12.3.2 Secondary endpoints

Additional variables of interest include progression to higher stage or grade, number of recurrences per patient, time to recurrence, disease free interval, disease free survival, and overall survival. The progression rate is defined as the percentage of recurrences that progress to either a higher stage or grade from the histologically confirmed stage and grade at time of randomization. The number of recurrences per patient is defined as number of cystoscopies positive for tumor during the course of the study. Time to recurrence is defined as the number of months from randomization to histologically confirmed recurrence of the patient's bladder tumor. Patients will be censored at time of death for time to recurrence; Disease Free Interval (DFI) is defined as the number of months from randomization to histologically confirmed progression of the patient's bladder tumor or death from any cause (definition requested by FDA); Disease Free

Survival (DFS) is defined as the number of months from randomization to histologically confirmed recurrence of the patient's bladder tumor or death from any cause; and Overall Survival (OS) is defined as the number of months from randomization to death from any cause.

12.4 Analysis Methods

For all binomial variables (i.e., recurrence rate, progression rate) the variables will be reported by calculating the proportion of patients with endpoints and the treatment difference will be analyzed using the Mantel-Haenszel Chi-Square.

For all time-to-event variables (i.e., time to recurrence, disease free interval, disease free survival, overall survival), the distribution of time will be displayed using Kaplan-Meier curves, and the treatment difference will be analyzed using a log-rank test.

For all continuous variables (i.e., number of recurrences per patient) the variables will be reported by calculating the mean, median and other summary statistics. The treatment difference will be analyzed using an analysis of variance (ANOVA) model with treatment in the model. Study center will be added to the models to test for treatment by center interactions.

All statistical analyses will be two sided and will be performed at the 5% significance level. All secondary analyses will be considered exploratory.

12.5 Analysis of Safety Endpoints

Safety analysis will include all patients randomized to the TUR-BT plus placebo group and all patients randomized to the TUR-BT plus EOquin® group who have received at least one dose of EOquin® and have had one safety assessment **(see section 12.1)**. Patients who have been randomized to the TUR-BT plus EOquin® group, but did not receive EOquin® will be excluded from the safety population.

12.5.1 Retention of Bladder Instillate

The duration of retention of instillate in the bladder will be recorded, as well as tolerability issues related to retention.

12.5.2 Adverse Events

AEs will be listed by patient ID number. Deaths and other SAEs will be listed and summarized by patient ID number. Additionally, AEs leading to discontinuations will be listed separately. Incidence of AEs will be summarized by preferred term, maximum grade reported, and relationship to study treatment. All AE tables will be presented by treatment group.

12.5.3 Bladder Capacity

Functional bladder capacity will be studied in a random subset of 150 patients at US sites. 3-day voiding diaries will record frequency and volume of urination and will be reported at screen, at year 1 and year 2 for both treatment groups. Also, voided volume and post void residual volume, obtained by ultrasound scan of the bladder, will be summed to estimate total bladder capacity. Summary statistics will be reported for all measures of bladder capacity by treatment group.

12.5.4 Laboratory Tests

The laboratory tests will be listed by patient ID number and visit number. In these listings, any abnormally high or low values will be flagged according to the standard normals of the laboratory. Laboratory tests will be displayed over time by Box Whisker plot.

13. ETHICAL AND REGULATORY CONSIDERATIONS

13.1 Protocol and Regulatory Compliance

The Investigator must conduct the study according to this protocol.

The study must be conducted by all Investigators in compliance with Good Clinical Practices (GCP) as defined in the U.S. FDA Code of Federal Regulations 21 CFR 312 (Investigational New Drug Application), 21 CFR 50 (Protection of Human Subjects), 21 CFR 54 (Financial Disclosure by Clinical Investigators), 21 CFR 56 (Institutional Review Boards) and ICH guidelines (Guideline to Good Clinical Practice).

13.2 Protocol Amendments

Any changes to this protocol will be initiated by the Sponsor as a protocol amendment. The Investigator must submit the amendment to the IRB/IEC, with a revised Informed Consent Document if applicable. The Investigator must receive written approval from the IRB/IEC before the amendment may take effect.

13.3 Regulatory Binder

To be in compliance with GCPs, the Investigator must maintain accurate, complete, and organized documentation supporting the conduct of the study. This documentation includes, but is not limited to, the following: study personnel's qualifications and training, IRB/IEC approvals and communications, communications with the Sponsor, Site Signature & Responsibility Log, laboratory accreditations and reference ranges, Form FDA 1572s, and Informed Consent Documents (copies of IRB/IEC-approved versions, signed/dated originals, or copies for all enrolled patients).

13.4 Informed Consent

Prior to the performance of any protocol-specific procedures, informed consent must be obtained and documented by the use of a written Informed Consent Document approved by the Sponsor and the IRB/IEC. The Informed Consent Document must be signed and dated by the patient or by the patient's legally authorized representative and by the person conducting the informed consent discussion. The Informed Consent Document must

fulfill the requirements as contained in the U.S. Code of Federal Regulations (21 CFR 50.25), the ICH guidelines (Section 4.8), and the Declaration of Helsinki. In addition to these requirements, the Informed Consent Document must contain wording whereby the patient permits the review of his/her relevant medical records by representatives of Spectrum Pharmaceuticals and by representatives of the U.S. Food and Drug Administration (FDA) or other applicable national or local regulatory or health authorities. The Informed Consent Document must be written in a language understandable to the patient or to the representative.

A signed and dated copy of the Informed Consent Document must be given to the person signing the document. The original must be retained by the Investigator with the study documentation and be available for inspection by persons conducting an audit of the study (e.g., regulatory authorities, Spectrum Pharmaceuticals representatives).

The Sponsor will provide a template Informed Consent Document to the study sites. Modifications to this template may be made by study site personnel to be in compliance with national, regional (e.g., state) or local laws and/or institutional requirements. All versions of the Informed Consent Document should be reviewed and approved by Spectrum Pharmaceuticals prior to the submission of the Informed Consent Document for IRB/IEC approval.

13.5 Institutional Review Boards and Independent Ethics Committees

The protocol, Informed Consent Document, patient recruitment procedures (e.g., advertisements), information about payments and compensation available to patients, and any amendments must be approved by a properly constituted IRB or IEC in compliance with current regulations of the U.S. FDA, ICH guidelines, and any country-specific regulations. Specifically, the study must not be initiated until the Investigator has provided Spectrum Pharmaceuticals with documentation of IRB/IEC approval of the protocol, the Informed Consent Document, and all recruiting materials. In addition, prior to their implementation or use, there must be documented IRB/IEC approval for the following: protocol amendments, revised Informed Consent Documents, patient

recruitment materials (e.g., advertisements), and study-related supplements that are provided to study patients.

13.6 IRB/IEC Communications

The Investigator must make timely and accurate reports to the IRB/IEC on the progress of the study, at intervals not exceeding one year, as well as satisfying any other local IRB/IEC regulations regarding reporting, including reporting on safety aspects of the study (e.g., SAEs, safety letters). The study must receive documented IRB/IEC approval annually. Furthermore, at the completion or early termination of the study, a final report must be made to the IRB/IEC by the Investigator within the applicable IRB/IEC timeframes.

It is the Investigator's obligation to maintain an IRB/IEC correspondence file and to make this available for review by Spectrum Pharmaceuticals representatives as part of the study monitoring process. Copies of all correspondence between the Investigator and the IRB/IEC (including all attachments to any correspondence) must be provided for the Spectrum Pharmaceuticals internal file.

13.7 Curriculum Vitae and Medical Licenses

The Principal Investigator is responsible for ensuring that the study is being conducted by qualified personnel. Documentation of these qualifications must be maintained within the Regulatory Binder, and includes the following:

Curriculum Vitae (CV): CVs for the Principal Investigator and all Subinvestigators listed on the Form FDA 1572 must be signed and dated. These CVs must show affiliation with the institution conducting the study and be current within two years of the personnel initiating their participation in the study.

Medical Licenses: Medical licenses (physicians, physician assistants, nurses) listed on the Form FDA 1572 must be kept current, and copies must be maintained in the Regulatory binder during the entire period of the person's participation in the study.

13.8 Patient Confidentiality

The Investigator must ensure that the patient's confidentiality is maintained. Patient medical information obtained for the purposes of this study is confidential, and disclosure to third parties, other than those noted below, is prohibited. Patients should not be identified by name, social security number or medical record number on any documents or materials (samples, slides) sent to Spectrum Pharmaceuticals or its representatives (e.g., data management organization) or during verbal communications. Patients should be identified only by their initials and protocol-assigned patient ID number. For those patients whose surgical specimen is processed and read by the central pathology laboratory, the patient's billing information will be requested by this laboratory and will not be shared with the sponsor or any of its affiliates or representatives.

For clinical sites in the US, study personnel should follow the requirements of the Health Insurance Portability and Accountability Act (HIPAA).

All clinical information is confidential, but data generated for this study must be available for inspection on request to representatives of the U.S. FDA, other national or local regulatory or health authorities, Spectrum Pharmaceuticals representatives, and the associated IRB/IEC.

All records must be kept in a secured area.

13.9 Financial Disclosure

Documentation of each Investigator's proprietary or financial interest in Spectrum Pharmaceuticals, Inc. is required by the U.S. Code of Federal Regulations (21 CFR 54). A financial disclosure form provided by the Sponsor must be completed, signed, and dated by the Principal Investigator and each Subinvestigator listed on the Form FDA 1572. This form must be executed prior to the personnel's participation in the study. The original form will be retained by the Sponsor. Each Investigator must inform the Sponsor of any change in his/her financial interest in the Sponsor for up to one year after the end of the study.

The U.S. Securities and Exchange Commission (SEC) prohibits any person who has material, non-public information concerning Spectrum Pharmaceuticals or a possible transaction involving Spectrum Pharmaceuticals from purchasing or selling securities in reliance upon such information or from communicating such information to any other person or entity under circumstances in which it is reasonably foreseeable that such person or entity is likely to purchase or sell such securities in reliance upon such information.

14. QUALITY ASSURANCE

14.1 Routine Clinical Site Monitoring

Spectrum Pharmaceuticals CRAs or representatives will make a pre-study site visit (if deemed necessary) to determine the qualifications of the Investigator, inspect the clinical facilities, and fully inform the Investigator of his/her responsibilities and the procedures for assuring adequate and correct documentation. During the course of the study, a Spectrum Pharmaceuticals CRA or designated representatives will make routine contacts (e.g., telephone communications or site visits) at appropriate intervals to review protocol compliance; to examine CRFs and individual patient's medical records, the Regulatory Binder, the investigational product handling and accountability procedures, and data recording practices; and to ensure that the study is being conducted in compliance with applicable requirements. CRF entries will be verified against source documentation.

The Investigator and the site personnel are expected to cooperate with Spectrum Pharmaceuticals CRAs and designated representatives and to provide, upon request, all relevant study documentation that is requested at each site visit.

14.2 Site Audits

The Investigator must permit inspection of the study files (e.g., source documentation such as clinic notes, nurses' notes, radiological and laboratory records, CRFs, Regulatory Binder) by a Sponsor representative and by authorized representatives of the U.S. FDA or other applicable regulatory agencies. If the site is informed of an inspection by any regulatory authority, the Investigator should notify Spectrum Pharmaceuticals immediately.

15. DATA MANAGEMENT AND RECORDKEEPING

15.1 CRF Completion and Transmittal

Spectrum Pharmaceuticals will supply a protocol-specific set of CRFs for each patient. CRFs should be completed in a timely manner and must be available for review during routine monitoring visits. All CRFs should be completed in black ink and in a legible manner. All references to specific patients must be made by use of initials and by patient ID number, not by name. Patient confidentiality should be maintained by obscuring all names, social security numbers or patient record numbers (using a black marker) in any reports or records sent to the Sponsor or its representatives. The Principal Investigator is responsible for reviewing each page of the CRF and for signing the appropriate forms. By signing the CRF, the Investigator attests to the accuracy and completeness of the information contained in the CRFs.

CRFs will be sent via facsimile transmission to the data management group no more than seven days from the patient visit. The Clinical Data Fax system will fax a receipt of confirmation of the CRF to the clinic.

At the completion or termination of the study, the original CRF will be collected by the Sponsor, and a copy will be maintained by the Investigator.

15.2 Data Corrections

All corrections to source documents or to entries in the CRF must be initialed and dated by the individual making the correction. Corrections must be made by drawing a single line through the incorrect entry and recording the correct entry nearby. Incorrect entries should not be obliterated; the original text should remain legible. Use of opaque correction fluid, correction tape, or highlighters is prohibited.

15.3 Record Retention

Records that individually or collectively permit the evaluation of the conduct of the study and the quality of the data produced with this study must be maintained for review by the Sponsor's representatives and by U.S. and non-U.S. regulatory authorities. The

Investigator must retain these records minimally for a period of two years following the date of the last marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region, or for at least two years following the formal discontinuation of clinical development of the investigational product. These documents should be retained for a longer period, however, if required by the applicable regulatory requirements or by an agreement with the Sponsor.

The Sponsor will inform the Investigator in writing when the study-related records are no longer needed. The Investigator must notify the Sponsor in writing at least 30 days prior to the intended date of disposal of any study records related to this protocol. If the Investigator leaves the institution where the study was conducted, the Investigator must inform the Sponsor in writing where the records associated with this protocol are archived and who is responsible for their security.

16. COMPENSATION, INSURANCE AND INDEMNITY

Information regarding compensation, insurance and indemnity will be provided to the Investigator in the Clinical Trial Agreement.

17. USE OR PUBLICATION OF STUDY-RELATED INFORMATION

All information obtained as a result of this study should be regarded as confidential.

Information regarding use or publication of study-related information will be provided to the Investigator in the Clinical Trial Agreement.

18. INVESTIGATOR AGREEMENT

A Multicenter, Randomized, Double-Blind, Placebo-Controlled, Phase 3 Trial of Single-Dose Intravesical EOquin® as a Surgical Adjuvant Instilled in the Early Postoperative Period in Patients Undergoing Transurethral Resection for Noninvasive Bladder Cancer

I understand that all information concerning this study supplied to me by Spectrum Pharmaceuticals, Inc. is confidential information. I have read this protocol and agree to conduct the study according to Good Clinical Practice Guidelines and in accordance with the Clinical Trial Agreement.

I understand that this protocol and all amendments must be submitted to the appropriate IRB/IEC.

Investigator Name (PLEASE PRINT): _____

Signature: _____ _____

Date

Please sign and return this agreement to:

Attn: Shanta Chawla, MD
Medical Monitor
Spectrum Pharmaceuticals, Inc.
157 Technology Drive
Irvine, CA 92618

Please keep a copy for your records.

19. FUNCTIONAL BLADDER CAPACITY

Approximately 10-15 US sites will be selected to assess functional bladder capacity.

Patients randomized at these sites will comprise the 150 patient cohort in whom functional bladder capacity will be assessed.

Procedure for Functional Bladder Capacity Assessment:

Initial Assessment: Prior to randomization
Follow up Assessment: At year 1 and at year 2

At each of these prespecified visits patients will be asked to void in the office (full bladder). The voided volume will be recorded.

Post void ultrasound will be obtained to assess post void residual (PVR).

Patients will also receive a 3-day voiding diary to record the frequency and volume of urine voided on 3 successive days. Patients will be given a graduated container/urinal and will be asked to void in the container. The baseline assessment must occur prior to the TUR-BT.

Procedure	Between screen and randomization	Year 1	Year 2
Voided volume (full bladder)	X	X	X
Post void residual volume (Bladder ultrasound)	X	X	X
3-day voiding diary (frequency and volume)	X	X	X

20. SCHEUDLE OF EVENTS

			Wk[2]		Month[4]							
		0	3		3	6	9	12	15	18	21	24
		VISIT NUMBER										
Procedure	**Scr**	**1**	**2**	**Add Rx[3]**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**
Obtain informed consent	X											
Medical history	X											
Vital signs	X	X	X		X	X	X	X	X	X	X	X
Weight	X											
Physical examination	X											
CBC/chemistry panel	X	X[5]	X		X							
Urine analysis[6]	X	X[5]	X		X	X	X	X	X	X	X	X
Pregnancy Test[1]	X											
Urine cytology	X					X		X		X		X
Functional Bladder Capacity[7]	X							X				X
TUR-BT		X										
Randomization		X										
Instill study drug		X										
Brief physical exam			X		X	X	X	X	X	X	X	X
Cystoscopy					X	X	X	X	X	X	X	X
Adverse Events		X	X		X	X	GU	GU	GU	GU	GU	GU
Con Meds		X	X		X	X	GU	GU	GU	GU	GU	GU

1 All females of childbearing potential
2. Window is ±10 days
3. Additional treatment for higher grade/stage patients only
4. Window is ±10 days for Ta, G1-G2 patients: Window is ±20 days for higher grade and stage patients
5 May be performed up to 24 hours prior to surgery
6 Urine dipsticks will be provided by the sponsor
7 performed at selected US sites only, prior to randomization includes voided volume+postvoid bladder scan+3 day voiding diary

21. RELEVANT LITERATURE REFERENCES

1. Network, N.C.C., *Clinical Practice Guidelines in Oncology. Bladder Cancer Version 1.* 2006.

2. DeVita, V., et al., *Cancer. Principles and Practice of Oncology.* 7th ed. 2005: Lippincott Williams and Wilkins. 1168-1173.

3. Botteman, M., et al., *The health economics of bladder cancer: a comprehensive review of the published literature.* Pharmacoeconomics, 2003. **21**(18): p. 1315-1330.

4. Sylvester, R., et al., *A single immediate postoperative instillation of chemotherapy decreases the risk of recurrence in patients with stage Ta T1 bladder cancer: a meta-analysis of published results of randomized clinical trials.* J Urol, 2004. **171**(6 Pt 1): p. 2188-2180.

5. Solsona, E., et al., *Effectiveness of single immediate mitomycin C instillation in patients with low risk superficial bladder cancer: Short and long-term follow-up.* J Urol, 1999. **161**(4): p. 1120-1123.

6. Schellens, J., et al., *Phase I and pharmacologic study of the novel indoloquinone bioreductive alkylating cytotoxic drug EO9.* J Natl Cancer Inst, 1994. **86**(12): p. 906-912.