Official Title:	**A Multicenter, Multi Arm, Randomized, Multi-Dose, Placebo-Controlled, Double-Blind, Phase 3 Study of Intravesical Apaziquone (EOquin®) as a Surgical Adjuvant in the Immediate Postoperative Period in Patients Undergoing Transutheral Resection for Non-Muscle Invasive Bladder Cancer**
NCT Number:	NCT02563561
Document Date:	Protocol Version 1.0: 06-August-2015

CONFIDENTIAL
CLINICAL STUDY PROTOCOL

TITLE PAGE

Study Title:	**A Multicenter, Multi-Arm, Randomized, Multi-Dose, Placebo-Controlled, Double-Blind, Phase 3 Study of Intravesical Apaziquone (EOquin®) as a Surgical Adjuvant in the Immediate Postoperative Period in Patients Undergoing Transurethral Resection for Non-Muscle Invasive Bladder Cancer**
Study Number:	**SPI-EOQ-13-305**
Study Phase:	Phase 3
Study Drug:	Apaziquone (EOquin®)
IND Number:	73,572
Sponsor(s):	Spectrum Pharmaceuticals, Inc. 157 Technology Drive Irvine, CA, USA

Protocol Version/Date: Original/06 Aug 2015

This study is to be conducted according to US and international standards of Good Clinical Practice (FDA Title 21 part 312 and International Conference on Harmonization guidelines), applicable government regulations and Institutional research policies and procedures.

Confidentiality Statement

The information contained in this document, particularly unpublished data, is the property or under control of Spectrum Pharmaceuticals, Inc. and is provided to you in confidence as an Investigator, potential Investigator, or consultant, for review by you, your staff, and an applicable Institutional Review Board/Ethics Committee. The information is only to be used by you in connection with authorized clinical studies of the investigational drug described in the protocol. You will not disclose any of the information to others without written authorization from Spectrum Pharmaceuticals, Inc. except to the extent necessary to obtain Informed Consent from those persons to whom the drug may be administered.

INVESTIGATOR SIGNATURE

Protocol Number: SPI-EOQ -13-305

A Multicenter, Multi-Arm, Randomized, Multi-Dose, Placebo-Controlled, Double-Blind, Phase 3 Study of Intravesical Apaziquone (EOquin®) as a Surgical Adjuvant in the Immediate Postoperative Period in Patients Undergoing Transurethral Resection for Non-Muscle Invasive Bladder Cancer

I have read this protocol and agree that it contains all the necessary details for performing the study in accordance with the Declaration of Helsinki and the International Conference on Harmonization (ICH) for Good Clinical Practice (GCP).

I will provide copies of the protocol and of the clinical and preclinical information on the investigational product, which was furnished to me by the Sponsor (Spectrum Pharmaceuticals, Inc.), to all members of the study team responsible to me who participate in the study. I will discuss this material with them to assure that they are fully informed regarding the study drug and the conduct of the study.

I will perform the study according to specifications outlined in the protocol and agree to implement protocol requirements only after the protocol and patient information/Informed Consent form have been approved by the Institutional Review Board/Ethics Committee (IRB/EC). I will submit any protocol modifications (amendments) and/or any Informed Consent form modifications to the IRB/EC, and approval will be obtained before any modifications are implemented.

I understand that the information presented in this study protocol is confidential, and I hereby assure that no information based on the conduct of the study will be released without prior consent from Spectrum Pharmaceuticals, Inc., unless this requirement is superseded by a regulatory authority (eg, FDA).

_____

Investigator Name (PLEASE PRINT):

Signature: _____ Date _____

SYNOPSIS

Title of Study: A Multicenter, Multi-Arm, Randomized, Multi-Dose, Placebo-Controlled, Double-Blind Phase 3 Study of Intravesical Apaziquone (EOquin®) as a Surgical Adjuvant in the Immediate Postoperative Period in Patients Undergoing Transurethral Resection for Non-Muscle Invasive Bladder Cancer

Name of Sponsor: Spectrum Pharmaceuticals, Inc.

Name of Investigational Product: Apaziquone (EOquin®)

Planned Number of Patients: Approximately 1869 patients will be enrolled to obtain 1557 evaluable patients across three treatment arms.

Study Centers: Approximately 100 study centers

Duration of Study: Approximately 5 years (3 years accrual + 2 years follow-up)	**Clinical Phase:** 3

Objectives:

Primary Objective(s)

- To evaluate the **Time to Recurrence** with either a one instillation of 4 mg apaziquone or two instillations of 4 mg apaziquone relative to placebo instillation following TURBT in patients with non-muscle invasive bladder cancer (NMIBC) who receive transurethral resection bladder tumor (TURBT)

Secondary Objectives

1. To evaluate the **2-Year Recurrence Rate** with either one instillation of 4 mg apaziquone or two instillations of 4 mg apaziquone relative to placebo instillation following TURBT in patients with NMIBC who receive TURBT.
2. To evaluate the **1-Year Recurrence Rate** with either one instillation of 4 mg apaziquone or two instillations of 4 mg apaziquone relative to placebo instillation following TURBT in patients with NMIBC who receive TURBT.
3. To evaluate the **Time to Progression** with either one instillation of 4 mg apaziquone or two instillations of 4 mg apaziquone relative to placebo instillation following TURBT in patients with NMIBC who receive TURBT
4. To evaluate the safety with either one instillation of 4 mg apaziquone or two instillations of 4 mg apaziquone relative to placebo instillation following TURBT in patients with NMIBC

Study Design and Treatment Plan:

This is a Phase 3, randomized, multicenter, multi-arm, placebo-controlled, double-blind study of apaziquone in patients with ≤4 non-muscle invasive bladder tumors, ≤3.5 cm in diameter, all of which must have been fully resected at TURBT.

In addition to **Screening**, patients will undergo an assessment of urothelial carcinoma of the bladder via cystoscopy for clinically apparent tumor Ta, G1-G2.

Following TURBT on **Day 1**, eligible patients will be randomized to one of three treatment arms in a 1:1:1 ratio:

- **Arm 1- One Dose of Apaziquone:**
  - **Day 1:** administration of 4 mg of apaziquone 60 ± 30 minutes post-TURBT
  - **Day 15** (±5 days)**:** administration of placebo
- **Arm 2- Two Doses of Apaziquone**:
  - **Day 1:** administration of 4 mg of apaziquone 60 ± 30 minutes post-TURBT

- **Day 15** (±5 days)**:** administration of 4 mg of apaziquone

- **Arm 3**- **Placebo:**
  - **Day 1:** administration of placebo 60 ± 30 minutes post-TURBT
  - **Day 15** (±5 days)**:** administration of placebo

Once randomized, **Day 1** study drug instillation will occur 60 ± 30 minutes post TURBT. Patients will return on **Day 15 (**±5 days) for a second instillation unless their pathology results are available and show non Ta, G1-G2 histology; in the absence of local pathology results by the **Day 15** visit, patients will receive a second instillation of study drug. All histology specimens will be reviewed by a local pathology laboratory and all clinical treatment decisions and study analyses will be based on the local pathology review. Patients whose pathology is other than Ta, G1-G2 will be followed for safety at **Day 35** (±5 days) from the last dose of study drug and then discontinued from the study.

Patients with pathology confirmed Ta, G1-G2 disease will be followed according to the schedule below:

- Cystoscopic examination and urine cytology every 90 days (±10 days) (calculated from date of TURBT) through 24 months for tumor recurrence and progression.
- If at any time during the 24 month follow up period there is a tumor recurrence, the patient will continue on study with follow-up cystoscopic examination and urine cytology every 90 days (±10 days) (calculated from date of TURBT) through the end of 24 months. Patients with a recurrence are permitted to have a follow-up TURBT.
- If at any time during the 24 month follow up period there is a tumor recurrence and/or patient is started on another therapy, the patient will be followed by telephone, for safety every 90 days (±10 days) (calculated from date of TURBT) through the end of 24 months.

Duration of Study: The duration of the study for each patient will be approximately 24 months including:

- **Screening Period**: 30-days
- **Treatment Period**: **Day 1** and **Day 15** (±5 days)
- **Safety and Follow-up Period**: 24-months

Patient Replacement Strategy: Patients who discontinue from the study after the initial TURBT and study drug instillation will not be replaced.

Inclusion & Exclusion Criteria:

Inclusion Criteria:

1. Patient must have a diagnosis with urothelial carcinoma of the bladder with clinically apparent tumor Ta, G1-G2.
2. Patient will have ≤4 tumors, none of which exceeds 3.5 cm in diameter.
3. Patient must be willing to give written informed consent and must be able to adhere to dosing and visit schedules, and meet all study requirements.
4. Patient is at least 18 years of age at randomization.
5. Patient must be willing to practice two forms of contraception, one of which must be a barrier method, from study entry until at least 35 days after the last dose of the study drug.
6. Females of childbearing potential must have a negative pregnancy test within 30 days prior to randomization. Females who are postmenopausal for at least 1 year (defined as more than 12 months since last menses) or are surgically sterilized do not require this test.

Exclusion Criteria:

1. Patient has an active concurrent malignancy/life-threatening disease. If there is a history of prior malignancies/life-threatening diseases, the patient is to be disease free for at least 5 years. Patients with other prior malignancies less than 5 years before study entry may still be enrolled if they have received

treatment resulting in complete resolution of the cancer and currently have no clinical, radiologic, or laboratory evidence of active or recurrent disease.

2. Patient has positive urine cytology for malignancy at **Screening**.
3. Patient has an active uncontrolled infection, including a urinary tract infection, underlying medical condition, or other serious illness that would impair the ability of the patient to receive protocol treatment.
4. Patient has used any investigational drugs, biologics, or devices within 30 days prior to study treatment or plans to use any of these during the course of the study.
5. Patient has had any prior intravesical chemotherapy, immunotherapy, or previous exposure to apaziquone.
6. Patient has or has ever had
   - Upper tract Transitional Cell Carcinoma (TCC).
   - Urethral tumor (prostatic urethra included).
   - Any invasive bladder tumor known to be other than tumor Ta, G1-G2.
   - Any evidence of lymph node or distant metastasis.
   - Any bladder tumor with histology other than TCC.
   - Carcinoma in situ (CIS).
7. Patient has a tumor in a bladder diverticulum.
8. Patient has received any pelvic radiotherapy (including external beam and/or brachytherapy.)
9. Patient has a bleeding disorder or a screening platelet count $<100\times10^9$/L.
10. Patient has screening hemoglobin <10 mg/dL.
11. Patient has any unstable medical condition that would make it unsafe to undergo TURBT.
12. Patient has a history of interstitial cystitis.
13. Patient has a history of allergy to red color food dye.
14. For patients with recurrent tumor, the patient had at least a 6-month cystoscopically-confirmed tumor-free interval between the last tumor recurrence and screening cystoscopic examination.
15. Patient is pregnant or breast-feeding.

Dose and Route of Administration:

The first dose of either 4 mg/40 mL apaziquone or placebo will be administered by intravesical administration into the bladder at 60 ± 30 minutes post TURBT (randomization date, **Day 1**) via an indwelling 100% Silicone Foley catheter. The second dose of either 4 mg/40 mL apaziquone or placebo will administered by intravesical administration via an indwelling catheter on **Day 15 (**±5 days).

Efficacy Assessments:

Cystoscopy every 90 days (±10 days) calculated from the date of TURBT through 24 months.

Primary Endpoint:

- **Time to Recurrence** in patients with either one instillation of 4 mg apaziquone or two instillations of 4 mg apaziquone relative to placebo instillation following TURBT.

Secondary Endpoints:

1. The **2-Year Recurrence Rate** of bladder cancer
2. The **1-Year Recurrence Rate** of bladder cancer
3. **Time to Progression** to higher stage

Safety Assessments:

Safety will be assessed by reported/elicited AEs, laboratory assessments, and physical examinations.

Safety Endpoints

- All adverse events
- Related adverse events
- Serious Adverse Events (SAEs)
- AEs leading to discontinuation
- Vital signs (temperature, blood pressure and heart rate) and routine laboratory parameters (complete blood count with 3-part differential, chemistry)
- Deaths

Adverse Event and Serious Adverse Event Reporting:

All adverse events from the time of randomization until 35 days after the last dose of study treatment will be recorded. After 35 days and through 24 months, only SAEs and AEs ≥Grade 3 will be recorded. From the time the study Informed Consent is signed through the day of study drug administration, only SAEs that are related to study procedures are to be recorded.

Statistical Methods:

A formal statistical analysis plan (SAP) will be provided with full technical details of the methods of analysis of study data.

The primary analysis population is the **Target (Ta, G1-G2) Population**. The **Target (Ta, G1-G2) Population** includes all patients who have undergone TURBT and have local pathology confirmed Ta, G1-G2 NMIBC. The **Safety Population** includes all patients with TURBT and have received at least one instillation of study drug (apaziquone or placebo).

The enrolled patients will be randomized in a 1:1:1 ratio into one of the following three treatment arms: **Arm 1:** one dose of apaziquone, **Arm 2:** two doses of apaziquone, or **Arm 3:** placebo, using a permuted block design. The primary endpoint of the study is **Time to Recurrence** in the **Target (Ta, G1-G2) Population**. The primary endpoint analysis involves two pairwise tests of comparisons: one dose of 4 mg apaziquone vs. placebo and two doses of 4 mg apaziquone vs. placebo. No comparison of **Arm 1** (one dose of apaziquone) vs. **Arm 2** (two doses of apaziquone) will be performed. The primary analyses of tests of pairwise comparisons of **Arm 1** (one dose of apaziquone) vs. **Arm 3** (placebo) and **Arm 2** (two doses of apaziquone) vs. **Arm 3** (placebo) arms will be performed using 2-sided log-rank test each at 5% level of significance.

The primary analysis will be conducted using a hierarchical procedure of hypothesis testing. Hochberg procedure will be used to control the overall Type I error rate due to multiple comparisons for the primary endpoint. If the larger p-value of the two comparisons (one dose of apaziquone vs placebo, two doses of apaziquone vs. placebo) is ≤0.05, then both comparisons will be considered statistically significant. If the larger p-value of the two comparisons is >0.05 but the smaller p-value is ≤0.025, the comparison associated with the smaller p-value will be considered statistically significant. If the larger p-value of the two comparisons is >0.05 and the smaller p-value is >0.025, then neither comparison will be considered statistically significant. If both comparisons are statistically significant, the Type I error will be used to test the list of secondary endpoints for each pairwise comparison in the order listed until the p-value of a particular comparison is >0.05.

Approximately 1869 patients will be enrolled and treated in this study. Accrual time is estimated as 36 months and follow-up time as 24 months. Assuming 54% of patients will be recurrence-free for placebo and 60.5% recurrence-free for the apaziquone treatment arms (assumed to be the same for each arm) at the end of 24 month follow-up, sample sizes of 519 confirmed Ta, G1-G2 patients per treatment arm will achieve 80% power to detect superiority in each comparison, using log-rank test at 5% level of significance. At the 2 year follow up, this total number of patients is assumed to provide 336 recurrence events in the **Placebo Treatment Arm** and 295 events in each **Apaziquone Treatment Arm**. Based on the data from prior studies on misclassification of stage and grade diagnosis at **Screening** for enrollment, an additional 20% of patients need to be enrolled. Therefore, the study will enroll and randomize 623 patients per arm for a total of 1869 patients.

To determine whether enrollment should be discontinued in an inefficacious arm, a futility analysis will be conducted once 100 of the expected 336 recurrence events are observed in the **Placebo Treatment Arm** of the study. The required number of events will be determined by independent, unblinded data monitoring personnel.

The final analysis of **Time to Recurrence** will be conducted once all 336 recurrence events in the **Placebo Treatment Arm** are accrued.

If both primary endpoint comparisons are statistically significant, secondary analyses will be conducted using pairwise comparisons between the **Apaziquone Treatment Arms** vs. the **Placebo Treatment Arm** using the same procedure as above. All treatment emergent adverse events will be graded according to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 4.03, and grouped by the MedDRA System Organ Class and Preferred Term, and summarized by worst grade severity per patient.

Original Protocol: 06 Aug 2015

Figure 1 Study Design Diagram

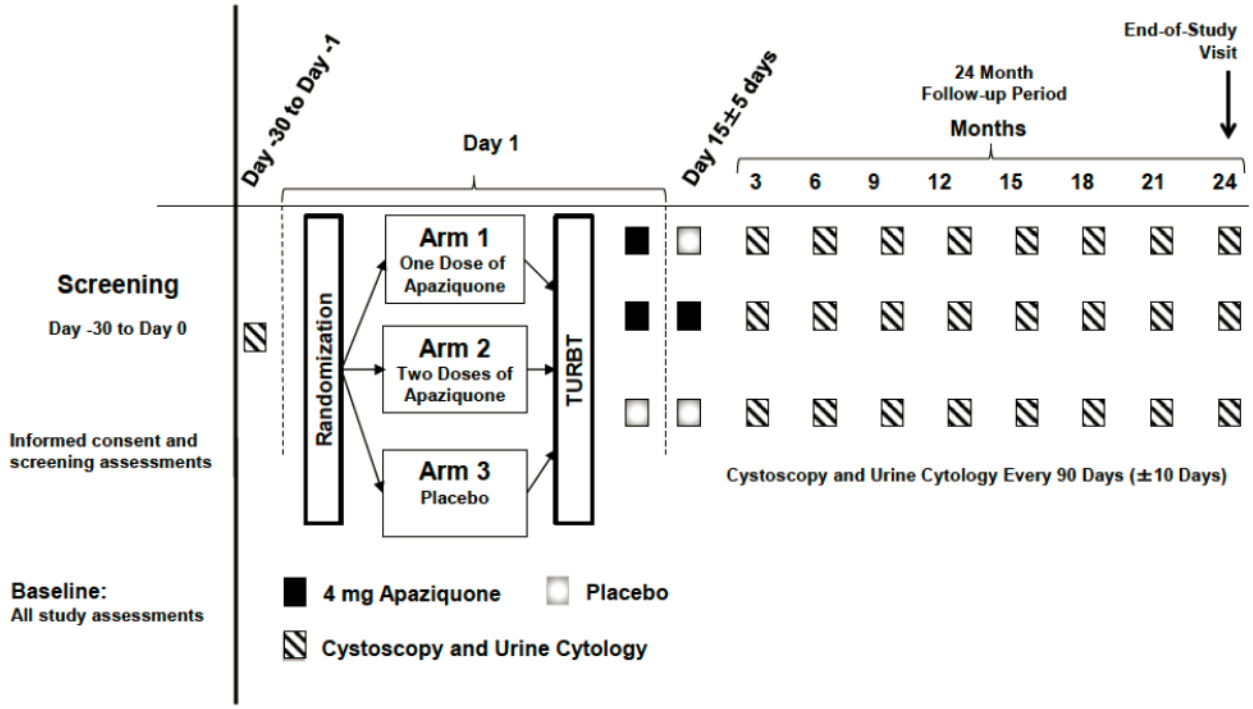


Figure 2 Study Flow Chart

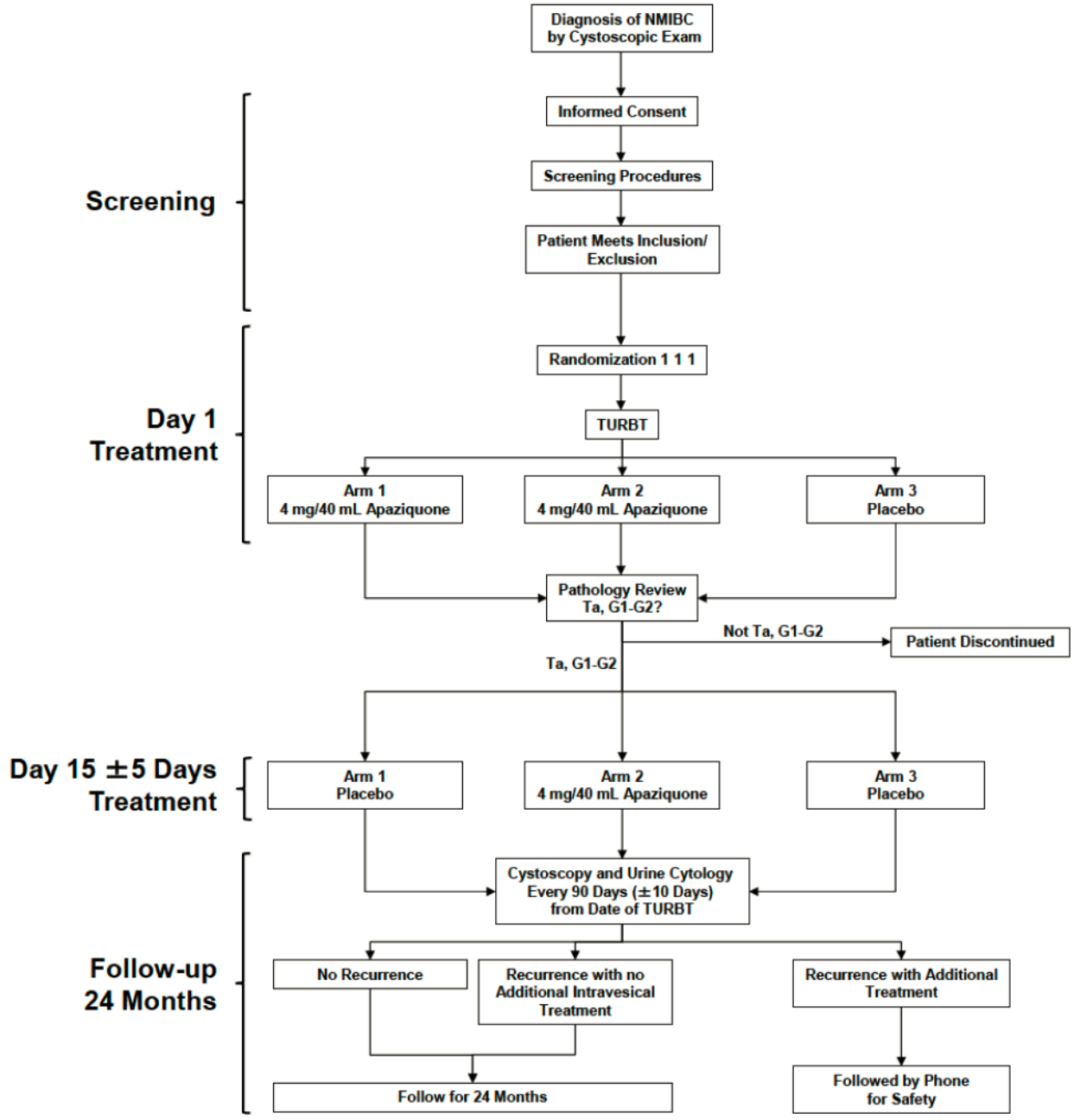


Table 1 Schedule of Study Assessments and Procedures

Assessments	Screening	Randomization/ Treatment #1	Treatment #2	Post-TURBT Follow-up [a] (90 ± 10 days)							End-of-Study Visit
	Day -30 to 1	Day 1	Day 15 (±5 days)	Month 3	Month 6	Month 9	Month 12	Month 15	Month 18	Month 21	Month 24 [b]
	Visit 0	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8	Visit 9	Visit 10
Informed Consent (IC)	x										
Cystoscopy	x [c]			x	x	x	x	x	x	x	x
Medical history	x										
Vital signs	x	x	x								
Weight and height	x										
Physical examination [d]	x										x
Complete Blood Count	x	x [e]	x								
Chemistry	x	x [e]	x								
Pregnancy test	x										
Urine dip stick	x	x [e]	x	x	x	x	x	x	x	x	x
Urine cytology	x	x	x	x	x	x	x	x	x	x	x
TURBT		x									
Randomization		x									
Apaziquone or Placebo instillation [f]		x	x								
Concomitant medications	x	x	x	x	x	x	x	x	x	x	x
Adverse event assessment [g]	x	x	x	x	x	x	x	x	x	x	x

a) Follow up visits, cystoscopies, and urine cytology for patients with Ta, G1-G2 histology only are to be conducted every 90 days (±10 days) calculated from the date of TURBT for 24 months.
b) For Patients who complete 24 months of follow-up, **Month 24** visit (**Visit 10**) will be the **End-of-Study Visit**.
c) The qualifying cystoscopy may be performed up to 30 days prior to signing the informed consent. Patients with the study qualifying tumor number, size, and appearance may be presented with the study informed consent.
d) A complete physical examination will be performed at **Screening** and at the **Month 24/End-of-Study Visit**. At all other visits, a physical examination is only required as indicated.
e) If the screening assessments for the physical examination, hematology, chemistry, urine dipstick were performed within 3 days (72 hours) prior to **Day 1**/TURBT, these assessments do not need to be repeated at the **Day 1** visit.
f) Instillation of study drug (apaziquone or placebo) is to be performed at 60 ± 30 minutes post-TURBT procedure on **Day 1** and is to be retained in the bladder for 60 minutes (±5 minutes).

g) All adverse events from the time of randomization until 35 days after the last dose of study treatment will be recorded. After 35 days and through 24 months, only SAEs and AEs ≥Grade 3 will be recorded.

TABLE OF CONTENTS

List of Tables

List of Figures

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation/ Acronym	Definition
AE	Adverse event
AUA	American Urological Association
BCG	Bacillus Calmette-Guérin
BUN	Blood urea nitrogen
CBC	Complete blood count
CFR	Code of Federal Regulations
CR	Complete response
CI	Confidence interval
CIS	Carcinoma *in situ*
CRF	Case report form
CRA	Clinical Research Associate
CRF	Case Report Form
CTCAE	Common Toxicity Criteria Adverse Events
CUP	Carcinoma of unknown primary
EAU	European Association of Urology
EC	Ethics Committee
FDA	Food and Drug Administration
FICBT	First International Consultation on Bladder Tumors
GCP	Good Clinical Practice
IBCG	International Bladder Cancer Group
ICH	International Conference on Harmonization
IRB	Institutional Review Board
LLOQ	Lower limit of quantitation
NCI	National Cancer Institute
NCCN	National Comprehensive Care Network
NMIBC	Non-muscle Invasive Bladder Cancer
NR	No Response
NSCLC	Non-small cell lung cancer
SAE	Serious adverse event
SAER	Serious adverse event report
TCC	Transitional cell carcinoma
TEAE	Treatment-emergent adverse event

Abbreviation/ Acronym	Definition
TURBT	Transurethral resection bladder tumor
US	United States of America
WHO	World Health Organization

1 INTRODUCTION AND BACKGROUND

1.1 Non-Muscle Invasive Bladder Cancer

In the US, 74,000 new cases of bladder cancer and 16,000 deaths are projected to occur in 2015 [1]. The median age at diagnosis is 73 years and the treatment of bladder cancer is frequently complicated by the presence of significant comorbidities [2].

The clinical spectrum of bladder cancer can be divided into 3 broad categories that differ in prognosis and management. The first category consists of non-muscle invasive bladder cancer (NMIBC), for which treatment is directed at local treatment and reducing recurrences and preventing progression to more advanced stages. These NMIBCs can be further subdivided, based on their relative risk of progression, into low, intermediate or high risk groups. The second category of tumors is comprised of the locally advanced, muscle invasive lesions. For these patients, surgical removal of the bladder and adjacent organs, cystectomy with urinary diversion, is the standard of care with prevention of metastasis. For the third category, metastatic disease, systemic treatment is aimed at attempting to prolong survival. Numerous chemo- and immunotherapies have shown activity in this disease, yet to date, patients with metastatic bladder cancer are largely incurable. The issue for the clinician is how best to use the available agents to achieve the most satisfactory outcome for the patient, while new agents are being developed to address the unmet medical need for the treatment of bladder cancers.

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) [3]. 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 [3]. As these tumors are highly recurrent, patients require frequent follow up surveillance and retreatment, resulting in significant expense and morbidity. Health outcome data indicate that bladder cancer is the most expensive tumor to treat on a per lifetime basis [4, 5].

Tumor recurrence is attributed to a combination of missed tumors, an incomplete resection, and implantation of tumor cells released during transurethral resection bladder tumor (TURBT) or growth of a new tumor. The initial treatment for NMIBC is a good quality TURBT followed by an immediate postoperative instillation of a chemo- or immunotherapeutic, as recommended by American Urological Association (AUA) and European Association of Urology (EAU) guidelines [6-8]. Furthermore, National Comprehensive Care Network (NCCN) guidelines recommend “in addition to observation, the clinician should consider administering a single dose of immediate intravesical chemotherapy (not immunotherapy) within 24 hours of resection” [9]. The immediate postoperative instillation of a chemotherapeutic agent is thought to mediate its effect by destroying floating tumor cells released during TURBT that potentially can implant in the bladder wall and/or by ablating residual tumors cells at the resection site.

The primary objective of adding immediate postoperative intravesical therapy after TURBT in patients with NMIBC is to delay recurrence of bladder cancer, hence enabling patients to have the longest possible “recurrence free” interval. Reducing recurrence rates, would lead to a reduced need for subsequent surgical intervention and anesthesia, which would further favorably impact patients’ quality of life, reducing the risks of progression, anxiety, and economic burden [4]. Additionally, the repeated tumor resections required due to tumor recurrences with NMIBC

may result in reduced bladder capacity from scarring, which in turn leads to urinary symptoms of urgency, frequency, etc., further negatively impacting patients' quality of life.

The medical literature and international treatment guidelines recommend immediate instillation of a chemotherapeutic agent following TURBT, because of the potential impact on reducing tumor recurrence and disease progression.

Underlying these treatment recommendations are the results of a published meta-analysis of seven randomized trials including 1476 patients, that demonstrated a 12% decrease in **Recurrence Rates** (48.4% TURBT alone vs. 36.7% TURBT+ single instillation of a chemotherapeutic agent) [10]. This analysis supports the value of a single immediate postoperative instillation of a chemotherapeutic agent in reducing the incidence of tumor recurrence, which in turn leads to fewer required subsequent surgical interventions [10].

The First International Consultation on Bladder Tumors (FICBT), the published literature, and the International Bladder Cancer Group (IBCG) also recommend TURBT plus an immediate postoperative chemotherapeutic instillation [11]. The goals of this treatment are:

1. To prevent recurrence
2. To prevent progression to muscle invasive disease
3. Decrease the need for repetitive invasive procedures such as cystoscopy and TURBT with the inherent risk of infection, bleeding and perforation
4. Ultimately to delay or avoid the need for cystectomy

However, there is no currently approved agent for this indication in the United States and there remains a high unmet medical need.

1.2 Apaziquone for Intravesical Instillation

Apaziquone (EOquin®, EO9) is a fully synthetic bioreductive alkylating indoloquinone that is a prodrug activated by reductase enzymes to generate reactive and cytotoxic intermediates. The activity of apaziquone is enhanced in tumor cells which contain higher amounts of reductive enzymes compared to normal cells; bladder carcinoma cells contain high levels of such reductive enzymes [12]. The antitumor activity of apaziquone has been confirmed in *in vitro* studies in four human transitional cell cancer cell lines [13] and *in vivo* in a rat orthotopic bladder cancer model [14]. Additionally, Phase 1 to Phase 3 clinical studies conducted with apaziquone have confirmed its activity in patients with NMIBC.

1.3 Summary of Nonclinical Studies with Apaziquone

1.3.1 *In vitro* Apaziquone Activity in Urothelial Cancer Cell Lines

The cytotoxicity of apaziquone and other commonly used intravesical chemotherapeutic agents (mitomycin C, epirubicin and gemcitabine) was investigated *in vitro* in four human transitional cell cancer cell lines (RT112, T24, 253J, RT4). In these bladder cancer cell lines, apaziquone was shown to be the most potent agent in terms of cytotoxicity compared to mitomycin C, epirubicin, and gemcitabine. For example, activity of apaziquone was 5 to 75 fold higher than mitomycin C in these cell lines [13].

1.3.2 Dermal Irritation Study

Dermal irritation potential of the apaziquone formulation was evaluated in female New Zealand White rabbits by topical administration (non-occlusive) of apaziquone formulation or vehicle control as a single dose for 4 hours, followed by skin examination at Baseline and at various time points for 3 days post administration, after removal of excess material.

No mortality or significant drug-related clinical/dermal observations were observed in any of the treatment sites exposed to apaziquone or vehicle control. Slight transient erythema responses were observed at the 4 hour and 24 hour time points post exposure in apaziquone- and vehicle-treated sites. All erythema responses were resolved by 48 hour examination time point. No other significant adverse effects were observed. (**TX09068_TX**)

1.4 Clinical Studies with Apaziquone

1.4.1 Intravenous Administration Studies

The initial studies of intravenous apaziquone in humans were conducted at a dose schedule of 12 mg/m^2 weekly or 22 mg/m^2 every 3 weeks in patients with breast, non-small cell lung cancer (NSCLC), gastrointestinal cancers and carcinoma of unknown primary (CUP). Despite reports of 3 partial responses in one Phase 1 study in 2 patients with CUP and one patient with bile duct carcinoma, no responses were observed in subsequent Phase 2 studies. The lack of efficacy of apaziquone was attributed to its short half-life (0.8 to 19 minutes) due to the agent's rapid inactivation by the significant red blood cell fraction present in the systemic circulation, since it was recognized that red blood cells have the ability to inactivate apaziquone **[15]**. Since apaziquone is inactivated by red blood cells, the drug was considered more suitable for use with non-intravenous administration to tumor sites in readily accessible compartments, such as the urinary bladder, where the drug could have direct contact with tumor cells and which typically has few or no red blood cells. Hence, apaziquone was considered an ideal candidate for the treatment of bladder cancer by intravesical instillation, which would allow for a 1 hour retention time that would increase exposure time to bladder cancer cells. Although minimal systemic uptake was expected via intravesical administration, any drug reaching the systemic circulation from the bladder, by whatever mechanism, would be rapidly cleared, minimizing the risk of systemic toxicity.

1.4.2 Intravesical Studies

There have been 3 studies of apaziquone administered by the intravesical route.

1.4.2.1 Phase 1 Marker Lesion Study (ND019903)

ND019903 was an intrapatient dose escalation study performed in patients (n=6) with recurrent NMIBC (Ta-T1, G1-G2) in which all but one "marker" lesion had been removed at TURBT. Apaziquone was given weekly for 6 weeks beginning 2 weeks post-TURBT. The doses studied included 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 6 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, the 4 mg per instillation dose was determined to be the Maximum Tolerated Dose (MTD). More patients (n=6) were enrolled and treated with the fixed dose of 4 mg in 40mL. Four of these 6 patients (67%) experienced a complete histologic response of their marker lesions **[16]**.

Apaziquone was well tolerated at this dose with the majority of side effects referable to the bladder and of mild to moderate severity. Pharmacokinetic testing did not reveal the presence of apaziquone in the plasma of any patients with a limit of detection of 20 ng/mL.

The second part of the study planned to recruit 14 to 25 additional patients. After treating 6 patients with a fixed dose of apaziquone 4 mg/40 mL once a week times 6 instillations, complete responses (CR) were observed in 4 of the 6 (67%) patients. This study was, therefore, closed to recruitment, and a Phase 2 multicenter study (**ND03020**) was planned to enroll a larger number of patients.

Tumor response evaluation 2 weeks after the last instillation of apaziquone is presented in **Table 2** for both the dose-escalation and the fixed-dose cohorts. Based on these data, a dose of 4 mg/40 mL instillate of apaziquone was shown to be effective and well tolerated, and was, therefore, selected as the dose to be studied in Phase 2.

Table 2 Response to Intravesical Treatment in the Dose-Escalation and Fixed-Dose Cohorts

Response to Therapy	Intrapatient Dose Escalation (n)	Fixed Dose (n)	Total n (%)
Complete Response	4	4	8 (67)
No Response	2	2	4 (33)

1.4.2.2 Phase 2 Marker Lesion Study (ND03020)

ND03020 was a Phase 2 marker lesion clinical study of apaziquone in patients with primary or recurrent, multiple tumors, Stage Ta-T1, G1-G2 NMIBC conducted in the Netherlands and in the United Kingdom. This study followed a similar design as the Phase 1 study where all tumors were resected except for one marker lesion (0.5 to1 cm), which was left intact at the initial TURBT. Apaziquone (4 mg/40 mL) was instilled weekly for 6 weeks starting 2 to 4 weeks post-TURBT. This was followed by cystoscopy 2 to 4 weeks after the last apaziquone instillation. If no tumor was visualized on cystoscopy, the marker lesion tumor site was biopsied, and if the marker lesion tumor was present, it was resected in its entirety.

This study enrolled 46 patients and the histologically proven CR rate was 67% (30/46), similar to what was observed in Phase 1 **[17]**. The most commonly reported AEs related to apaziquone were hematuria (33%), dysuria (28%), and urinary frequency (20%). Grade 3 hematuria was reported in 1 patient and Grade 3 urinary frequency was reported in 2 patients. Two patients discontinued after 5 instillations due to hematuria (one SAE of grade 2 hematuria and one AE of Grade 1 recurrent hematuria). The safety and tolerability of apaziquone observed in this study compared favorably to that reported for other chemotherapeutic agents used for intravesical instillation in patients with NMIBC.

1.4.2.3 Phase 2 High-risk Study (SPI-05-003)

SPI-05-003 was a Phase 2 multicenter study conducted in the Netherlands. It was an open-label study in heavily pre-treated patients with multiple, highly recurrent, ≥3 recurrences in 24 months), stage T1 any grade, Stage Ta, Grade 2 to Grade 3 papillary tumors including carcinoma *in situ* (CIS). A total of 53 patients were enrolled, 49 patients had papillary tumors and 4 patients

had CIS. All patients received an induction course of 6 weekly intravesical instillations of 4 mg/40 mL of apaziquone, and patients with CIS were further treated with 3 weekly instillations of 4 mg/40 mL of apaziquone every 3 months if CIS did not recur. The follow-up consisted of surveillance cystoscopy every 3 months for 18 months.

Of 49 patients with papillary disease, 27 patients (55%) remained recurrence free at the 18-month follow up cystoscopy **[18]**. The two patients with CIS discontinued after 6 instillations each and did not receive any maintenance dose of apaziquone due to cystitis and recurrent papillary disease. The other 2 patients with CIS completed the induction course. One patient received only three maintenance doses and discontinued due to urinary incontinence. The other remaining patient received 6 maintenance doses and discontinued due to dysuria after receiving a total of 12 doses. Of the 4 patients with CIS, 3 were disease free at 3 month follow-up and the other 1 patient developed progressive disease. All four patients with CIS had a complete response by histology at 3 months, but discontinued the study after 6, 6, 9, and 12 doses of apaziquone (3, 3, 5, and 12 months after study inclusion, respectively), due to cystitis, recurrent papillary disease (T1, G3), urinary incontinence, and dysuria, respectively.

1.4.2.4 Pilot Study- Safety and PK of Single Instillation of Apaziquone Immediately After TURBT (SPI-515)

SPI-515 was a safety and tolerability study of single dose apaziquone (4 mg/40mL) administered within 6 hours of TURBT in patients with Stage Ta-T1, Grade G1-G2 noninvasive bladder cancer that accrued 20 patients. All patients (n=20) dosed tolerated apaziquone 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 10 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 (apaziquone) nor its metabolite EO5a was detected in plasma samples with a lower limit of quantitation (LLOQ) for EO9 and EO5a at 0.5ng/mL **[19]**.

1.4.2.5 Phase 3 Studies of a Single, Immediate, Post-TURBT Instillation of Apaziquone (Studies SPI-611 and SPI-612)

Two large randomized (1:1), double-blind, placebo-controlled studies of apaziquone enrolled a total of 1615 patients (**SPI-611**, 802 patients; **SPI-612**, 813 patients) with NMIBC diagnosed by visual appearance at TURBT as Ta, G1-G2. All patients received a single instillation of either apaziquone or placebo within 6 hours of TURBT with the study drug retained in the bladder for 60 minutes. Ta, G1-G2 disease was confirmed by central pathology for 566 patients in **SPI-611** and 580 patients in **SPI-612**. These data provide the basis for the selection of dose and schedule for the newly proposed Phase 3 study.

1.4.2.5.1 Primary Endpoint Analysis- 2-Year Recurrence Rates-

Individual Study Analysis (SPI-611 and SPI-612)

In **SPI-611**, the primary endpoint of **2-Year Recurrence Rate** in the **Ta, G1-G2 Population** for the **Apaziquone Treatment Group** (N=295) was 38.0% (95% CI 32.4 to 43.7) and 44.6% (95% CI 38.6 to 50.8) in the **Placebo Treatment Group** (N=271). This study demonstrated a clinically meaningful 6.7% reduction in the **2-Year Recurrence Rate** with apaziquone (χ^2 P=0.107), although this difference relative to placebo was not statistically significant **(Table 3)**.

In **SPI-612**, the primary endpoint of **2-Year Recurrence Rate** in the **Ta, G1-G2 Population** for the **Apaziquone Treatment Group** (N=282) was 39.7% (95% CI 34.0 to 45) and in the **Placebo Treatment Group** (N=298) was 46.3% (95% CI 40.5 to 52.2). This study also demonstrated a clinically meaningful 6.6% reduction in the **2-Year Recurrence** Rate for apaziquone-treated pateints (χ^2 P=0.109), although this difference, relative to placebo, was not statistically significant (**Table 3**).

Table 3 Individual Study Primary Endpoint- 2-Year Recurrence Rate in the Ta, G1-G2 Population (SPI-611, SPI-612)

	Ta, G1-G2 Population Total			
	SPI-611		SPI-612	
	Apaziquone N=295	Placebo N=271	Apaziquone N=282	Placebo N=298
2-Year Recurrence Rate				
Patients Recurred,[a] n (%)	112 (38.0)	121 (44.6)	112 (39.7)	138 (46.3)
(95% CI)[b]	32.4 to 43.8	38.6 to 50.8	34.0 to 45.7	40.5 to 52.2
P-value[c]	0.107		0.109	
Difference (95% CI)	-6.7 (-14.8 to 1.4)		-6.6 (-14.6 to 1.4)	
Odds Ratio (95% CI)	0.76 (0.54 to 1.06)		0.76 (0.55 to 1.06)	

a) Recurrence is defined as first documented recurrence of bladder tumor on or before 2 years.

b) Exact 95% confidence interval

c) Mantel-Haenszel Chi-Square Test

Integrated Study Analysis (SPI-611 + SPI-612)

Of the total 1615 patients enrolled in both Phase 3 studies (**SPI-611** and **SPI-612**), 1146 patients were confirmed by central pathology to have Ta, G1-G2 histology. The integrated efficacy data for the **Ta, G1-G2 Target Population** showed a statistically significant (p=0.022) and clinically meaningful 6.7 % reduction in the **2-Year Recurrence Rate**, the primary endpoint of the study, in the **Apaziquone Treatment Group** compared to the **Placebo Treatment Group** (**Table 4**). In addition, this analysis demonstrated an approximate 24% reduction in the **Risk of Tumor Recurrence at 2 Years** based on the Odds Ratio of Recurrence.

Table 4 Integrated Study Primary Endpoint Data- 2-Year Recurrence Rate in the Ta, G1-G2 Population (SPI-611 + SPI-612)

Parameter	Integrated SPI-611 + SPI-612 Data Ta, G1-G2 Population Total	
	Apaziquone N=577	Placebo N=569
2-Year Recurrence Rate		
Patients Recurred,[a] n (%)	224 (38.8)	259 (45.5)
(95% CI)[b]	34.8 to 42.9	41.4 to 49.7
P-value[c]	0.022	
Difference (95% CI)	-6.7 (-12.4 to -1.0)	
Odds Ratio (95% CI)	0.76 (0.60 to 0.96)	

a) Recurrence is defined as first documented recurrence of bladder tumor on or before 2 years.

b) Exact 95% confidence interval

c) Mantel-Haenszel Chi-Square Test

Individual Study Analysis- Drug Instillation Time Intervals Post-TURBT (SPI-611 and SPI-612)

Additional analyses of the **SPI-611** and **SPI-612** studies based on the time intervals of drug instillation post-TURBT (<30 minutes, 31 to 90 minutes, and >90 minutes) were also conducted. This analysis was undertaken because of the potential for apaziquone to be inactivated by whole blood in the early period following TURBT, during which postoperative bleeding is not uncommon. Analysis of the efficacy data for the **Ta, G1-G2 Target Population** who were administered apaziquone in the 31- to 90-minute window showed clinically meaningful and statistically significant 20.3% to 20.8% reductions in the **2-Year Recurrence Rate**, compared to patients administered placebo in the same window, in both **SPI-611** (p=0.035) and **SPI-612** (p=0.024) **(Table 5)** studies, respectively. These data demonstrated the maximum benefit from intravesical instillation of apaziquone in the group receiving instillation at 31 to 90 minutes post-TURBT, and support the proposed dosing of apaziquone in this new Phase 3 study at 60 ± 30 minutes post-TURBT. In addition, these analyses demonstrated an approximate 61% and 58% reduction in the **Risk of Tumor Recurrence at 2 Years** in **SPI-611** and **SPI-612**, respectively, based on the Odds Ratio of Recurrence. The reductions in both the **2-Year Recurrence Rate** and **Tumor Recurrence at 2 Years** were greater than the reductions observed in the total populations.

Table 5 Individual Study Primary Endpoint Data- 2-Year Recurrence Rate in the Ta, G1-G2 Population in the 31 to 90 Minute Post-TURBT Window (SPI-611 and SPI-612)

Parameter	Ta, G1-G2 Population 31 to 90 Minute			
	SPI-611		SPI-612	
	Apaziquone (n=60)	Placebo (n=39)	Apaziquone (n=57)	Placebo (n=61)
2-Year Recurrence Rate				
Patients Recurred,[a] n (%)	14 (23.3)	17 (43.6)	19 (33.3)	33 (54.1)
(95% CI)[b]	(13.4, 36.0)	(27.8, 60.4)	(21.4, 47.1)	(40.8, 66.9)
p-value[c]	0.035		0.024	
Difference (95% CI)	-20.3 (-39.1, -1.4)		-20.8 (-38.3, -3.3)	
Odds Ratio (95% CI)	0.39 (0.16, 0.94)		0.42 (0.20, 0.89)	

a) Recurrence is defined as first documented recurrence of bladder tumor on or before 2 years.

b) Exact 95% confidence interval

c) Mantel-Haenszel Chi-Square Test

1.4.2.5.2 Key Secondary Endpoint Analysis- Time to Recurrence

Time to Recurrence, a secondary study endpoint, was defined as the time from **Randomization** to the date of the first histologically confirmed recurrence of the patient's bladder tumor. The **Time to Recurrence** endpoint is generally considered to be a more powerful endpoint, since it uses data from the entire 2-year follow up rather than just a single time point.

Individual Study Analysis (SPI-611 and SPI-612)

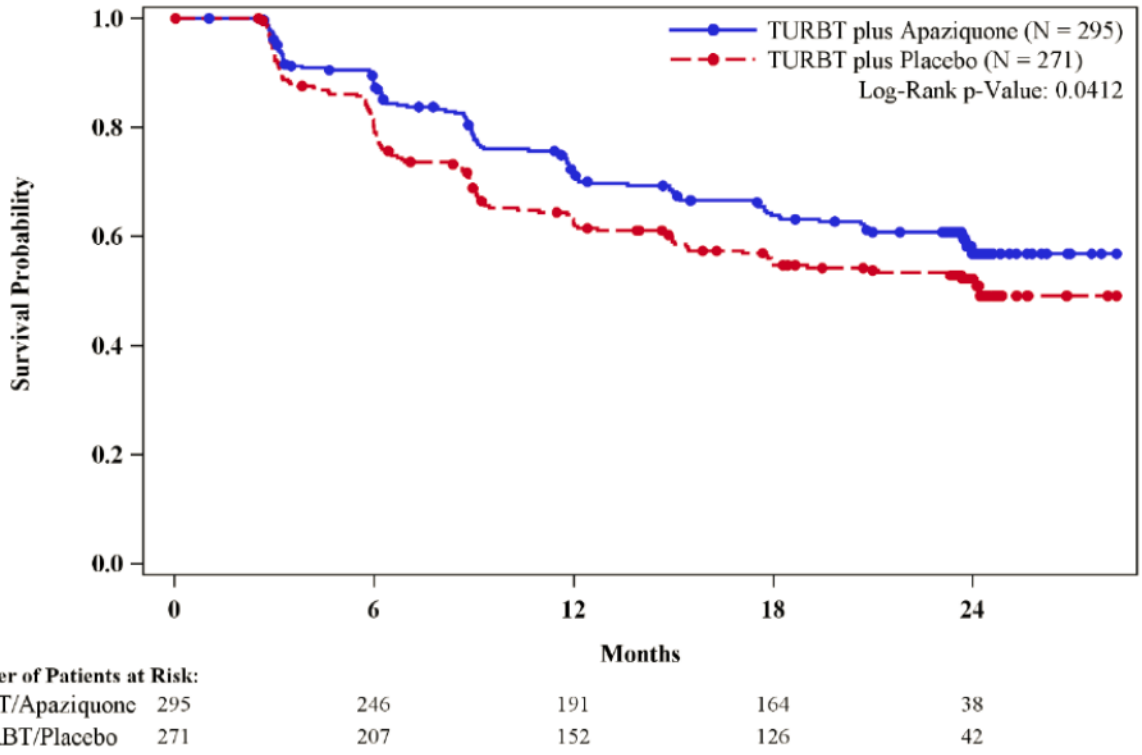
The analysis of the key secondary endpoint of **Time to Recurrence** in the **SPI-611** study showed a trend in favor of apaziquone treatment with a log-rank p=0.041 and a hazard ratio=0.77 (95% CI 0.59 to 0.99). Similar results were observed for the **SPI-612** study with a log-rank p-value=0.106 and hazard ratio=0.81 (95% CI 0.63 to 1.05). Results are summarized in **Table 6**. The survival probabilities over 24 months for patients in each study, **SPI-611** and **SPI-612**, are presented in the Kaplan-Meier graphs in **Figure 3** and **Figure 4**, respectively.

Table 6 Individual Study Key Secondary Endpoint- Time to Recurrence in the Ta, G1-G2 Population (SPI-611, SPI-612)

	Ta, G1-G2 Population Total			
	SPI-611		SPI-612	
	Apaziquone N=295	Placebo N=271	Apaziquone N=282	Placebo N=298
Number of Events (%)	112 (38.0)	121 (44.6)	112 (39.7)	138 (46.3)
Median Time-to-Recurrence (mo)	N/A	24.2	NE	NE
95% Confidence Limits	NE to NE	17.8 to NE	24.2 to NE	18.1 to NE
Log-Rank Test p-Value	0.041		0.106	
Hazard Ratio (EOQ:PBO)	**0.77**		**0.81**	
95% Confidence Limits	0.59 to 0.99		0.63 to 1.05	

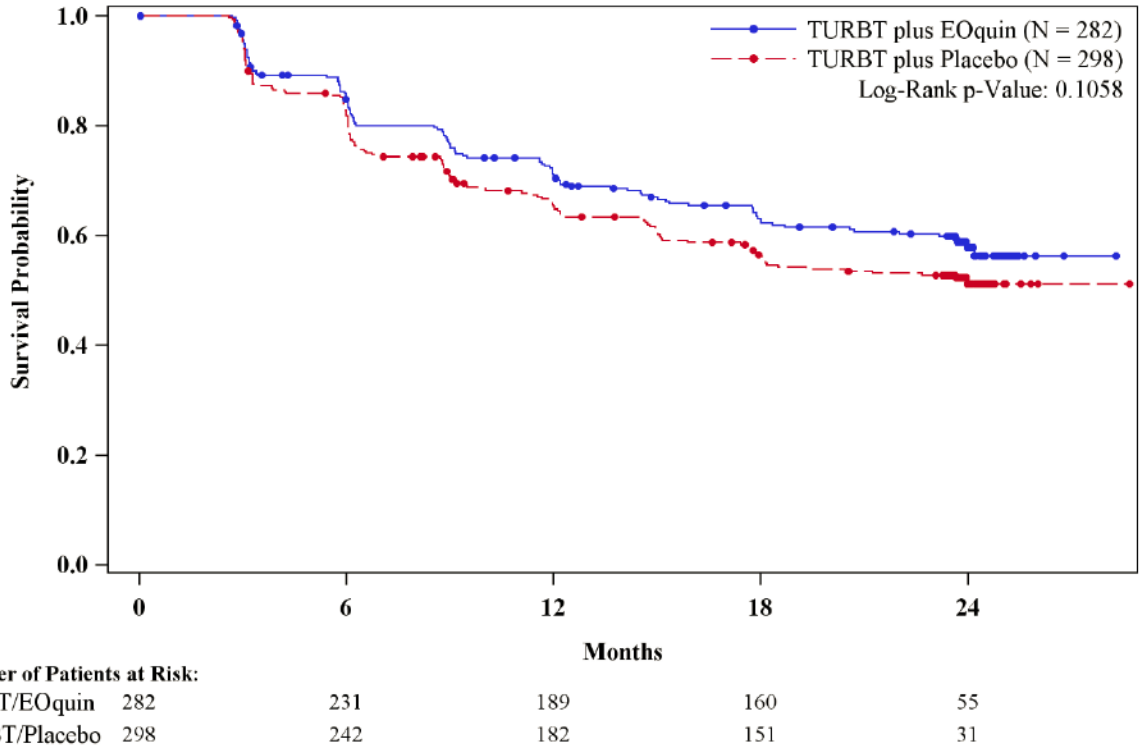
EOQ=apaziquone; mo=months; NE = not estimable; PBO=placebo

Figure 3 Individual Study Time to Recurrence in the Ta, G1-G2 Population (SPI-611)



Solid Circles represent censored

Figure 4 Individual Study Time to Recurrence in the Ta, G1-G2 Population (SPI-612)



Integrated Study Analysis (SPI-611 + SPI-612)

Time to Recurrence- From Time of Instillation

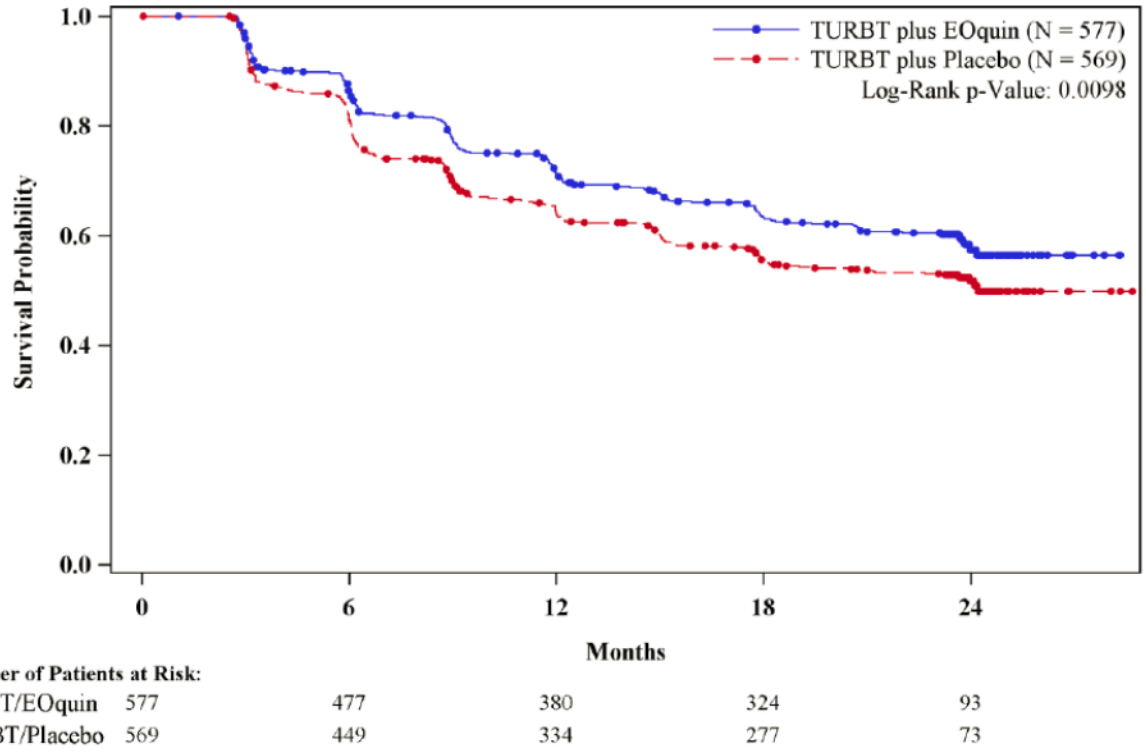
The **Time to Recurrence**, based on time from TURBT to instillation, was also shown to be statistically different between treatment groups in the integrated analysis, favoring apaziquone treatment with a log rank p-value of 0.0098 and a hazard ratio of 0.79 (**Table 7**). Integrated data of the survival probability over 24 months for patients in **SPI-611** and **SPI-612** are presented in the Kaplan-Meier graph in **Figure 5**.

Table 7 Integrated Study Secondary Endpoint- Time to Recurrence in the Ta, G1-G2 Population (SPI-611 + SPI-612)

Parameter	SPI-611 + SPI-612 Ta, G1-G2 Population Total	
	Apaziquone N=577	Placebo N=569
Number of Events (%)	224 (38.8)	259 (45.5)
Median Time-to-Recurrence (mo)	NE	24.2
95% Confidence Limits	NE to NE	19.0 to NE
Log-Rank Test p-Value	0.0098	
Hazard Ratio (EOQ:PBO)	**0.79**	
95% Confidence Limits	0.66 to 0.95	

EOQ=apaziquone; mo=months; NE = not estimable; PBO=placebo

Figure 5 Integrated Study- Time to Recurrence (SPI-611 + SPI-612)



Solid Circles represent censored

Individual Study Analysis- Drug Instillation in the 31- to 90-Minute Time Interval Post-TURBT (SPI-611 and SPI-612)

The analyses of the key secondary endpoint of **Time to Recurrence** for patients with Ta, G1-G2 histology who were administered study drug (apaziquone or placebo) during the 31- to 90-minute window following TURBT in **SPI-611** and **SPI-612** are presented in **Table 8**. The survival probabilities over 24 months for these patients are presented in the Kaplan-Meier graphs in **Figure 6**.

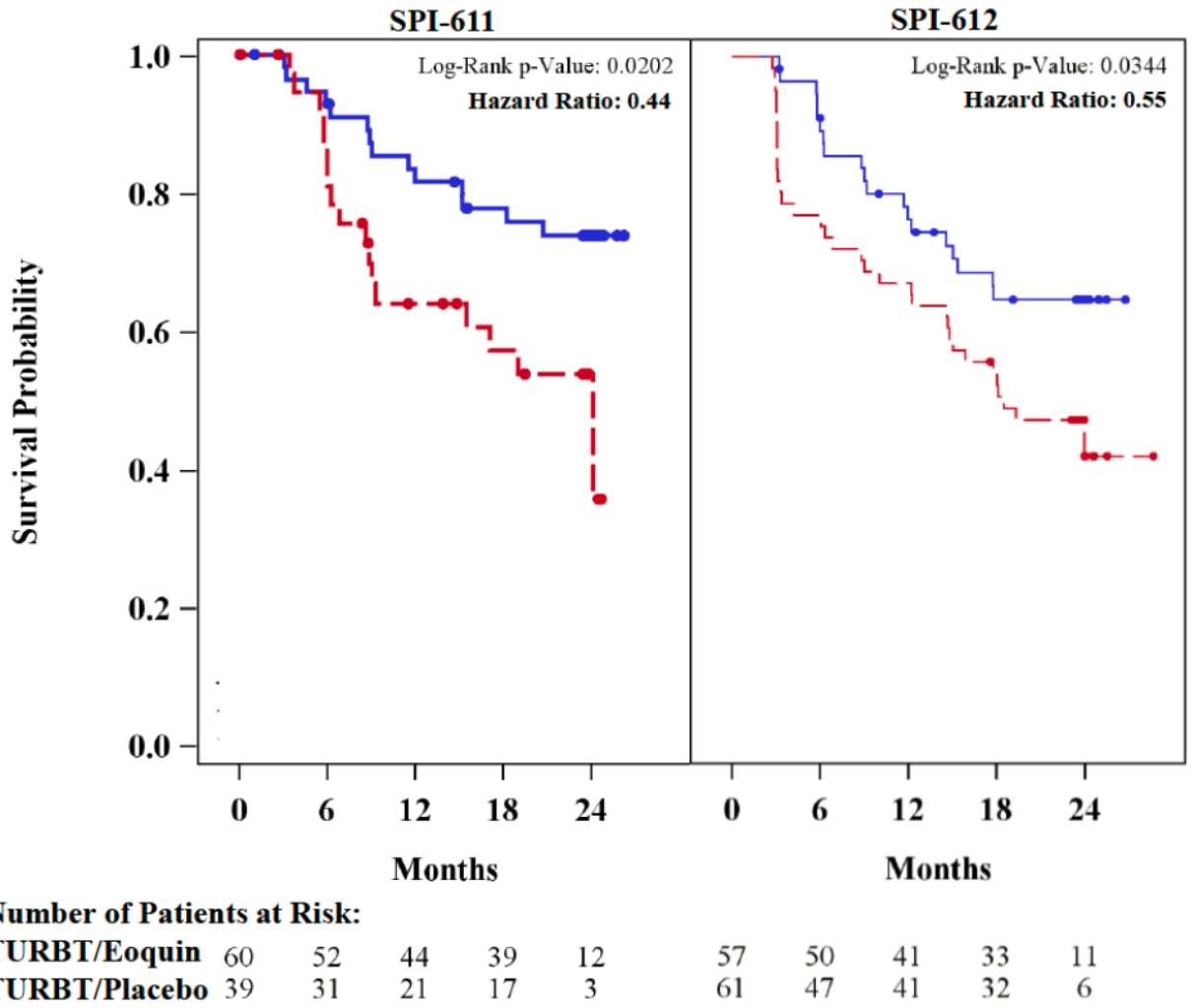
In **SPI-611**, there was a trend in favor of apaziquone treatment for **Time to Recurrence** with a log-rank p=0.020 and a hazard ratio=0.44 (95% CI 0.22 to 0.90). Similar results were observed in the **SPI-612** study with a log-rank p-value=0.034 and hazard ratio=0.55 (95% CI 0.31 to 0.97). These results demonstrate that the administration of apaziquone to patients with Ta, G1-G2 histology in the 31- to 90-minute window, post-TURBT results in a greater survival probability compared to the total **Ta, G1-G2 Population**.

Table 8 Individual Study Key Secondary Endpoint in the Ta, G1-G2 Population for the 31- to 90-Minute Post-TURBT Instillation Window (SPI-611 and SPI-612)

	Ta, G1-G2 Population 31 to 90 Minute Window			
	SPI-611		SPI-612	
	Apaziquone N=60	Placebo N=39	Apaziquone N=57	Placebo N=61
Number of Recurrence Events (%)	14 (23.3)	17 (43.6)	19 (33.3)	33 (54.1)
Median Time-to-Recurrence (mo)	NE	24.1	NE	18.5
95% Confidence Limits	NE to NE	9.1 to NE	NE to NE	14.6 to NE
Log-Rank Test p-Value	0.020		0.034	
Hazard Ratio (EOQ:PBO)	**0.44**		**0.55**	
95% Confidence Limits	0.22 to 0.90		0.31 to 0.97	

EOQ=apaziquone; mo=months; NE = not estimable; PBO=placebo

Figure 6 Individual Study Time to Recurrence- Instillation Window 31 to 90 Minutes post-TURBT (SPI-611, SPI-612)



1.4.2.6 Phase 3 Studies of Multi-Dose, Post-TURBT Instillation of Apaziquone

Two multi-instillation studies of apaziquone in patients with NMIBC (**SPI-1011** and **SPI-1012**) were initiated and subsequently terminated for business reasons. Although final analyses were not performed, safety profiles between single and multi-instillation studies were similar. In addition, preliminary analysis of the available efficacy data from these multi-dose studies (apaziquone, n=27; placebo, n=32) suggested an additional benefit from the repeat administration of apaziquone with a 19% to 28% reduction in recurrence rates with multi-dose installation versus 6% in the prior single-dose studies.

1.5 Rationale

All expert urology societies recommend a high quality TURBT as the initial treatment for patients with NMIBC. However despite the improvements in instrumentation and surgical techniques, there continues to be a high frequency of tumor recurrence and progression of the

disease to more advanced stages. Therefore, a key focus for improving the treatment of NMIBC is to identify new treatment strategies that reduce the rate of recurrence and progression.

The medical literature supports, and international guidelines recommend, immediate instillation of a chemotherapeutic agent following TURBT because of its potential impact in reducing tumor recurrence. Theoretically, the high rate of tumor recurrence is attributed to a number of putative factors:

- Incomplete initial tumor resection
- Inability to visualize all tumors
- Implantation of floating tumor cells, which are released into the bladder during TURBT
- Growth of a new tumor due to unknown or poorly understood factors predisposing to the development of bladder cancer.

The goal of immediate postoperative instillation of a chemotherapeutic agent into the bladder is to decrease recurrence rates by destroying floating tumor cells released during the TURBT procedure, which have the potential to implant in the bladder wall. Postoperative instillation of a chemotherapeutic agent may also provide benefit by ablating residual tumor cells remaining at the resection site.

Apaziquone is a prodrug that is specifically activated into a potent alkylating agent in tumor cells, which contain high amounts of reductive enzymes. The antitumor activity of apaziquone has been demonstrated in *in vitro* studies in four human bladder cancer cell lines, where it was shown to be the most potent cytotoxic agent compared to mitomycin C, epirubicin, and gemcitabine, with activity that was 5- to 75- fold higher than mitomycin C. Phase 1 and Phase 2 clinical studies showed the activity of apaziquone, following intravesical instillation, inducing the regression of bladder cancer marker lesions with CR rates as high as 67% in heavily pretreated patients. Phase 3 single instillation studies (**SPI-611**, n=802; **SPI-612**, n=813) demonstrated clinically meaningful reductions of 6.7% and 6.6%, respectively, in the **2-Year Recurrence Rate** by apaziquone in the **Ta, G1-G2 Population**. Although these differences were not statistically significant in the individual studies, an integrated analysis of data from both Phase 3 studies (n=1615) showed a clinically meaningful 6.7 % reduction in the **2-Year Recurrence Rate** in the **Apaziquone Treatment Group** that was also statistically significant (p=0.022). In addition, it demonstrated an approximate 24% reduction in the risk of tumor recurrence at 2 years based on the Odds Ratio of Recurrence. Intravesical treatment was also shown to be well tolerated with the main AEs including those expected in patients with bladder cancer, eg, hematuria, dysuria, and urinary frequency.

Apaziquone has been shown to be inactivated by red blood cells [15]. Hematuria, both microscopic and macroscopic, is the most common adverse event in the immediate post-TURBT period. Therefore, any bleeding in the post-operative period following TURBT could inactivate apaziquone following its immediate, postoperative instillation, reducing its efficacy. This provided the rationale for the further analysis of the Phase 3 study data for **SPI-611** and **SPI-612** based on the time interval of drug instillation post-TURBT (<30 minutes, 31 to 90 minutes, and >90 minutes). This analysis demonstrated a robust 20.3% reduction in the **2-Year Recurrence Rate** in apaziquone-treated patients in the **Ta, G1-G2 Population** who received treatment 31 to 90 minutes after TURBT, compared to patients treated with placebo in the same time interval (23.3% vs 43.6%); this difference was statistically significant (p=0.0346), with the odds ratio

(0.39; 95% CI 0.16, 0.94) in favor of apaziquone. Since the maximum benefit from intravesical instillation was seen in the group of patients receiving instillation at 31 to 90 minutes post-TURBT, this dosing window was selected for instillation of study drug (apaziquone or placebo) (60 ± 30 minutes post-TURBT) in the new proposed Phase 3 study.

The proposed Phase 3 study includes two apaziquone dosing arms; **Arm 1:** a single instillation of apaziquone; and **Arm 2:** two apaziquone instillations, 2 weeks apart. The rationale for this second apaziquone dose is twofold: 1) it permits treatment at a point in time when the possibility of post-TURBT bleeding is low, minimizing the potential for apaziquone inactivation; and 2) preliminary data from multi-installation studies with apaziquone (**SPI-1011** and **SPI-1012**) suggested an additional benefit from repeat administration of apaziquone with a 19% to 28% reduction in **Recurrence Rates** with multi-dose installation, versus 6% in the single-dose studies; safety profiles between single and multi-instillation studies were similar. Thus, the proposed Phase 3 study is designed to include a treatment arm (**Arm 2**) with a primary objective of assessing the treatment benefit of two intravesical instillations of apaziquone in patients with NMIBC, one in the immediate post TURBT period and the second instillation 2 weeks later; this dosing strategy may further delay or prevent the recurrence of NMIBC.

1.5.1 Summary of Risks and Benefits

1.5.1.1 Potential Risks

Apaziquone has been administered to over 1100 patients as a single instillation or as multiple instillations either within 6 hours of TURBT or starting 2 weeks post-TURBT. The demonstrated safety profile of apaziquone is similar to placebo with reported adverse events being limited to the bladder ie, dysuria, hematuria, urinary tract infection, and bladder pain etc. In the 1615 patients treated in two Phase 3 studies (**SPI-611** and **SPI-612**), the 4 mg apaziquone instillation was retained for 1 hour in 98% of patients. In studies performed to date, apaziquone 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-TURBT period. Patients with an extensive resection, possible bladder perforation, or significant postoperative bleeding should not receive apaziquone instillation.

1.5.1.2 Potential Benefits

As outlined above, Phase 1 and Phase 2 studies have demonstrated tumor regressions following apaziquone treatment with 67% of patients having histologically proven complete responses. The two completed Phase 3 single instillation studies of apaziquone given intravesically immediately after TURBT have demonstrated a clinically meaningful 6.7/6.6% reduction in **2-Year Recurrence Rates** in the individual studies, and a 6.7% reduction in **2-Year Recurrence Rate** that was statistically significant (p=0.022) on integrated analysis, with an approximate 24% reduction in the risk of tumor recurrence at 2 years based on the Odds Ratio of Recurrence. Importantly, patients who received treatment with apaziquone at 31 to 90 minutes after TURBT (**Ta, G1-G2$_{31\text{-}90\ \text{minute}}$ Population**) were shown to have a robust 20.3% reduction in **2-Year Recurrence Rate** compared to patients treated with placebo in the same time interval (23.3% vs 43.6%); this difference was statistically significant (p=0.0346), with the odds ratio (0.39; 95% CI 0.16, 0.94) in favor of apaziquone (**Table 5**). Intravesical treatment with apaziquone was also shown to be well tolerated with the main AEs including those expected in patients with bladder

cancer, eg, hematuria, dysuria, and urinary frequency. There is therefore, a potential clinical benefit for patients with NMIBC who receive intravesical apaziquone in the immediate post-TURBT period.

1.5.2 Justification of the Dose, Schedule and Route of Administration of Apaziquone

As discussed above, the 4 mg in 40 mL dose of apaziquone administered intravesically was established in a Phase 1 dose-escalation study that demonstrated both the safety and antitumor activity of 6 weekly instillations of this apaziquone dose in patients with NMIBC. This same dose was used in the two subsequent single dose Phase 3 studies that further demonstrated the anti-tumor activity of apaziquone, while also showing it to be safe and well tolerated. The conclusion from these clinical studies was that apaziquone, administered as a single intravesical instillation of 4 mg in 40 mL was chemoablative with a clinically meaningful reduction in **2-Year Recurrence Rates** of approximately 6.6%; the adverse event profile of apaziquone was similar to placebo. These data provide the justification for the proposed apaziquone dose in **Treatment Arm 1** and **Arm 2**.

Because of the potential for the inactivation of apaziquone by blood in the immediate post-TURBT period, the proposed apaziquone dosing is targeted to be delivered 60 ± 30 minutes post-TUBT. This dosing window is supported by the analysis of **2-Year Recurrence Rates** by time interval following TURBT in the Phase 3 single dose studies (**SPI-611**, **SPI-612**), which demonstrated 20.3% and 20.8% reductions, respectively, in **2-Year Recurrence Rate** for patients who received treatment 31 to 90 minutes post-TURBT, compared to patients treated with placebo in the same time interval; **SPI-611** (23.3% vs 43.6%; p=0.0346) and **SPI-612** (33.3% vs 54.1%; p=0.0238). The odds ratios for **SPI-611** (0.39; 95% CI 0.16, 0.94) and **SPI-612** (0.42; 95% CI 0.20, 0.89) favored apaziquone treatment. Therefore, although previous studies instilled drugs within 6 hours of TURBT, the Phase 3 data obtained from **SPI-611** and **SPI-612** clearly support the proposed dosing for apaziquone in this new study at 60 ± 30 minutes post-TURBT; these data justify the proposed apaziquone dosing regimen in **Treatment Arm 1** and **Arm 2**.

Preliminary analysis of the available efficacy data from two multiple instillation studies (**SPI-1011** and **SPI-1012**) suggested an additional benefit from the repeat administration of apaziquone in patients with NMIBC. In these multi-instillation studies, a 19% to 28% reduction in **Recurrence Rates** was demonstrated for apaziquone compared to the approximately 6% reduction seen in the prior single-dose studies; safety profiles between the single- and multi-instillation studies were similar. These data suggest that in addition to the clinical benefit demonstrated with a single post-TURBT instillation of apaziquone for patients with NMIBC, a second apaziquone dose may provide further benefit in reducing tumor **Recurrence Rates** or increasing **Time to Tumor Recurrence**. Therefore, the new proposed Phase 3 study includes an additional arm (**Arm 2**) that includes a second apaziquone dose administered approximately 2 weeks following the initial post-TURBT dosing. An additional rationale for this second instillation is that it will occur 2 weeks post-TURBT, when hematuria is likely to have resolved; these data support the proposed apaziquone dosing regimen in **Treatment Arm 2**. In order to ensure that treatment remains blinded in the proposed 3-arm study, all patients will get two doses of either study drug, apaziquone or placebo, or one of each based on the randomized treatment arm.

2 STUDY OBJECTIVES

2.1 Primary Objective(s)

- To evaluate the **Time to Recurrence** with either one instillation of 4 mg of apaziquone or two instillations of 4 mg apaziquone relative to placebo instillation following TURBT in patients with non-muscle invasive bladder cancer (NMIBC) who receive transurethral resection bladder tumor (TURBT)

2.2 Secondary Objectives

1. To evaluate the **2-Year Recurrence Rate** with either one instillation of 4 mg apaziquone or two instillations of 4 mg apaziquone relative to placebo instillation following TURBT in patients with NMIBC who receive TURBT.
2. To evaluate the **1-Year Recurrence Rate** with either one instillation of 4 mg apaziquone or two instillations of 4 mg apaziquone relative to placebo instillation following TURBT in patients with NMIBC who receive TURBT.
3. To evaluate the **Time to Progression** with either one instillation of 4 mg apaziquone or two instillations of 4 mg apaziquone relative to placebo instillation following TURBT in patients with NMIBC who receive TURBT
4. To evaluate the safety with either one instillation of 4 mg apaziquone or two instillations of 4 mg apaziquone relative to placebo instillation following TURBT in patients with NMIBC

3 INVESTIGATIONAL PLAN

3.1 Study Design and Treatment Plan

This is a Phase 3, randomized, multicenter, placebo-controlled, double-blind study of apaziquone in patients with ≤4 non-muscle invasive bladder tumors, ≤3.5 cm in diameter, all of which must have been fully resected at TURBT.

In addition to **Screening**, patients will also undergo an assessment of urothelial carcinoma via cystoscopy for clinically apparent tumor Ta, G1-G2.

Following TURBT, eligible patients will be randomized in a 1:1:1 ratio to one of the three following arms:

- **Arm 1**- One Dose of Apaziquone:
  - **Day 1:** administration of 4 mg of apaziquone 60 ± 30 minutes post-TURBT
  - **Day 15** (±5 days)**:** administration of placebo
- **Arm 2**- Two Doses of Apaziquone:
  - **Day 1:** administration of 4 mg of apaziquone 60 ± 30 minutes post-TURBT
  - **Day 15** (±5 days)**:** administration of 4 mg of apaziquone
- **Arm 3**- Placebo:
  - **Day 1:** administration of placebo 60 ± 30 minutes post-TURBT
  - **Day 15** (±5 days)**:** administration of placebo

Once randomized, **Day 1** study drug instillation will occur at 60 ± 30 minutes post TURBT. Patients whose tumor is determined to be Ta, G1-G2 will return on **Day 15** (±5 days) for a second instillation. If the pathology results are available and show non Ta, G1-G2 histology, the patient will not return on **Day 15 (**±5 days) for a second instillation. In the absence of local pathology results by the **Day 15** visit, the patient will receive a second instillation of study drug. All histology specimens will be reviewed by a local pathology laboratory and all clinical treatment decisions and study analyses will be based on the local pathology review. Patients whose pathology is other than Ta, G1-G2 will be followed up for safety at **Day 35** (±5 days) from the last dose of study drug and will then be discontinued from the study at the **End of Study Visit**.

Patients who have pathology confirmed Ta, G1-G2 histology will be followed for 24 months according to the schedule below:

- Cystoscopic examination and urine cytology every 90 days (±10 days) (calculated from date of TURBT) through 24 months for tumor recurrence and progression.
- If at any time during the 24 month follow up period there is a tumor recurrence, the patient will continue on study with follow-up cystoscopic examination and urine cytology every 90 days (±10 days) (calculated from date of TURBT) through the end of 24 months. Patients with a recurrence are permitted to have a follow-up TURBT.
- If at any time during 24 month follow up period there is a tumor recurrence and/or patient is started on another intravesical therapy, the patient will be followed by telephone, for safety every 90 days (±10 days) (calculated from date of TURBT) through the end of 24 months.

3.2 Study Duration

The estimated duration of the study is approximately 5 years (3 years for accrual and 2 years for treatment and follow-up).

The total duration of the study for each patient will be approximately 24 months including:

- **Screening Period**: 30-days
- **Treatment Period**: **Day 1** and **Day 15** (±5 days)
- **Safety Follow-up Period**: 24-months

4 PATIENT POPULATION

4.1 Inclusion Criteria

1. Patient must have a diagnosis of urothelial carcinoma of the bladder with clinically apparent tumor Ta, G1-G2.
2. Patient with ≤4 tumors, none of which exceeds 3.5 cm in diameter.
3. Patient must be willing to give written informed consent and must be able to adhere to dosing and visit schedules, and meet all study requirements.
4. Patient is at least 18 years of age at randomization.

5. Patient must be willing to practice two forms of contraception, one of which must be a barrier method, from study entry until at least 35 days after the last dose of the study drug.
6. Females of childbearing potential must have a negative pregnancy test within 30 days prior to randomization. Females who are postmenopausal for at least 1 year (defined as more than 12 months since last menses) or are surgically sterilized do not require this test.

4.2 Exclusion Criteria

1. Patient has an active concurrent malignancy/life-threatening disease. If there is a history of prior malignancies/life-threatening diseases, the patient is to be disease free for at least 5 years. Patients with other prior malignancies less than 5 years before study entry may still be enrolled if they have received treatment resulting in complete resolution of the cancer and currently have no clinical, radiologic, or laboratory evidence of active or recurrent disease.
2. Patient has positive urine cytology for malignancy at Screening.
3. Patient has an active uncontrolled infection, including a urinary tract infection, underlying medical condition, or other serious illness that would impair the ability of the patient to receive protocol treatment.
4. Patient has used any investigational drugs, biologics, or devices within 30 days prior to study treatment or plans to use any of these during the course of the study.
5. Patient has had any prior intravesical chemotherapy, immunotherapy, or previous exposure to apaziquone.
6. Patient has or has ever had:
   - Upper tract Transitional Cell Carcinoma (TCC)
   - Urethral tumor (prostatic urethra included)
   - Any invasive bladder tumor known to be other than tumor Ta, G1-G2
   - Any evidence of lymph node or distant metastasis
   - Any bladder tumor with histology other than TCC
   - Carcinoma in situ (CIS)
7. Patient has a tumor in a bladder diverticulum.
8. Patient has received any pelvic radiotherapy (including external beam and/or brachytherapy.)
9. Patient has a bleeding disorder or a screening platelet count <100×109/L.
10. Patient has screening hemoglobin <10 mg/dL.
11. Patient has any unstable medical condition that would make it unsafe to undergo TURBT.
12. Patient has a history of interstitial cystitis.
13. Patient has a history of allergy to red color food dye.
14. For patients with recurrent tumor, the patient had at least a 6-month cystoscopically-confirmed tumor-free interval between the last tumor recurrence and screening cystoscopic examination.
15. Patient is pregnant or breast-feeding

4.3 Patient Discontinuation/Withdrawal Criteria

Patients can withdraw from participation in this study at any time, for any reason, specified or unspecified, and without prejudice.

Patients must be withdrawn from study participation for the following reasons:

- It is determined by final pathology review that the patient has histology other than Ta, G1-G2
- Development of an adverse event (AE) that interferes with the patient's participation
- Patient withdrawal of informed consent
- Investigator decision
- Sponsor decision
- The patient refuses a follow-up cystoscopy
- The patient is lost to follow-up – if the patient has missed two consecutive follow up cystoscopies
- Patient has a cystectomy
- Patient has recurrence and receives therapy (Patient will be followed by telephone for safety)
- Death
- Pregnancy

The reason for the patient discontinuing study treatment or terminating from the study must be recorded on the case report form (CRF). Patients who discontinue treatment or who are withdrawn from treatment will return for a **Safety Follow-up Visit,** 35 days (±5 days) after the date of early discontinuation.

5 STUDY PROCEDURES

The study design diagram is presented in **Figure 7**, the study flow chart is presented in **Figure 8**, and the Schedule of Study Assessments and Procedures is presented **Appendix 1**.

Figure 7 Study Design Diagram

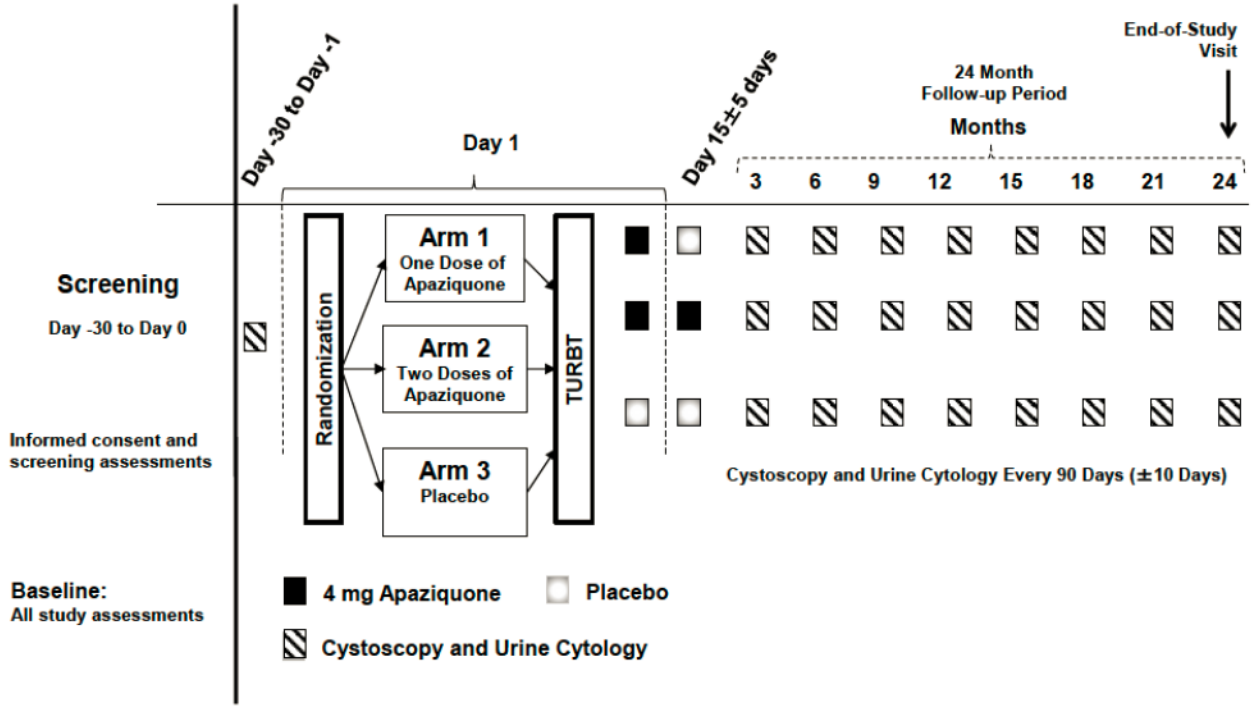
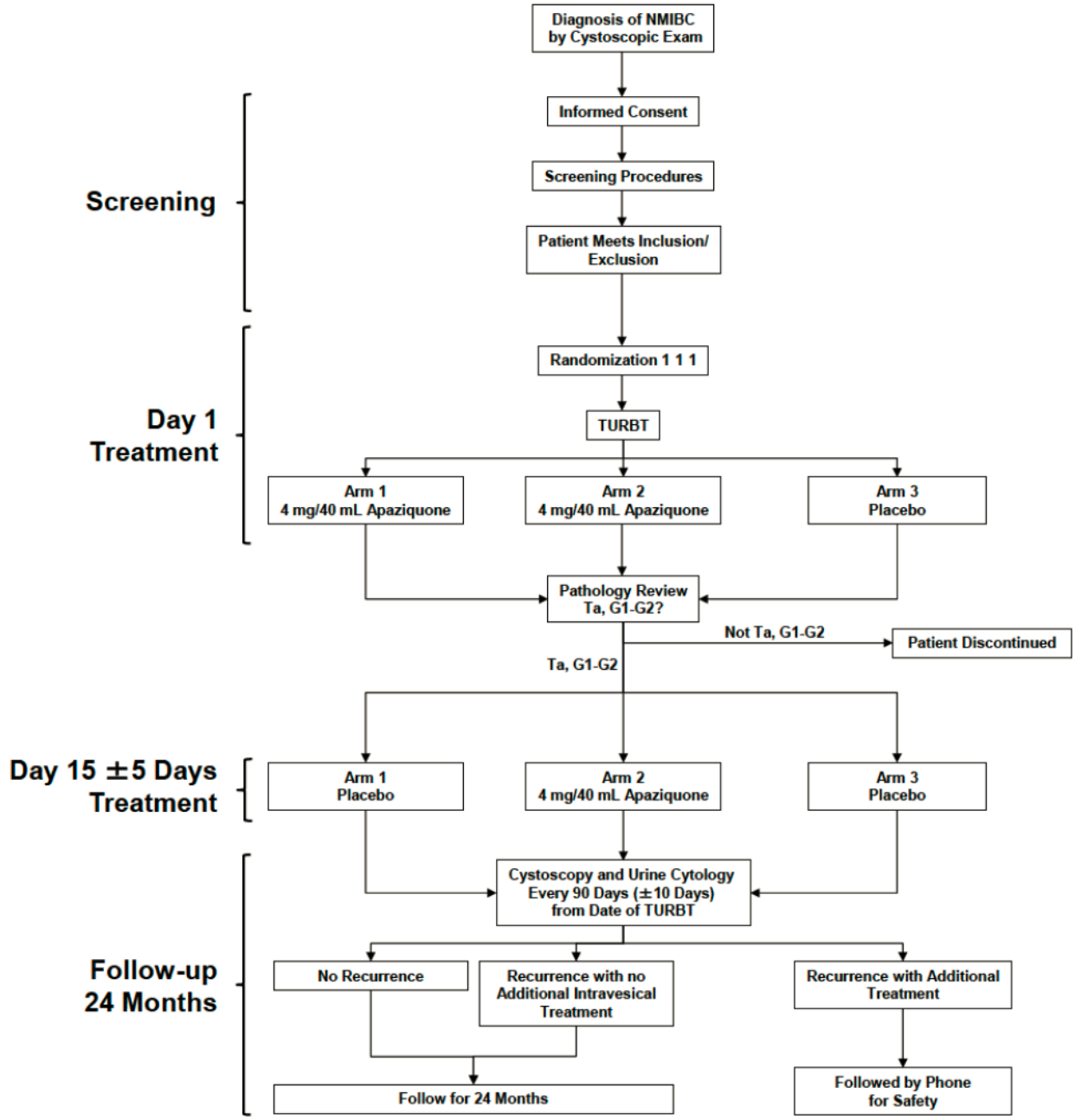


Figure 8 Study Flow Chart



5.1 Screening

Informed consent is to be obtained prior to the start of any protocol-specified assessments or procedures. The procedures and evaluations required for enrollment into the study are summarized below. All potential study patients will be screened and eligibility determined prior to enrollment. Screening assessments performed prior to the signing of informed consent as part of the site's routine standard of practice will be allowed at the discretion of Spectrum. This information should be discussed with the Medical Monitor before the patient is randomized and enrolled in the study.

All procedures are to be performed as outlined in **Appendix 1** prior to the start of study treatment, unless otherwise noted. The screening includes a cystoscopic exam in order to assess the stage and grade of the bladder tumor. An exam conducted as part of the standard practice within 30 days prior to randomization may serve as the assessment as long as stage and grade of tumor are reported using the World Health Organization (WHO) 1973 grading system.

5.2 Patient Assignment

Confirmation of eligibility is to be received by the investigational site from Spectrum prior to enrollment of a patient. After a patient has signed the ICF, the Investigator or site staff should log into IWRS and obtain a Patient ID. The Patient ID will include two parts: the site number comprised of 5 digits with a 2-digit alphabetic country code [Reference ISO 3166] followed by a 3-digit site specific numeric code and a 3-digit patient sequential number, unique to a site, separated by a hyphen (ie, [redacted]).

Once the Investigator or site staff have completed the required eCRFs, and approval for randomization has been received from Spectrum, the site will randomize the patient using a pre-specified randomization scheme. Please refer to the study binder for detailed instructions regarding enrollment.

5.3 Timing of Assessments and Procedures

5.3.1 Screening

The following screening assessments should be performed within 30 days of **Day 1** (**Day -30** to **Day -1**).

- Informed Consent
- Cystoscopic Exam (may be obtained prior to signing of IC and may be used for Screening purposes as long as they are performed prior to **Day 1**)
- Complete medical history
- Vital signs (temperature, blood pressure, and heart rate)
- Demographic data
- Physical examination
- Height and weight
- Complete blood count (CBC) with 3-part differential
- Chemistry
- Urine cytology
- Urine dipstick
- Pregnancy test (beta human chorionic gonadotropin [β-HCG]) in women of childbearing potential
- Adverse events using NCI CTCAE Version 4.03
- Concomitant Medications

5.3.2 Treatment Period Visit 1 (Day 1)

- Vital signs (temperature, blood pressure, and heart rate)
- Complete blood count with 3-part differential
- Chemistry
- Urine dipstick
- Randomization
- TURBT and pathology specimens to be sent to local pathology
- Urine cytology
- Apaziquone or placebo administration
- Adverse events using NCI CTCAE Version 4.03
- Concomitant Medications

5.3.3 Treatment Period Visit 2 (Day 15 [±5 days])

- Review of tumor pathology to determine continued patient eligibility based on Ta, G1-G2 histology (Can be performed any time between **Visit 1** and **Visit 2**)
- Vital signs (temperature, blood pressure, and heart rate)
- Complete blood count with 3-part differential
- Chemistry
- Urine dipstick
- Urine cytology
- Apaziquone or placebo administration
- Adverse events using NCI CTCAE Version 4.03
- Concomitant medications

5.3.4 Long-Term Follow-up Visits - Visits 3 through 10 (Every 90 days [±10 days] Post-TURBT)

- Urine dip stick
- Physical exam (as needed)
- Urine cytology
    - Cystoscopy
    - Adverse events using NCI CTCAE Version 4.03 (All AEs will be collected until 35 days after the last dose of study treatment. Only SAEs and AEs ≥Grade 3 will be recorded for the rest of the follow-up period.)
    - Concomitant medications

5.3.5 Safety Follow-up Visit (Day 35 (±5 days) After Date of Early Discontinuation or Last Dose of Study Drug)

- Physical examination

- Urine dip stick
- Adverse events using NCI CTCAE Version 4.03 (Only SAEs and AEs ≥Grade 3)
- Concomitant medications

5.4 Description of Study Assessments and Procedures

5.4.1 Explain Study and Obtain Written Informed Consent

Informed consent is to be obtained prior to the start of any protocol-specified assessments or procedures (including required washout of any prohibited medications). The Principal Investigator or designee is to discuss the study fully with the patient and obtain written Informed Consent. The written ICF is to be signed by the patient and the Principal Investigator or designee. A copy of the signed ICF is to be given to the patient.

5.4.2 Medical History

Medical history includes the history of the neoplastic disease, its previous therapy and investigations as well as significant past and all co-existing diseases and current medications for the previous 5 years.

5.4.3 Review Inclusion/Exclusion Criteria

At **Screening** and prior to enrollment, the Inclusion and Exclusion Criteria will be reviewed by the Principal Investigator or other qualified healthcare professional to ensure that the patient qualifies for the study.

5.4.4 Physical Examination

A complete physical examination, including a description of external signs of the neoplastic disease and co-morbidities is performed at **Screening** and at the **End-of-Study Visit** (**Visit 10** or date of discontinuation). A physical examination is only performed at all other visits if it is deemed clinically necessary. Physical examinations are to be completed by a physician or other healthcare professional licensed to perform such examinations. Findings will be documented in the patient's medical record and on the appropriate CRF pages. Any abnormalities after enrollment are to be recorded on the AE CRF.

5.4.5 Vital Sign Assessments

Temperature, blood pressure, and heart rate are to be recorded at **Screening** and at each treatment visit.

5.4.6 Clinical Laboratory Tests

A local laboratory will be used to process all clinical specimens. The following clinical laboratory parameters will be evaluated in this study:

- **CBC** - Including WBC with 3-part differential. The results of the laboratory assessments should be evaluated and medically accepted by the responsible physician for the assessment of clinical significant abnormalities.
- **Chemistry Panel** - Comprehensive chemistry and electrolytes including BUN, creatinine, creatinine clearance, AST/SGOT, ALT/SGPT, alkaline phosphatase, total

bilirubin, uric acid, and calcium. The results of the laboratory assessments should be evaluated and medically accepted by the responsible physician for the assessment of clinical significant abnormalities.

- **Urinalysis** - Urinalysis will be performed using urine dipsticks.

5.4.7 Urine Cytology

Urine cytology will be obtained for all patients at **Screening**, **Treatment Visit 1**, **Treatment Visit 2**, and every 90 days ± 10 days, from the date of TURBT, through 24 months.

5.4.8 Cystoscopy

Cystoscopy will be performed at **Screening** and every 90 days ± 10 days, from the date of TURBT, through 24 months. An operative report should contain the number, size and location of the recurrent tumors, if any. All lesions should be biopsied and sent for pathological review; recurrences are to be reported on the appropriate CRF. 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.

5.4.9 TURBT

TURBT will be performed according to each site's standard operating procedure. 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 local pathologist. A check for significant bleeding in the bladder will be performed post-TURBT in order to evaluate patients for study drug instillation. Within the administration window (60 ± 30 minutes post TURBT), study drug administration should be delayed to allow for resolution of significant bleeding. Patients with significant complications from TURBT (ie, bladder perforation, ongoing bleeding) should not receive study drug. 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 using the WHO 1973 grading system.

Prior to **Treatment Visit 2**, pathology will be reviewed by the Investigator and if the patient's tumor(s) is other than Ta, G1-G2, the patient will be discontinued from the study and will not receive any further treatment. Patients who are discontinued will return at **Day 35** (±5 days) for a **Safety Follow-up Visit**. If the final pathology is unavailable at the time of the second dose, the original clinical assessment that qualified the patient for the study will be used and the patient should receive the second dose of investigational product.

5.4.10 Adverse Event

At every visit, the Investigator or designee will question the patient about adverse events and intercurrent illnesses since the last visit, according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) Scale Version 4.03 for AE grading, and will record the pertinent information on the CRF. All AEs will be recorded until 35 days after the last dose of study treatment. Only SAEs and AEs ≥Grade 3 will be recorded for the rest of the 24 month follow-up period. From the time the study Informed Consent is signed

through the day of study drug administration, only SAEs that are related to study procedures are to be recorded.

5.4.11 Concomitant Medications

All medications administered from the time Informed Consent is signed through 24 months post TURBT will be recorded on the CRF. Start and stop dates and reasons for medication use will be noted.

6 STUDY DRUG AND PHARMACEUTICAL INFORMATION

6.1 Apaziquone and Placebo

Apaziquone and placebo will be supplied by Spectrum.

6.1.1 Composition of Apaziquone

Apaziquone for intravesical instillation is a sterile, non-pyrogenic, lyophilized product supplied in 10 mL clear glass vials. Each vial contains 4 mg apaziquone, 50 mg mannitol, and 5 mg sodium bicarbonate. After reconstitution, apaziquone has a reddish appearance similar to that of cranberry juice.

6.1.2 Composition of Placebo

Matching placebo containing 12 mg FD&C red #40, 15 mg sodium chloride, and 10 mg mannitol is supplied in identical appearing vials. Reconstitution and instillation procedures for placebo are the same as for apaziquone.

6.1.3 Composition of Diluent for Apaziquone and Placebo

The diluent for apaziquone and placebo is a sterile solution supplied in a 50 mL clear Type I glass vial. Each vial contains 41.2 mL of the diluent containing sodium bicarbonate, propylene glycol, disodium EDTA, and sterile water for injection.

6.1.4 Shipping and Storage of Study Drug

Study drug is shipped on cool packs in insulated containers, and should be stored in a secure area with limited access. Study drug is to be refrigerated (approximately 2°C to 8°C) in a secure area and should be protected from direct light. Diluent for study drug may be refrigerated or stored at room temperature.

6.2 Dose, Route of Administration, and Schedule of Study Drug

6.2.1 Dose and Route of Administration of Study Drug

Randomized patients will receive either apaziquone 4 mg reconstituted with 40 mL of diluent or matching placebo. Reconstitution procedures are outlined in the Pharmacy manual. The 40 mL of reconstituted study drug is to be instilled into the bladder via an indwelling 100% Silicone Foley catheter, where it is to be retained for 60 minutes (±5 minutes).

6.2.2 Schedule of Study Drug Administration

The first dose of the study drug on **Day 1** is to be administered at 60 ± 30 minutes post-TURBT. The second dose will be given on **Day 15** (±5 days) post-TURBT for all patients except those

whose pathology results show non Ta, G1-G2 disease; in the absence of local pathology results by the **Day 15** visit, patients will receive a second instillation of study drug. Within the administration window (60 ± 30 minutes post TURBT), study drug administration should be delayed to allow for resolution of significant bleeding. Patients with significant complications from TURBT (ie, bladder perforation, ongoing bleeding) should not receive study drug.

6.2.2.1 Preparation of Study Drug

Equipment needed: one 4 mg vial of apaziquone or placebo, one vial of Diluent , one 50 mL or 60 mL Luer-lok syringe, 18 gauge needle, protective clothing.

- Wear protective clothing.
- Draw up 40 mL of diluent in the syringe (approximately 5 mL will remain in the vial).
- Inject approximately 5 mL to 10 mL of diluent into the study drug vial.
- Gently agitate the vial and attached syringe until no undissolved particles are visible (Do not detach the syringe from the study drug vial).
- Withdraw all dissolved study drug into the syringe.
- Withdraw the syringe from the study drug vial.
- Cover the needle with needle cover.
- Invert the syringe at least 10 times to ensure adequate mixing.
- Carefully expel all trapped air in the syringe.
- The final volume in the syringe should be 40 mL.

If study drug is reconstituted, and not used within 6 hours, it must be discarded; resupply of new study drug kits may not always be possible in a reasonable time. Therefore, patient eligibility should be confirmed prior to drug reconstitution. The following criteria are to be met prior to drug reconstitution:

- Patient has ≤4 tumors;
- No single tumor is greater than 3.5 cm;
- Visual appearance consistent with a Ta, G1-G2 histology;
- No evidence of bladder perforation;
- Complete hemostasis is obtained, urine appears clear upon visual inspection;
- Post-TURBT diuretic has not been administered;
- Patients are at 60 ± 30 minutes post-TURBT.

6.2.2.2 Instillation of the First dose of the Study Drug on Day 1

Following drainage, study drug is to be instilled into the bladder via a 100% Silicone Foley catheter at 60 ± 30 minutes post-TURBT. Adequate hemostasis should be obtained, and the urine should appear visually clear (No macroscopic evidence of bleeding) before study drug instillation. Within the administration window (60 ± 30 minutes post TURBT), study drug administration should be delayed to allow for resolution of significant bleeding. Patients with significant complications from TURBT (ie, bladder perforation, ongoing bleeding) should not receive study drug. The bladder should be emptied before instilling the study drug. The 40 mL of

the study drug should be slowly instilled into the bladder taking care not to introduce air. The Foley catheter should be clamped for 60 minutes (±5 minutes).

If during the retention period, there is any leakage around the catheter, the amount of study drug leaked should be estimated and recorded. After 60 minutes (±5 minutes) of retention, the bladder contents should be drained and the drained bladder contents disposed of according to institutional policy. The institution's routine guidelines for the postoperative care should be followed.

No diuretics are allowed prior to instillation on the study drug instillation days. Study drug should not be instilled if a subclinical or clinical bladder perforation is suspected.

6.2.2.3 Instillation of the Second Dose of the Study Drug on Day 15 (±5 days) post-TURBT

A second dose of study drug is to be administered to all patients unless their pathology results are available and show non Ta, G1-G2 histology; in the absence of local pathology results by the **Day 15** visit, patients will receive a second instillation of study drug. For the second dose instillation, the patient's bladder should be drained via a 100% silicone Foley catheter followed by instillation of the study drug. The 40 mL of the study drug should be slowly instilled into the bladder taking care not to introduce air. The Foley catheter should be clamped for 60 minutes (±5 minutes).

If during the retention period there is any leakage around the catheter, the amount of study drug leaked should be estimated and recorded. After 60 minutes (±5 minutes) of retention, the bladder contents should be drained and the drained bladder contents disposed of according to institutional policy. The institution's routine guidelines for the postoperative care should be followed.

No diuretics are allowed prior to instillation on the study drug instillation days. Study drug should not be instilled if a subclinical or clinical bladder perforation is suspected.

6.3 Disposal of Study Drug

At the end of the 60 minute (±5 minutes) period of retention, study drug should be carefully drained/voided into a suitable container, and disposed of according to the institution's policies for disposal of hazardous waste.

6.4 Product Accountability

The site and/or the pharmacy 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 per the institution's policy.

All expired vials of study drug and diluent should be retained. The Clinical Research Associate (CRA) will periodically conduct an accountability of the expired study drug and diluent 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.

6.5 Treatment Blinding Procedures

This study is double-blind with respect to treatment assignment; all study participants (ie, subject, study staff including the physician, and all non-study individuals) and the Sponsor remain blinded until the study is complete and unblinded. An IWRS will be set up with appropriate access structure in order to keep the above study team blinded. Pharmacy will have access to the IWRS to get the treatment allocation.

The patients enrolled in this study will be randomized in a 1:1:1 ratio to one of three treatment arms: **Arm 1:** one instillation of 4 mg apaziquone, **Arm 2:** two instillations of apaziquone or **Arm 3:** placebo at each study site. A randomization scheme using permuted block design will be developed. An IVRS/IWRS system will be used to assign randomization ID once patients meet eligibility criteria and are ready to be randomized. The randomization code will be different than Patient ID that has been assigned to a patient and a mapping of randomization ID-Patient ID will be kept in a secured database.

In the case of a significant safety concern, a patient's treatment may be unblinded. The Investigator should first contact the Medical Monitor immediately to discuss and agree on the merits and need for unblinding a patient's treatment. The reasons and rationale for breaking the treatment blind will be documented in writing and maintained in the study file.

The study includes a futility analysis once 100 of the expected 336 recurrence events are observed in the **Placebo Treatment Arm**; this will enable a determination whether enrollment should be discontinued in an inefficacious **Apaziquone Treatment Arm**. An independent, unblinded data monitoring personnel will conduct this futility analysis. Data monitoring personnel will receive treatment allocation information directly from IWRS to monitor events and to perform statistical analysis. The entire study team will be unblinded only once all data are entered and locked and ready for final analysis.

6.6 Non-Study Treatments

6.6.1 Prior and Concomitant Medications

All concomitant medications, including over the counter supplements, should be recorded from **Screening** (**Visit -1**) through 24 months post-TURBT. Patients may use acetaminophen or antipyretics to manage side effects associated with TURBT and administration of study drug. Aspirin or products containing acetylsalicylic acid should not be used for 24 hours after the initial TURBT.

The Investigator may also prescribe standard post-operative medications.

6.6.2 Prohibited Medications

Prior to recurrence, patients with tumor histology of Ta, G1-G2 should not receive other medications to treat bladder cancer. If a patient starts another therapy for recurrence/progression, the patient will be withdrawn from the study after undergoing the end of study procedures, and followed up for safety at **Day 35** (±5 days) from last dose of study drug for a **Safety Follow-up Visit**.

No diuretics are allowed prior to instillation on study drug instillation days.

7 SAFETY ASSESSMENT

7.1 Safety Measures

It is the responsibility of the Principal Investigator to oversee the safety of the subjects at their site and to report all AEs/SAEs that are observed or reported during the study, regardless of relationship to study drug or clinical significance.

Safety data will also be reviewed on a regular basis by Spectrum's study monitoring team, which includes a Clinical Research Associate (CRA), the Medical Monitor, and other personnel from the company or its designee.

Adverse events will be characterized by intensity (severity), causality, and seriousness by the Investigator based on the regulatory definitions included below.

This study will utilize the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) Scale Version 4.03 for AE grading.

7.2 Adverse Events

An AE is defined as any untoward medical occurrence in a patient or clinical investigation patient, temporally associated with the use of a medicinal product or study procedure, whether or not considered related to the medicinal product. Therefore, an AE can be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a medicinal product. A treatment-emergent AE (TEAE) is any AE that occurs from the first dose of study treatment until 35 days (±5 days) after the last dose of study drug administration or 35 days (±5 days) after the date of patient early discontinuation. Only SAEs and AEs ≥Grade 3 will be recorded for the remainder of the 24 month follow-up period. From the time the study Informed Consent is signed through the day of study drug administration, only SAEs that are related to study procedures are to be recorded. The study will record all AEs according to the information in **Section 7.3**.

Examples of AEs **include**:

- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition.
- New conditions detected or diagnosed after investigational product administration.
- Signs, symptoms, or the clinical sequelae of a suspected drug interaction.
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either investigational product or a concurrent medication.

- AEs may include pre-treatment or post-treatment events that occur as a result of protocol-mandated procedures, ie, invasive procedures.

Abnormal laboratory results are to be recorded as AEs, if any of the following conditions are met:

- The abnormal laboratory value leads to a therapeutic intervention.
- The abnormal laboratory value is considered to be clinically significant by the Investigator.
- The abnormal laboratory value is predefined as an AE in the protocol or in another document communicated to the Investigator by Spectrum or designee.

Examples of events that **do not** constitute AEs include:

- Medical or surgical procedures (eg, endoscopy, appendectomy); the condition that leads to the procedure is an AE.
- Situations where an untoward medical occurrence does not occur (eg, social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.
- Planned and prescheduled hospitalizations and procedures.
- Progressive disease.

7.3 Guidelines for Recording and Attribution Scoring of Adverse Events

Timely and complete reporting of all AEs is required for all patients. Monitoring and documentation of all AEs allows for identification of potential study-drug or dose-related AEs, and for adherence to regulatory requirements. Please refer to the CRF Completion Guidelines located in the study binder for detailed instructions for AE reporting.

7.3.1 Recording of Adverse Events

All AEs that occur from the time of randomization until 35 days after the last dose of study drug will be recorded on the AE CRF. After 35 days and through 24 months, only SAEs and AEs ≥Grade 3 will be recorded. From the time the study Informed Consent is signed through the first dose of study drug administration, only SAEs that are related to study procedures are to be recorded.

All AEs should include resolution at the end of study for a patient. The following conventions should be followed when patient completes or discontinues from the study

- If a patient dies, the date of death should be the date of AE stop for all ongoing AEs at the time of death.
- If a patient discontinues study drug due to an AE(s), the outcome of the AE is to be followed for 35 days (±5 days) from the date of discontinuation or until the AE has returned to Grade≤1 or returned to baseline conditions for the patient.

The status of the AE and the date of last contact with the patient will be captured. If the AE has not returned to Grade≤1 or to Baseline conditions for the patient by the end of the study, the AE stop date should be left as ongoing.

All AEs will be classified by intensity/severity (**Section 7.3.2**), relationship to study drug (**Section 7.5**), and as serious or nonserious (**Section 7.7**).

7.3.2 Grading of Adverse Events

This study will utilize the NCI CTCAE Scale Version 4.03 for AE grading.

7.4 Follow-up of Adverse Events

All AEs and significant abnormal laboratory values are to be followed up in accordance with the International Conference on Harmonization (ICH) Good Clinical Practice (GCP) guidelines, and other applicable regulatory requirements (eg, United States [US] Code of Federal Regulations [CFR]).

7.5 Relationship

The Investigator must make a causality assessment and document their assessment as to the relationship of all AEs and SAEs to study treatment (**Table 9**).

Table 9 Investigator Assessment of Adverse Event Causality

Relationship	Description
Not Related	The event is clearly related to factors other than study treatment, such as the patient's clinical state, therapeutic interventions, or concomitant medications administered to the patient.
Unlikely Related	The temporal association, patient history and/or circumstances are such that the study drug or treatment is not likely to have had an association with observed event.
Possibly Related	The event follows a reasonable temporal sequence from the time of study treatment administration, and/or follows a known response pattern to study treatment, but could have been produced by other factors, such as the patient's clinical state, therapeutic interventions, or concomitant medications administered to the patient.
Probably Related	The event follows a reasonable temporal sequence from the time of study treatment administration, and follows a known response pattern to study treatment, and cannot be reasonably explained by other factors, such as the patient's clinical state, therapeutic interventions, or concomitant medications administered to the patient.

Relationship	Description
Definitely Related	The event follows a reasonable temporal sequence from the time of study treatment administration, and follows a known response pattern to study treatment, and cannot be reasonably explained by other factors, such as the patient's clinical state, therapeutic interventions, or concomitant medications administered to the patient. In addition, the event either occurs immediately following study treatment administration, improves on stopping study treatment, reappears on repeat exposure, or there is a positive reaction at the application site.

7.6 Expectedness

For investigational drugs, an AE is judged "expected" if its description agrees in nature and severity with the description of AEs previously noted with the study drug as detailed in the current Investigator's Brochure. An "unexpected" AE is one for which the specificity or severity is neither consistent with the current Investigator's Brochure or the risk information described in the general investigational plan. Spectrum will be responsible for assessing the expectedness of AEs.

7.7 Serious Adverse Events

In the interest of patient care and to allow Spectrum to fulfill all regulatory requirements, any serious adverse event (SAE), regardless of causal relationship to study treatment, is to be reported to Spectrum within 24 hours of knowledge of the event. SAEs are defined (21 CFR 312.32, ICH of Technical Requirements for Registration of Pharmaceuticals for Human Use E2A Guideline) as those AEs that meet any of the following criteria:

- Results in death
- Is life-threatening (Grade 4): ie, any event that, in the opinion of the Investigator, poses an immediate risk of death from that event
- Requires inpatient hospitalization or prolongation of existing hospitalization (excluding hospitalizations for study therapy, disease-related procedures, or placement of an indwelling catheter, unless associated with other SAEs)
- Results in a persistent or significant disability/incapacity
- Results in a congenital anomaly/birth defect
- Includes important medical events that may not be immediately life threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the outcomes listed in this definition

Adverse events that do not meet any of the above criteria for serious should be regarded as non-serious.

7.7.1 Serious Adverse Event Reporting

All SAEs that occur from the time the study Informed Consent is obtained and through 35 days after the last dose of study drug or 35 days (±5 days) after the date of early discontinuation. Only

SAEs and AEs ≥Grade 3 will be recorded for the remainder of the 24 month follow-up period and are to be reported to Spectrum within 24 hours of knowledge of the event.

SAEs (regardless of their relationship to study treatment) are to be reported and the serious adverse event report (SAER) faxed or emailed within 24 hours of knowledge of the event to:

Spectrum Pharmaceuticals, Inc.
Primary Contact: Pharmacovigilance Department
Fax: [redacted]
E-mail: [redacted]

Spectrum or its designee may request additional information from the Investigator to ensure the timely completion of accurate safety reports. Safety data that are critical to the reportability of an SAE, such as causality assessment and serious criteria, should be included in the initial faxed SAER. If omitted, a timely response to drug safety data queries received from Spectrum or a Spectrum designee is expected.

The Investigator is to take all appropriate therapeutic measures necessary for resolution of the SAE. Any medications necessary for treatment of the SAE are to be recorded in the concomitant medication section of the patient's CRF.

SAEs that are study-treatment related will be followed until resolution or until they have returned to Baseline/Grade 1, whichever is longer, or until it is determined that the outcome will not change with further follow-up.

Additionally, the SAE is to be entered in the AE section of the CRF. Follow-up SAERs need to be submitted to Spectrum within 24 hours, once additional information regarding the event becomes available (eg, diagnosis is made, laboratory or test results, event course, outcome, etc). The Spectrum Clinical Research Associate (CRA) or designee will collect the original SAER from the site.

Spectrum/designee will be responsible for reporting SAEs to the regulatory authorities in accordance with applicable expedited reporting regulatory guidelines. The Investigator is responsible for submitting SAEs to his/her Institutional Review Board (IRB)/Ethics Committee (EC). Copies of each SAER, and documentation of IRB/EC notification and acknowledgement of receipt, will be kept in the Site's Regulatory Binder.

7.7.2 Exclusions to Serious Adverse Event Reporting Requirements

The following are not considered SAEs:

- Situations where an untoward medical occurrence did not occur (eg, social and/or convenience admission to a hospital, hospitalization for diagnostic tests such as CT scans)
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected prior to first study treatment administration that do not worsen
- Planned and prescheduled hospitalizations and procedures
- Progressive disease

7.8 Reproductive Risks

To date, there are no adequate and well-controlled studies of apaziquone in pregnant women. Because the reproductive risks have not been studied in pregnant women, apaziquone is not recommended for use during pregnancy.

Pregnancies involving a study patient or a patient's partner, that occur from the first dose of study treatment through 35 days (±5 days) after the last dose of study treatment, must be reported within 24 hours after the Investigator has gained knowledge of the event via fax or e-mail (see contact information in **Section 7.7.1**). Follow up information regarding the outcome of the pregnancy will be requested by the Spectrum Pharmacovigilance Department.

All patients who become pregnant during participation in this study are to be withdrawn from the study.

8 STATISTICAL DESIGN AND ANALYSIS

This section contains a brief overview of the statistical analyses planned for this study. A formal statistical analysis plan (SAP) will be finalized before database lock.

8.1 Sample Size

In two randomized placebo-controlled clinical trials (**SPI-611** and **SPI-612**) of apaziquone in patients with Ta, G1-G2 bladder tumors (N= 802; 813), the **Recurrence Rate** in the **Placebo Treatment Arm** was approximately 46%. By taking into account the **Recurrence Rates** overall in the above two studies, the **Recurrence Rate** in the **Apaziquone Treatment Arm** from the two studies was assumed to be 39.5%, which results in a hazard ratio of approximately 0.80.

The enrolled patients will be randomized in a 1:1:1 ratio into one of three treatment arms including: **Arm 1:** one dose of apaziquone, **Arm 2:** two doses of apaziquone, or **Arm 3:** placebo, using a permuted block design. The primary endpoint of the study is **Time to Recurrence**. The primary endpoint analysis involves 2 pairwise tests of comparisons: one dose of 4 mg apaziquone vs. placebo and two doses of 4 mg apaziquone vs. placebo. No comparison of the treatment arms that received one dose of apaziquone vs. two doses of apaziquone will be performed.

The primary analyses of tests of pairwise comparisons of one dose vs. placebo and two doses vs. placebo arms will be performed using 2-sided log-rank test each at 5% level of significance. The primary analysis will be conducted using a hierarchical procedure of hypothesis testing. Hochberg procedure **[20]** will be used to control the overall Type I error rate due to multiple comparisons for the primary endpoint. If the larger p-value of the two comparisons (one dose vs placebo, two doses vs placebo) is ≤ 0.05, then both comparisons will be considered statistically significant. If the larger p-value of the two comparisons is >0.05 but the smaller p-value is ≤ 0.025, the comparison associated with the smaller p-value will be considered statistically significant. If the larger p-value of the two comparisons is >0.05 and the smaller p-value is >0.025, then neither comparison will be considered statistically significant.

The following procedure will be used to test the list of secondary endpoints for each pairwise comparison:

1. If both comparisons of primary endpoints (one dose vs. placebo, two doses vs. placebo) are significant ($p \leq 0.05$), the Type I error will be reused for the pairwise comparisons of

each secondary endpoint until a test p-value >0.05 in a pairwise comparison (one dose vs. placebo or two dose vs. placebo). No comparison will be made after this point.

2. If one of the comparisons of primary endpoints (either one dose vs. placebo or two doses vs. placebo) is not significant, no reuse of Type I error will be attempted for any of the secondary endpoints.

The order of secondary endpoints for the test of comparisons is listed below:

1. The **2-Year Recurrence Rate** of bladder cancer
2. The **1-Year Recurrence Rate** of bladder cancer
3. **Time to Progression** to higher stage

Approximately 1869 patients will be enrolled and treated in this study. Accrual time is estimated as 3 years and follow-up time as 24 months. Assuming 54% of patients are recurrence-free for placebo and 60.5% of patients are recurrence-free for the apaziquone treatment arms (assumed to be the same for each arm) at the end of 24 month follow-up, sample sizes of 519 per treatment arm will achieve 80% power to detect superiority in each comparison using log-rank test at 5% level of significance. The above sample size accounts for 5% of patients lost to follow-up. At the end of the 2-year follow up, this total is assumed to provide 336 recurrence events in the **Placebo Treatment Arm** and 295 recurrence events in each **Apaziquone Treatment Arm** (Hintze, J [2013]. PASS 12, NCSS, LLC, Kaysville, Utah, USA). The final analysis of the primary endpoint will be conducted once all 336 recurrence events in the **Placebo Treatment Arm** are accrued. .

Based on the data from prior studies on misclassification of stage and grade diagnosis at the screening for enrollment, an additional 20% patients may need to be enrolled in order to accrue the required **Target Ta, G1-G2 Population** in the study. Therefore, the study will enroll and randomize 623 patients per arm for a total of 1869 patients.

To determine whether enrollment should be discontinued in an inefficacious arm, a futility analysis will be conducted once the first 100 of the expected 336 recurrence events are observed in the **Placebo Treatment Arm** in the study. The required number of events needed to decide on the timing of the interim futility analysis will be tracked by independent, unblinded data monitoring personnel. The first 100 of the expected 336 recurrence events in the **Placebo Treatment Arm** will achieve 20% conditional power to detect the alternative hazard ratio of 0.8 at a significance level of 0.05 using a two-sided log-rank test. The corresponding z-value threshold of the data that have accrued for the futility analysis is -3.0. The futility index is 0.802. If the z-value of any of the pairwise comparisons (ie HR) between single dose apaziquone vs. placebo or two doses of apaziquone vs. placebo is less than -3.0, the corresponding non-efficacious **Apaziquone Treatment Arm** will be dropped and the study will be re-randomized to include the remaining **Apaziquone Treatment Arm** and **Placebo Treatment Arm** in a 1:1 ratio. No adjustment to Type I error will be made for the futility analysis as the final analysis will be conducted using a Type I error of 0.05 as stated in the protocol.

8.2 Method of Treatment Assignment, Randomization

Patients who meet all eligibility criteria may be considered for randomization. Eligibility of all patients will be reviewed and approved for randomization by the Sponsor's Medical Monitor, or

designee. Patients approved for randomization will be randomized 1:1:1 to receive one instillation of 4 mg apaziquone, two instillations of apaziquone, or two instillations of placebo.

The randomization plan will use a permuted block design and will not be stratified. Study drug kits will contain either 1 vial of apaziquone and 1 vial of placebo, 2 vials of apaziquone, or two vials of placebo and will be patient specific. Patients will be randomized within a center. Patient numbers will be assigned sequentially at each site.

Study drug should not be prepared until the number, size, and appearance of all bladder tumors are confirmed at TURBT. If for any reason, following TURBT the patient does not receive study drug, the Medical Monitor should be notified immediately via fax.

8.3 Analysis Populations

Four datasets will be analyzed:

- **Target (Ta G1-G2) Population**: all randomized patients with a local laboratory confirmed pathology of Ta, G1-G2 NMIBC, classified according to the treatment arms into which they were randomized, regardless of the actual treatment received. The analysis population for all efficacy endpoints will be the **Target (Ta, G1-G2) Population** based on local pathology.
- **Non-Target Population**: all randomized patients with a local laboratory confirmed non-Ta, G1-G2 NMIBC, classified according to the treatment arms into which they were randomized, regardless of the actual treatment received. No primary efficacy endpoint analysis will be provided in this population as they will not be under follow up.
- **Per-Protocol Population:** all randomized patients classified according to the actual treatment received who have local pathology confirmed Ta, G1-G2, regardless of random assignment. Randomized patients who receive no treatment or have major protocol deviations will be excluded from the analyses of efficacy.
- **Safety Population**: all randomized patients classified according to the actual treatment received, regardless of random assignment.

8.4 General Statistical Methods

Spectrum's Biostatistics and Data Management (BDM) group will be responsible for data management and statistical analysis of this study. All statistical analyses will be performed using SAS for Windows (version 9.3 or higher). Patient data listings and tabular presentations of results by treatment arms will be provided. Further details of the criteria and conduct of the statistical analyses will be included in the Statistical Analysis Plan for this study.

8.5 Efficacy Analyses

8.5.1 Efficacy Assessments

The primary efficacy assessment will be time to histologically documented recurrence reported in patients with histologically confirmed Ta, G1-G2 histology by local pathology, who received one or two instillations of apaziquone or placebo. These patients will be assessed cystoscopically and by urine cytology at 90 day (±10 days) intervals calculated from the date of TURBT. The date of the biopsy procedure at which the bladder tumor was confirmed histologically will be

used as the date of recurrence. Patients with Ta, G1-G2 histology who recur and do not receive any further intravesical therapy will continue to be followed for two years after randomization.

8.5.2 Primary Endpoint

- **Time to Recurrence** in patients with either one instillation of 4 mg apaziquone or two instillations of 4 mg apaziquone relative to placebo instillation following TURBT

8.5.3 Secondary Endpoints

1. The **2-Year Recurrence Rate** of bladder cancer
2. The **1-Year Recurrence Rate** of bladder cancer
3. **Time to Progression** to higher stage

8.5.4 Definitions

- **Recurrence**: any pathology confirmed bladder cancer in the patient's bladder
- **Progression**: any pathology confirmed bladder cancer in the patient's bladder with a higher stage

8.5.5 Primary Endpoint - Time to Recurrence

Time to Recurrence is the time from date of randomization to the date of first documentation of recurrent disease. **Time to Recurrence** of patients with no documented recurrence while on study will be censored at the date of last evaluable visit (cystoscopy or TURBT) on-study. **Time to Recurrence** of patients with no evaluable visit on-study will be censored at randomization.

The primary endpoint of **Time to Recurrence** will be analyzed using the **Target (Ta, G1-G2) Population** as defined above. The final analysis of **Time to Recurrence** will be conducted once all 336 of the expected recurrence events in the **Placebo Treatment Arm** are accrued. The primary endpoint analysis involves 2 pairwise tests of comparisons: one dose of 4 mg apaziquone vs. placebo and two doses of 4 mg apaziquone vs. placebo. No comparison of the treatment arms that received one dose of apaziquone vs. two doses of apaziquone will be performed. The primary analyses of tests of pairwise comparisons of one dose vs. placebo and two doses vs. placebo arms will be performed using 2-sided log-rank test each at 5% level of significance.

The primary analysis will be conducted using a hierarchical procedure of hypothesis testing. Hochberg procedure [20] will be used to control the overall Type I error rate due to multiple comparisons for the primary endpoint. If the larger p-value of the two comparisons (one dose vs placebo, two doses vs placebo) is ≤ 0.05, then both comparisons will be considered statistically significant. If the larger p-value of the two comparisons is >0.05 but the smaller p-value is ≤ 0.025, the comparison associated with the smaller p-value will be considered statistically significant. If the larger p-value of the two comparisons is >0.05 and the smaller p-value is >0.025, then neither comparison will be considered statistically significant.

In addition, the following additional analyses will be provided:

- Analysis of **Time to Recurrence** in **Target (Ta, G1-G2) Population** who received only one dose of apaziquone

- Analysis of **Time to Recurrence** in **Target (Ta, G1-G2) Population** who received both doses of apaziquone
- Analysis of **Time to Recurrence** in the **Per-protocol Population** in **Target (Ta, G1-G2) Population** receiving one dose of apaziquone and those receiving both doses of apaziquone

The following patients will be considered as protocol deviations and will be addressed in the analysis of **Time to Recurrence** using the **Per-Protocol Population** as exploratory:

- Analysis of **Time to Recurrence** with **Day 1** instillation that do not occur between 31 and 90 minutes post-TURBT
- Analysis of **Time to Recurrence** in patients whose follow up cystoscopy occurs outside the ±10-day window

For the above analyses, the following data handling rules will be used:

- Patients who change therapy prior to recurrence will be censored at the last assessment prior to change in therapy.
- Patients with two or more missing assessments immediately prior to the next visit with a documented recurrence will be censored at the last assessment with documentation of no recurrence.

The primary analysis will include all patients in the **Ta, G1-G2 Target Population** irrespective of lost pathology or no sample.

Distribution of **Time to Recurrence** will be estimated using the Kaplan-Meier product-limit method. The median times to recurrence with two-sided 95% confidence intervals will be estimated, together with the estimates at 6, 12, 18 and 24 months. The hazard ratio of the treatment effect will be estimated from a Cox proportional hazard regression model with treatment arm as the only covariate and tested using a log-rank test at the level of significance described above. Additional exploratory analysis of Cox proportional hazard regression will be used to estimate the hazard ratio, and its 95% confidence interval. The model will include treatment effect, study center, primary vs. recurrent disease as stratification factor in addition to any other baseline or demographics factors.

8.5.6 Secondary Endpoints

8.5.6.1 Secondary Endpoint - Recurrence Rates

1-Year and **2-Year Recurrence Rates** will be estimated using the Kaplan-Meier product-limit method along with two-sided 95% confidence intervals and will be compared using a two-sided log-rank test each at 5% level of significance. Since visits do not often occur at the specified intervals, a cut-off upper limit of 375 or 765 days from randomization will be used for the 12 or 24 month visits, respectively.

For the main analysis, the **Recurrence Rate** calculation includes patients who met recurrence criteria as confirmed by pathology at each visit. An additional analysis will be provided by counting patients who drop out prior to the above time point as having a recurrence. The **Recurrence Rates** will be cumulative at each visit from the time of study randomization.

8.5.6.2 Secondary Endpoint - Time to Progression

Time to Progression is the time from randomization to the first documentation of stage progression as confirmed by pathology in the **Target (Ta, G1-G2) Population**. **Time to Progression** of patients with no documented progression on-study will be censored at the time of last evaluable visit on-study. **Time to Progression** of patients with no evaluable visit on-study will be censored at randomization.

Distribution of **Time to Progression** will be estimated using the Kaplan-Meier method. Analysis of **Time to Progression** will be similar to the analysis of **Time to Recurrence**, above.

8.6 Safety Evaluation

Patients will be evaluated for safety if they have received any study treatment (**Safety Population**), and classified according to the treatment received.

8.6.1 Safety Endpoints

- All AEs
- Related Adverse Events
- Serious Adverse Events (SAEs)
- AEs leading to drug discontinuation
- Vital signs (blood pressure and heart rate) and routine laboratory parameters (hematology, chemistry)
- Deaths

8.6.1.1 Adverse Events

All treatment emergent adverse events will be graded according to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 4.03, and grouped by the MedDRA Preferred Term, and summarized by worst grade severity per patient.

8.6.1.2 Deaths

All deaths reported during the study will be tabulated and summarized by treatment arm.

8.6.2 Other Serious Adverse Events

Serious adverse events will be tabulated and summarized by MedDRA Preferred Term and treatment arm.

8.6.3 Clinical Laboratory Evaluations

Clinical laboratory results will be collected pretreatment and throughout study. All laboratory results will be classified according to the NCI CTCAE version 4.03, and will be summarized by worst grade per patient and treatment arm.

9 ADMINISTRATIVE PROCEDURES AND STUDY MANAGEMENT

9.1 Investigator Responsibilities

9.1.1 Good Clinical Practice

It is the responsibility of the Principal Investigator to oversee the safety of the patients at their site. The Investigator will ensure that this study is conducted in full compliance with the principles of the "Declaration of Helsinki" (as amended in Tokyo, Venice, Hong Kong, and South Africa), ICH guidelines, or with the laws and regulations of the country in which the research is conducted. By signing the US Form FDA 1572, "Statement of Investigator", the Investigator commits to adhere to applicable sections of the US CFR parts 50 "Protection of Human Patients", 54 "Financial Disclosure by Clinical Investigators", 56 "Institutional Review Boards", and 312 subpart D "Responsibilities of Sponsors and Investigators". All Investigators will ensure adherence to ICH guidelines for GCP and Clinical Safety Data Management.

9.1.2 Institutional Review Board/Ethics Committee Approval

The Investigator shall assure that the IRB/EC will provide initial and continuing review of the study. Prior to screening and enrollment of study patients, documented IRB/EC approval of the protocol, ICF and any patient materials must be obtained and provided to Spectrum or its designee.

9.1.3 Informed Consent

The investigator will ensure that the method of obtaining and documenting the Informed Consent complies with ICH-GCP and all applicable regulatory requirement(s). Informed Consent must be obtained before study procedures are performed, unless performed as standard of care. The subject's source documents shall document the informed consent process and that Informed Consent was obtained prior to study participation. A copy of each signed ICF must be provided to the patient or the patient's legally authorized representative. All signed ICFs must remain in each patient's study file and must be available for verification at any time.

9.1.4 Study Files and Retention of Records

The Investigator will retain all study records until at least 2 years after the last approval of a marketing application or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents will be retained for a longer period, however, if required by the applicable regulatory requirements or by an agreement with Spectrum. If the Investigator relocates, or for any reason desires to dispose of the records, the study records may be transferred to another institution, another investigator, or to Spectrum upon written agreement between the Investigator and Spectrum.

9.2 Recording and Collecting of Data

In accordance with ICH and GCP guidelines, the Investigator will maintain complete, accurate, legible, and easily retrievable data, and will allow personnel authorized by Spectrum access to all study data at any time. Such data shall also be secured in order to prevent loss of data.

9.2.1 Case Report Forms

At scheduled monitoring visits, CRFs will be verified against source documentation and submitted as final data. Any subsequent changes to the CRFs are to be performed in accordance with Spectrum's standard operating procedures for editing and clarifying CRFs. Data entry will be performed by the sites using an electronic data capture (EDC) system. Comment fields on the CRFs will be used as a means of clarification and communication between the Investigator and Spectrum; however, comments entered in these fields will not be edited or clarified.

9.2.2 Drug Accountability

In accordance with all applicable regulatory requirements, the Investigator or designated site staff is to maintain study treatment accountability records throughout the course of the study. This person(s) will document the amount of apaziquone administered to patients. The CRA will review inventory and accountability documentation during monitoring visits.

The Investigator will not supply investigational study drugs to other investigators not listed on the US Form FDA 1572 or equivalent. Investigational study drug use, other than as directed by this protocol, is not allowed.

All unused vials of apaziquone are to be accounted for at the site and maintained in a secured, locked storage area with access limited to authorized study personnel only. Used apaziquone vials will be destroyed per institution, local, and all applicable policies and procedures. After study conclusion, all unused vials of apaziquone may be destroyed at the site, following verification of accountability by a Sponsor representative.

9.3 Protocol Compliance

The Principal Investigator is responsible for ensuring the study is conducted in accordance with the procedures and evaluations described in this protocol.

9.4 Sponsor Responsibilities

9.4.1 Study Monitoring

The study will be monitored by employees or representatives of Spectrum. CRAs will monitor each site on a periodic basis and perform verification of source documentation for each patient as well as other routine compliance reviews. Spectrum's Medical Monitor and Pharmacovigilance Department will review safety data and be responsible for ensuring timely reporting of expedited SAERs to regulatory agencies and Investigators.

9.4.2 Safety Monitoring

The clinical drug safety of study treatment will be continuously evaluated by the study Medical Monitor or designee on an ongoing basis during the course of this clinical study. All SAEs related to study treatment in this study and all other ongoing clinical studies with study treatment will be processed in compliance with current regulatory guidelines by Spectrum's Pharmacovigilance Department. This processing will include a formal assessment of each SAE by drug safety. In addition, a cumulative review of all SAEs from all sources will be assessed periodically

9.5 Joint Investigator/Sponsor Responsibilities

9.5.1 Access to Information for Monitoring and Auditing

In accordance with ICH GCP guidelines and 21 CFR 312, the CRA/auditor is to have direct access to the patient's source documentation in order to verify the data recorded in the eCRFs. The CRA is responsible for routine review of the eCRFs at regular intervals throughout the study and to verify adherence to the protocol, as well as the completeness, consistency, and accuracy of the data being recorded. The CRA/auditor is to have access to any patient records needed to verify the entries on the eCRFs, as well as access to all other study-related documentation and materials. The Investigator agrees to provide the monitor with sufficient time and facilities to conduct monitoring.

9.5.2 Termination of the Study

For reasonable cause, either the Investigator or Spectrum may terminate the Investigator's participation in this study. In addition, Spectrum Pharmaceuticals Inc. may terminate the study at any time upon immediate notice for any reason, including but not limited to, Spectrum's belief that termination is necessary for the safety of patients.

9.5.3 Publication Policy

To coordinate the dissemination of data from this study, Spectrum encourages the formation of a publication committee consisting of the Principal Investigator and appropriate Spectrum staff. The committee is expected to solicit input and assistance from other Investigators and Sponsor staff as appropriate. Membership on the committee (both for Investigators and Staff) does not guarantee authorship- the criteria described below should be met for every publication.

Authorship of any publications resulting from this study will be determined on the basis of the Uniform Requirements for Manuscript Submitted to Biomedical Journals (International Committee of Medical Journal Editors, 2005), which states:

- Authorship credit should be based on the following; authors should meet all three conditions:
  1. Substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data;
  2. Drafting the article or revising it critically for important intellectual content; and
  3. Final approval of the version to be published.
- When a large, multicenter group has conducted the work, the group should identify the individuals who accept direct responsibility for the manuscript. These individuals should fully meet the criteria for authorship defined above.
- Acquisition of funding, collection of data, or general supervision of the research group alone does not constitute authorship.
- All persons designated as authors should qualify for authorship, and all those who qualify should be listed.
- Each author should have participated sufficiently in the work to take public responsibility for appropriate portions of the content.

All publications (eg, manuscripts, abstracts, oral/slide presentations, books chapters) based on this study must be submitted to Spectrum within 30 days (but no less than 10 days) prior to submission or publication for corporate review.

9.6 Confidentiality

All information provided to the Investigator by Spectrum, including nonclinical data, protocols, CRFs, and verbal and written information, will be kept strictly confidential and confined to the clinical personnel involved in conducting this study, and no disclosure shall be made except in accordance with any right of publication granted to the Investigator. All personnel will handle patient data in a confidential manner in accordance with applicable regulations governing clinical research. Upon request by a regulatory authority such as the US FDA and other regulatory authorities worldwide, the Investigator/institution is to make available for direct access all requested study-related records or reports generated as a result of a patient's participation in this study. This information may be related in confidence to the IRB/EC or other committee functioning in a similar capacity. In addition, no reports or information about the study or its progress will be provided to anyone not involved in the study other than to Spectrum, or in confidence to the IRB/EC or similar committee, except if required by law.

10 REFERENCES

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APPENDIX 1 SCHEDULE OF STUDY ASSESSMENTS AND PROCEDURES

Assessments	Screening	Randomization/ Treatment #1	Treatment #2	Post-TURBT Follow-up [a] (90 ± 10 days)							End-of-Study Visit
	Day -30 to 1	Day 1	Day 15 (±5 days)	Month 3	Month 6	Month 9	Month 12	Month 15	Month 18	Month 21	Month 24 [b]
	Visit 0	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8	Visit 9	Visit 10
Informed Consent (IC)	x										
Cystoscopy	x [c]			x	x	x	x	x	x	x	x
Medical history	x										
Vital signs	x	x	x								
Weight and height	x										
Physical examination [d]	x										x
Complete Blood Count	x	x [e]	x								
Chemistry	x	x [e]	x								
Pregnancy test	x										
Urine dip stick	x	x [e]	x	x	x	x	x	x	x	x	x
Urine cytology	x	x	x	x	x	x	x	x	x	x	x
TURBT		x									
Randomization		x									
Apaziquone or Placebo instillation [f]		x	x								
Concomitant medications	x	x	x	x	x	x	x	x	x	x	x
Adverse event assessment [g]	x	x	x	x	x	x	x	x	x	x	x

a) Follow up visits, cystoscopies, and urine cytology for patients with Ta, G1-G2 histology only are to be conducted every 90 days (±10 days) calculated from the date of TURBT for 24 months.
b) For Patients who complete 24 months of follow-up, **Month 24** visit (**Visit 10**) will be the **End-of-Study Visit**.
c) The qualifying cystoscopy may be performed up to 30 days prior to signing the informed consent. Patients with the study qualifying tumor number, size, and appearance may be presented with the study informed consent.
d) A complete physical examination will be performed at **Screening** and at the **Month 24/End-of-Study Visit**. At all other visits, a physical examination is only required as indicated.
e) If the screening assessments for the physical examination, hematology, chemistry, urine dipstick were performed within 3 days (72 hours) prior to **Day 1**/TURBT, these assessments do not need to be repeated at the **Day 1** visit.
f) Instillation of study drug (apaziquone or placebo) is to be performed at 60 ± 30 minutes post-TURBT procedure on **Day 1** and is to be retained in the bladder for 60 minutes (±5 minutes).
g) All adverse events from the time of randomization until 35 days after the last dose of study treatment will be recorded. After 35 days and through 24 months, only SAEs and AEs ≥Grade 3 will be recorded.