Official Title:	**A Randomized, Multicenter, Two-Arm, Single-Dose, Double- Blind, Placebo-CONtrolled Phase 3 Study of Intravesical Qapzola™ (Apaziquone) as a Chemotherapy Adjuvant to TransUrEthral Resection of Bladder Tumors in Patients with Low- to Intermediate-Risk Non-Muscle Invasive Bladder Cancer (CONQUER)**
NCT Number:	NCT03224182
Document Date:	Clinical Study Protocol Original: 22 December 2016

CONFIDENTIAL
CLINICAL STUDY PROTOCOL

TITLE PAGE

Study Title:	**A Randomized, Multicenter, Two-Arm, Single-Dose, Double-Blind, Placebo-CONtrolled Phase 3 Study of Intravesical Qapzola™ (Apaziquone) as a Chemotherapy Adjuvant to TransUrethral Resection of Bladder Tumors in Patients with Low- to IntermediatE-Risk Non-Muscle Invasive Bladder Cancer (CONQUER)**
Study Number:	**SPI-QAP-306**
Study Phase:	Phase 3
Study Drug:	Qapzola™ (Apaziquone)
IND Number:	73,572
Sponsor(s):	Spectrum Pharmaceuticals, Inc. 157 Technology Drive Irvine, CA, USA

Protocol Version/Date: Original/22 Dec 2016

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The information contained in this document, particularly unpublished data, is the property or under control of Spectrum Pharmaceuticals, Inc. and is provided to you in confidence as an Investigator, potential Investigator, or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-QAP-306

A Randomized, Multicenter, Two-Arm, Single-Dose, Double-Blind, Placebo-CONtrolled Phase 3 Study of Intravesical Qapzola™ (Apaziquone) as a Chemotherapy Adjuvant to TransUrethral Resection of Bladder Tumors in Patients with Low- to IntermediatE-Risk Non-Muscle Invasive Bladder Cancer (CONQUER)

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 Randomized, Multicenter, Two-Arm, Single-Dose, Double-Blind, Placebo-**CON**trolled Phase 3 Study of Intravesical **Q**apzola™ (Apaziquone) as a Chemotherapy Adjuvant to Trans**U**rethral Resection of Bladder Tumors in Patients with Low- to Intermediat**E**-**R**isk Non-Muscle Invasive Bladder Cancer (**CONQUER**)	
Name of Sponsor: Spectrum Pharmaceuticals, Inc.	
Name of Investigational Product: Qapzola™ (apaziquone)	
Planned Number of Patients: Approximately 500 patients will be enrolled to obtain 425 target disease patients in two treatment arms.	
Study Centers: Approximately 70 study centers globally.	
Duration of Study: Approximately 5 years (2.5 years accrual + 2.5 years follow-up)	**Clinical Phase:** 3

OBJECTIVES:

Primary Objective(s)

- To evaluate the Time to Recurrence in patients with low- to intermediate-risk non-muscle invasive bladder cancer (NMIBC) who receive either 8 mg Qapzola or placebo post transurethral resection of bladder tumor (TURBT).

Secondary Objectives

To evaluate the following in patients with low- to intermediate-risk NMIBC who receive either 8 mg Qapzola or placebo post-TURBT:

1. 2-Year Recurrence Rate
2. Extent of Disease at Recurrence (number, and location of tumors)
3. Time to Disease Progression (based on the tumor stage)
4. Safety

STUDY DESIGN AND TREATMENT PLAN:

This is a randomized, multicenter, two-arm, double-blind, placebo-controlled study of Qapzola in patients with low- to intermediate-risk NMIBC, assessed according to the 2016 American Urology Association (AUA) Guidelines. Specifically, only patients with tumor characteristics in **bold text** in the low- to intermediate-risk columns of the table below will be included in the study.

2016 American Urological Association Stratification for Non-Muscle Invasive Bladder Cancer

Low Risk	Intermediate Risk	High Risk
• **Low grade solitary Ta ≤3cm*** • **PUNLMP***	• **Recurrence within 1 year, low-grade Ta*** • **Solitary low-grade Ta >3 cm*** • **Low-grade Ta, multifocal*** • **High-grade Ta, ≤3 cm (solitary tumor)*** • Low-grade T1	• High grade T1 • Any recurrent, high grade Ta • High grade Ta, >3 cm (or multifocal) • Any CIS • Any BCG failure in high-grade patient • Any variant histology • Any lymphovascular invasion • Any high-grade prostatic urethral involvement

* - histology for evaluable target population

In addition to other Screening assessments, patients will undergo an assessment of urothelial carcinoma of the bladder via cystoscopy for clinically apparent tumor of Ta histology, including PUNLMP. The qualifying cystoscopy may be performed up to 45 days prior to signing the informed consent.

Eligible patients will be randomized in a 2:1 ratio to either:

- **Arm 1:** One dose of 8 mg Qapzola
- **Arm 2:** One dose of placebo

Once approved for randomization, patients will undergo TURBT on Day 1 and the study drug instillation will occur at 60 ± 30 minutes post-TURBT and will be retained for 60 minutes (±5 minutes) in the bladder. All histology specimens will be reviewed by a local pathology laboratory and all clinical treatment decisions will be based on the local pathology review. Patient target disease will be confirmed and efficacy analyses will be performed based on the pathology results. The target study population is low- to intermediate-risk patients who have Ta histology, including PUNLMP, as confirmed by a pathology laboratory. Patients whose tumor histology does not meet the criteria for eligibility, as confirmed by pathology (Non-Target Population), will be followed up for safety on Day 35 (±5 days) (Safety Follow-up Visit) and will be discontinued from the study. If the pathology results are delayed beyond 35 days, the Safety Follow-up Visit will be conducted when the results are available for these patients.

Patients who have pathology confirmed target histology will not receive additional medications to treat NMIBC during the follow-up while on study. All target disease patients will be followed until either a confirmed tumor recurrence, additional bladder cancer treatments, or until the End-of-Study, whichever occurs first.

The primary analysis will be conducted once the required number of recurrence events are observed as detailed in the Statistical Methods below. A recurrence is defined as any pathologically confirmed disease of ≥Ta histology or CIS post-treatment. The number of events needed to perform the final primary endpoint analysis was estimated based on the recurrence rate at 24 months from previous studies. The follow-up schedule is below:

- Cystoscopic examination and urine cytology every 3 months (±30 days) (calculated from date of TURBT) for 2 years for tumor recurrence and progression and then every 6 months (±60 days) until either a confirmed tumor recurrence or the End-of-Study, whichever occurs first.
- If at any time during the study there is a histologically confirmed tumor recurrence, the patient will be discontinued from the study at that time and may then be treated per the Investigator's standard of care.

The study will end (End-of-Study) when the required number of events for the primary endpoint analysis are accrued.

Duration of Study: The duration of the study for each patient will be as follows:

- **Screening Period:** up to 30-days
- **Treatment:** Day 1
- **Safety Follow-up:** Day 35 (±5 days) (non-Target Population) or Month 3 Follow-up Visit (Target Population)
- **Follow-up Period:** No follow-up in non-Target Population. Until either a confirmed tumor recurrence or the End-of-Study, whichever occurs first in Target Population.

Patient Replacement Strategy: If a patient is confirmed to have non-target disease after TURBT, the patient will not be considered evaluable for analysis. Enrollment will continue until the study reaches the required number of target-disease evaluable patients.

INCLUSION & EXCLUSION CRITERIA:

Inclusion Criteria:

1. Patient must have a clinical diagnosis of low- to intermediate-risk non-muscle invasive bladder cancer according to the 2016 American Urological Association (AUA) Guidelines
2. 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.
3. Patient is at least 18 years of age and <90 years of age at the time Informed Consent is signed.
4. 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 study treatment. Patients surgically sterilized or who are postmenopausal for at least 1 year (defined as more than 12 months since last menses) do not require contraception.
5. 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 malignancy or life-threatening systemic disease or a history of advanced, serious, life-threatening malignancy/disease within the last 5 years, except very low-risk prostate cancer
2. Patient has used any investigational drugs, biologics (vaccines, antibodies), or devices within 30 days prior to study treatment or has plans to use any of these during the course of the study
3. Patient has received any pelvic radiotherapy (including external beam and/or brachytherapy).
4. Patient has a history of allergy to red color food dye or any other component of Qapzola, placebo, or their diluents
5. Patient has had a surgical procedure 4 weeks prior to TURBT or will have other surgical procedures performed at the time of TURBT or within 4 weeks after TURBT
6. Patient has any unstable or uncontrolled medical condition that would make it potentially unsafe to undergo TURBT including a previous stroke or myocardial infarction within 6 months
7. 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 study treatment or undergo study procedures
8. Patient has a bleeding disorder or a screening platelet count $<100\times10^9$/L, or requires continuous anticoagulation or bridging anticoagulation during the procedure
9. Patient has a hemoglobin value <10 g/dL at Screening
10. Patient has ever had confirmed extravesical urothelial disease (upper tract and urethral including prostatic urethral)
11. Patient with a history of previous bladder cancer:
    - High-Risk NMIBC as classified per the 2016 AUA Guidelines
    - Bladder cancer that was muscle invasive or positive for lymph node or distant metastasis

12. Patient has received any previous intravesical therapy for bladder cancer- chemotherapy, immunotherapy, or previous exposure to Qapzola in the last 3 years
13. Patient has a tumor in the bladder diverticulum
14. Patient has a history of interstitial cystitis
15. Patient is pregnant or breast-feeding

DOSE AND ROUTE OF ADMINISTRATION:

One dose of either 8 mg/50 mL Qapzola or volume and appearance matched placebo will be administered by intravesical administration into the bladder at 60 ± 30 minutes post TURBT (Day 1) via an indwelling 100% Silicone Foley catheter and will be retained in the bladder for 60 ± 5 minutes.

EFFICACY ASSESSMENTS:

Cystoscopic examination and urine cytology test every 3 months (±30 days) (calculated from date of TURBT) for the first 2 years for tumor recurrence and progression and then every 6 months (±60 days) until either a confirmed tumor recurrence or the End-of-Study, whichever occurs first. Pathology review will be performed by local laboratories on tissue/tumor specimens from cystoscopy or TURBT, whichever is conducted for the follow-up assessment.

Primary Endpoint:

- Time to Recurrence in patients with low- to intermediate-risk NMIBC who receive either 8 mg Qapzola or placebo following TURBT.

The primary analysis will be conducted once a total of 208 recurrence events have occurred in the study.

Secondary Endpoints:

1. 2-Year Recurrence Rate
2. Extent of Disease at Recurrence (number and location of tumors)
3. Time to Disease Progression (based on the tumor stage)
4. Safety

SAFETY ASSESSMENTS:

Safety will be assessed by reported/elicited adverse events (AEs), laboratory test assessments, and physical examinations.

Safety Endpoints

- All AEs
- Treatment-related adverse events
- Serious Adverse Events (SAEs)
- AEs leading to discontinuation
- AEs of special interest (≥grade 3 dysuria and hematuria)
- Vital signs (body temperature, blood pressure and heart rate) and routine laboratory test parameters (complete blood count and blood chemistry)
- Deaths

Adverse Event and Serious Adverse Event Reporting:

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. For all non-Target population patients, all adverse events from the time of study drug administration until Day 35 (±5 days) post-TURBT will be recorded. For Target population patients, all adverse events will be recorded from the time of study drug administration until the 3-month Follow-up Visit. Only deaths and AEs related to study procedures will be recorded for the remainder of the follow-up period.

Independent Data Monitoring Committee (IDMC)

The safety of the 8 mg/50 mL Qapzola dose will be evaluated by an IDMC for the first 30 patients treated in the study. Continuation of the study at this dose level will be determined based on the IDMC evaluation. The IDMC is also responsible for the review of the unblinded futility analysis.

STATISTICAL METHODS:

The primary analysis population is the Target Population, which will consist of all patients with confirmed low- to intermediate-risk NMIBC. The stage and grade determination for the Target Population will come from the pathology review. Tumors will be graded using 2004 WHO/ISUP criteria.

The Safety Population includes all patients who have had a TURBT and have received treatment of study drug (Qapzola or placebo).

The enrolled patients will be randomized in a 2:1 ratio to either Qapzola or placebo. The primary endpoint is Time to Recurrence in the Target Population. The primary endpoint analysis involves a test of comparison: 8 mg Qapzola vs. placebo using 2-sided log-rank test at 5% level of significance.

The Time to Recurrence is defined as time from Day 1 Treatment to the date of the first histologically confirmed recurrence (using the date of corresponding cystoscopy) of the patient's bladder tumor. Patients without recurrence at the time of the primary analysis will be censored at the last available date of cystoscopy. Patients who died due to any cause before confirmed recurrence will be censored at the last available date of cystoscopy.

The following sensitivity analyses will be performed for the primary analysis.

1. Analysis of time to recurrence by excluding patients who miss 2 consecutive cystoscopies or lost to follow-up either prior to recurrence or prior to the date of the primary analysis – Completer analysis
2. Analysis of time to recurrence by excluding patients who miss 2 consecutive cystoscopies or lost to follow-up either prior to recurrence or prior to patient's follow-up duration of 24 months – Completer 24 Month analysis
3. Analysis of time to recurrence by considering patients with no recurrence who miss 2 consecutive cystoscopies or lost to follow-up prior to date of the primary analysis as recurred.

The primary analysis will be conducted using a hierarchical procedure of hypothesis testing at a 5% level of significance. The primary endpoint, Time to Recurrence, will be examined first, and if significant, the secondary endpoint, 2-Year Recurrence Rate, will be examined next, and if also significant, Extent of Disease at Recurrence, and Time to Disease Progression will then be examined in that order.

Approximately 500 patients will be enrolled and treated in this study. Accrual time is estimated as 24 months and follow-up time as approximately 24 months. For the sample size calculation, a hazard ratio (HR) of 0.65 is assumed for the improvement in Time to Recurrence in favor of Qapzola as compared to the placebo with a hazard rate of 0.3 in placebo arm. In a 2:1 randomization of Qapzola and placebo, sample sizes of 284 in APZ and 141 in PBO Target disease patients (total of 425) will provide 85% power. This sample size is estimated to provide a total of 208 recurrence events during the follow-up duration of at least 24 months. The primary analysis will be conducted once a total of 208 recurrence events are observed. The events will be monitored in a blinded fashion regardless of the treatment assignment to determine the timing of the primary analysis. All secondary endpoint analyses will be conducted at the time of the primary analysis.

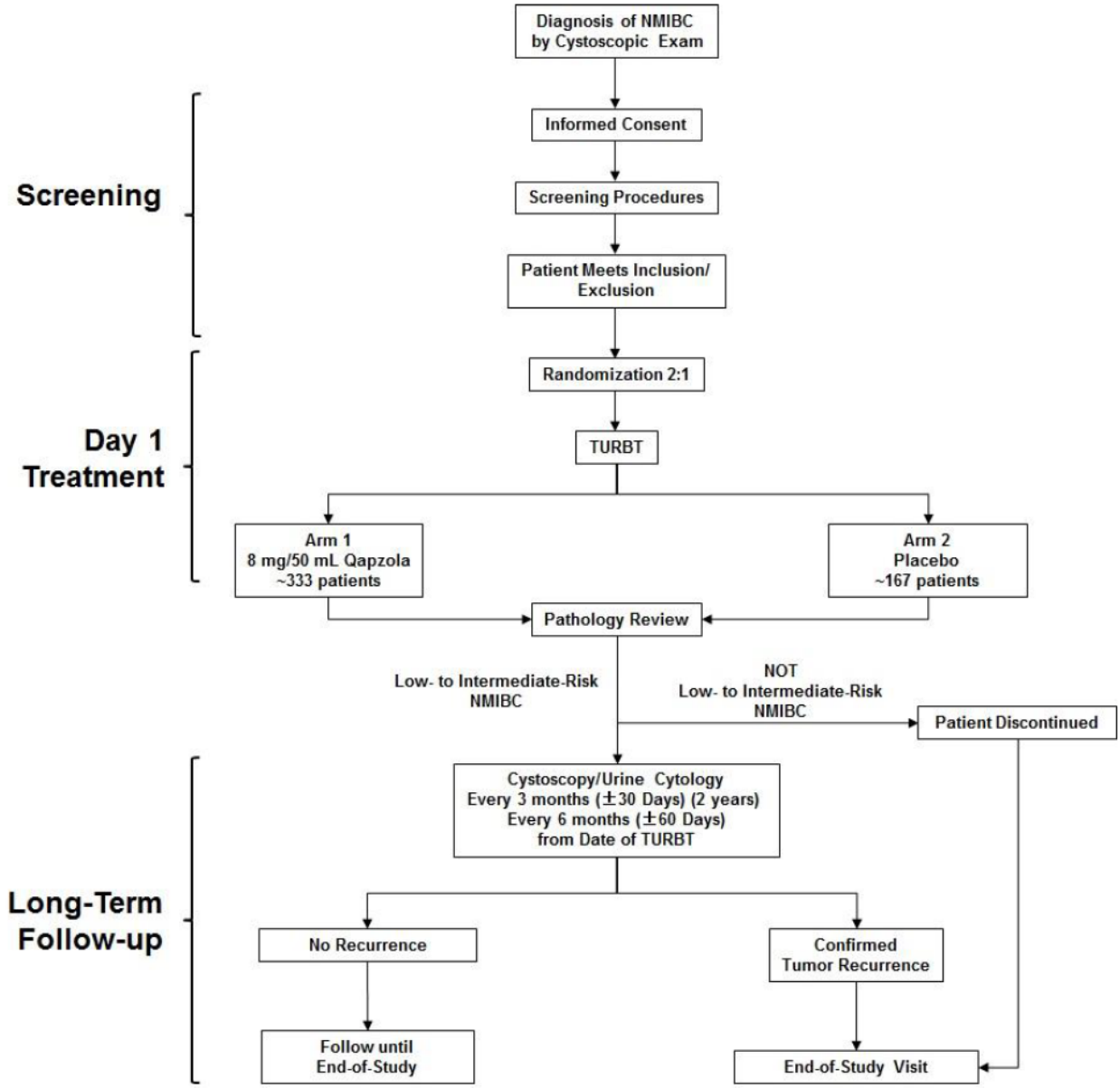
Since the Target population is confirmed by the pathology review and this will be performed after patients are randomized and have undergone TURBT procedure, the study will account for misclassification in Target disease population. Accounting for 15% misclassification of randomized patients, the study will enroll approximately 500 patients. However, the study will continue to enroll patients until the required number of Target disease patients are accrued.

A futility analysis will be performed during the study conduct to determine the study continuation. The futility analysis will be conducted in the Target patients once 60 events are observed. The study will be stopped for futility if the calculated z-value from the log-rank test of HR is >1.0. No adjustment for multiplicity of comparison will be made for futility analysis and the final analysis will be performed at 5% level of significance.

The interim analysis will also be used to determine if additional subjects should be recruited to ensure that enough events would be accumulated at approximately 2-year follow-up from drug instillation. Based on the expected events of 208 out of 425 subjects after 2-year follow-up, we anticipate that the first 123 subjects should have completed 2-year follow-up visits at the futility analysis when 60 events are observed. However, if lower

overall recurrence rate is observed, additional patients in the Target Population will be recruited in order to accrue required number of events. The interim analysis will be performed by an Independent Data Monitoring Committee (IDMC) that will have access to the unblinded data. The study team will be blinded to the treatment allocation during the follow-up period. 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: 22 Dec 2016

Study Flow Chart



Schedule of Study Assessments and Procedures

Assessments	Screening	Randomize/ Treatment	Safety Follow-up Visit [a]	Long-Term Post-TURBT Follow-up [b]								
	Day -30 to 1	Day 1	Day 35	Month								
				3 [a]	6	9	12	15	18	21	24	Every 6 Months
	Visit 0	Visit 1	Visit 2	Visits 3-10								Visits 11+
Informed Consent (IC)	x											
Urine cytology	x [c]			x	x	x	x	x	x	x	x	x
Cystoscopy	x [c]			x	x	x	x	x	x	x	x	x
Medical history	x											
Vital signs	x	x	x	x								
Weight and height	x											
Physical examination [d]	x		x	x								
Complete Blood Count	x	x [e]	x	x								
Chemistry	x	x [e]	x	x								
Pregnancy test	x											
Urine dip stick	x	x [e,f]	x	x	x	x	x	x	x	x	x	x
TURBT and Specimen Collection		x [g]										
Randomization		x										
Qapzola or Placebo instillation [h]		x										
Concomitant medications [i]	x	x	x	x	x	x	x	x	x	x	x	x
Adverse event assessment [j]	x	x	x	x	x	x	x	x	x	x	x	x

a) Only patients who don't have pathology confirmed study-eligible NMIBC after TURBT, or patients who discontinue during follow-up, will return on Day 35 (±5 days) for the Safety Follow-up Visit. Patients in the Target Population will have the Safety Follow-up at the 3-month visit.
b) Follow-up visits for patients with Ta histology are to be conducted every 3 months (±30 days) calculated from the date of TURBT for the first 2 years and then every 6 months (±60 days) until tumor recurrence or the End-of-Study, whichever occurs first.
c) The qualifying cystoscopy and urine cytology may be performed up to 45 days prior to signing the informed consent.
d) A complete physical examination will be performed at Screening and the Safety Follow-up Visit/Month 3 Follow-up 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. If patient is on anticoagulation therapy or has bleeding disorder risk, PT/PTT test should be ordered at Screening per investigator discretion.
f) Urine dipstick to be done just prior to study drug instillation (60 ± 30 minutes) once gross hematuria is resolved.
g) Each tumor/lesion resected during TURBT should be submitted to the local pathology lab in a separate container, noting the location, to ensure that the tumor location, size, stage, and grade for each tumor/lesion, according to the 2004 WHO/ISUP grading system along with the presence/absence of muscle fiber in the lesion, is assessed.
h) Instillation of study drug (Qapzola 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 ± 5 minutes.
i) During the Follow-up Period, only medications to treat NMIBC will be recorded for concomitant medications.
j) All adverse events from the time of study drug administration until 35 days after the last dose of study treatment will be recorded. From the 3-month visit through the End-of-Study, only deaths and AEs related to study procedures will be recorded.

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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
UCC	Urothelial Cell Carcinoma
US	United States
WHO	World Health Organization

1 INTRODUCTION AND BACKGROUND

1.1 Non-Muscle Invasive Bladder Cancer

Bladder cancer is the sixth-most common cancer in the United States (US) and the fourth-most common cancer in men, and is approximately three times more prevalent in men than in women. According to the latest figures from the Surveillance, Epidemiology, and End Results (SEER) Program of the National Cancer Institute (NCI) [1], ~600,000 people were living with bladder cancer in the US in 2013. In 2016, it is estimated that ~77,000 people will be newly diagnosed with bladder cancer and ~16,000 people will die from the disease. The median age at diagnosis is 73 years, and more than 90% of patients are 55 years of age or older [1]. Because of the ongoing diagnostic and therapeutic requirements for recurrent disease, as well as for disease progression, bladder cancer is expected to remain the most expensive cancer to treat. [2-3]. The total US annual cost of bladder cancer is expected to rise to $5 billion by 2020 [2-3].

In the US, urothelial (transitional cell) carcinomas comprise 90% of all histologic subtypes of bladder cancer [4]. Of these, NMIBC accounts for 70% of newly diagnosed cases (ie, ~54,000 patients this year). Initial diagnosis and staging of NMIBC is based on cystoscopic examination under anesthesia. Primary treatment with TURBT, if indicated, is an invasive procedure that can have a detrimental effect on a patient's health-related quality of life (HRQoL). It also carries inherent surgical risks (eg, bleeding, infection, perforation) and a risk of medical complications arising from anesthesia. These are important considerations given that the majority of patients who undergo TURBT are elderly and likely to have medical comorbidities [4]; the median age at diagnosis of bladder cancer is 73 years, and more than 90% of patients are 55 years of age or older [1].

To reduce the risk of tumor recurrence, and hence the need for repeat TURBT, the National Comprehensive Cancer Network (NCCN) [4], the American Urological Association (AUA) [5], the Canadian Urological Association (CUA) [6], the European Association of Urology (EAU) [7], and the European Society for Medical Oncology (ESMO) [8] recommend that patients with clinically apparent low- or intermediate-risk NMIBC receive a single intravesical instillation of a chemotherapeutic agent immediately following resection. Compliance with the guideline recommendation is poor partly because the currently available agents including mitomycin C (MMC) or epirubicin are not approved for this indication. Any additional treatments or instillations are guided by tumor histology based on surgical pathology. [4].

Because of the high risk of tumor recurrence and the potential risk for progression to muscle invasive bladder cancer (MIBC), patients with NMIBC require frequent, diligent follow-up including regular 3- to 4-month clinic visits with urine analyses, urine markers, and repeat cystoscopies. Diagnosis, treatment, continued surveillance, and, if necessary, repeat TURBT may thus contribute to the significant morbidity and economic burden for the management of NMIBC and is why on a lifetime, per-patient basis, bladder cancer is, and is expected to remain, the most expensive cancer to treat [3, 9-10].

1.2 Qapzola for Intravesical Instillation

Qapzola™ (apaziquone, EO9) is a novel, fully synthetic, bioreductive alkylating indoloquinone. Qapzola is a pro-drug that is activated by the enzyme DT-diaphorase also known as NQO1 (NAD(P)H:quinone oxidoreductase-1) and other reductases to generate cytotoxic species. The mechanism of activation of Qapzola involves reduction by cellular enzymes that transfer one or

two electrons, forming a semiquinone and a hydroquinone, respectively. Oxidation of the semiquinone under aerobic conditions results in a redox cycle that can cause cell death by forming reactive oxygen species or depletion of NADH and NADPH. The semiquinone/ hydroquinone can alkylate and crosslink DNA and other macromolecules, a process that is enhanced under hypoxic conditions. In both pathways, DNA damage activates the biochemical pathways of apoptosis leading to cell death.

1.3 Clinical Studies with Qapzola

Spectrum has conducted 9 clinical studies with Qapzola administered by the intravesical route.

1.3.1 Clinical Efficacy of Qapzola

The efficacy results from the two randomized placebo-controlled pivotal Phase 3 studies (SPI-611 and SPI-612) are the basis for the NDA application. The primary objective of SPI-611 and SPI-612 was to assess the 2-Year Recurrence Rate of bladder cancer in patients with Ta, G1-G2 NMIBC who underwent TURBT randomized to receive one Qapzola instillation (4 mg/40 mL) versus those who underwent TURBT and received a matching placebo instillation. Although Spectrum initially designed the studies with Time to Recurrence as the primary endpoint, the Oncology Division of the FDA, after consultation with Division of Reproductive and Urologic Products, recommended 2-Year Recurrence Rate as the primary efficacy variable in SPI-611 and SPI-612, and Time to First Recurrence as the key secondary efficacy variable (Meeting Minutes 5 Feb 2007). Additional secondary efficacy endpoints were Progression to higher stage or grade, Number of Recurrences per Patient, Disease-free Interval, Disease-free Survival, and Overall Survival.

Sample size calculations for SPI-611 and SPI-612 were based on the treatment effect reported in a meta-analysis conducted by Sylvester et al (2004) **[11]**. This meta-analysis showed recurrence rates of 48.4% for TURBT alone and 36.7% for TURBT plus intravesical therapy, an absolute difference of 11.7% and relative improvement of 39% (odds ratio [OR] 0.61, 95% confidence interval [CI] 0.49, 0.75; $p<0.0001$) for intravesical therapy over TURBT at a median follow-up of 3.4 years. Consequently, SPI-611 and SPI-612 were designed to detect a 12% absolute difference between Qapzola and placebo in the primary endpoint at a 5% level of significance and powered at 80%.

Eligible patients, based on a visual assessment underwent TURBT at Visit 1 (Day 0) after which they were randomized to receive either Qapzola or placebo instilled into the bladder immediately (within 6 hours) following TURBT. After a 60-minute retention, study drug was drained from the bladder. A postoperative follow-up visit was scheduled 3 weeks later. Patients with confirmed Ta, G1-G2 disease based on central pathology review, received no further treatment and were followed cystoscopically every 3 months through Year 2 for tumor recurrence. Patients with tumors other than Ta, G1 or G2 received further treatment in accordance with contemporaneous treatment guidelines or standard of care, and were also followed up cystoscopically every 3 months through Year 2 for tumor recurrence. Note that while patients were enrolled based on visual diagnosis at cystoscopy, the target population for the primary efficacy analysis was determined by histological confirmation of Stage Ta, G1-G2 by central pathology. Thus, patients with higher stage disease (T1, Tis) were enrolled but were not included in the efficacy analyses for the pre-specified Ta, G1-G2 Target Population (but were included in the intent-to-treat [ITT] analyses).

Treatment groups were balanced with respect to demographic and baseline characteristics in each study. Most of the patients in each study were male (~70%), White (~97%), and ≥65 years old (~60%), reflecting the target population of patients in the US. Most patients (~60%) in each study had primary tumors and most had (~60%) only a single lesion. Median lesion size was 1.5 cm in both studies, ranging from 0.2 cm to 5.5 cm (SPI-611) or 5.0 cm (SPI-612). Patients with >5 lesions or with lesions >3.5 cm were excluded from the Ta, G1-G2 Target Population.

1.3.1.1 2-Year Recurrence Rate

Fewer patients treated with Qapzola than with placebo had recurrence of tumors, with consistent outcomes in each study with respect to magnitude of treatment effect. Thus, for SPI-611, the 2-Year Recurrence Rate was 38.0% for patients treated with Qapzola compared to 44.6% for patients treated with placebo. For SPI-612, the 2-Year Recurrence Rate was 39.7% for patients treated with Qapzola compared to 46.3% for patients treated with placebo. Though the difference between treatments was not significant in either study (absolute difference of 6.7% in SPI-611 and 6.6% in SPI-612) **(Table 1)**, when the data from the two nearly identically designed clinical studies were pooled, the resulting 6.7% difference was significant *p*-value of 0.0218 (OR 0.76; 95% CI 0.60, 0.96). Note that since the differences in the primary efficacy analysis did not achieve statistical significance, all other analyses report nominal p-values.

Table 1 Two-Year Recurrence Rate after a Single Intravesical Administration of Qapzola Post-TURBT (Ta, G1-G2 Target Population)

Parameter	SPI-611		SPI-612		Overall	
	QAP (n=295)	PBO (n=271)	QAP (n=282)	PBO (n=298)	QAP (n=577)	PBO (n=569)
Patients with Recurrence[a], n (%)	112 (38.0)	121 (44.6)	112 (39.7)	138 (46.3)	224 (38.8)	259 (45.5)
95% CI[b]	32.4, 43.8	38.6, 50.8	34.0, 45.7	40.5, 52.2	34.8, 42.9	41.4, 49.7
p-value[c]	0.1068		0.1094		0.0218[d]	
Difference (95% CI)	-6.7 (-14.8, 1.4)		-6.6 (-14.6, 1.4)		-6.7 (-12.4, -1.0)	
Odds ratio (95% CI)	0.76 (0.54, 1.06)		0.76 (0.55, 1.06)		0.76 (0.60, 0.96)	
Relative Change (%)	–15.0		–14.2		–14.7	

CI=confidence interval; NC=not calculable; PBO=placebo; QAP=Qapzola; SE=standard error; TURBT=transurethral resection of bladder tumor.
(a) Recurrence is defined as first documented recurrence of bladder tumor on or before 2 - Year follow-up visit.
(b) Exact 95% confidence interval.
(c) Mantel-Haenszel chi-Square Test.
(d) Nominal p-value; analysis was not prespecified.

The results in the **ITT Population** were similar to those in the Ta, G1-G2 Population.

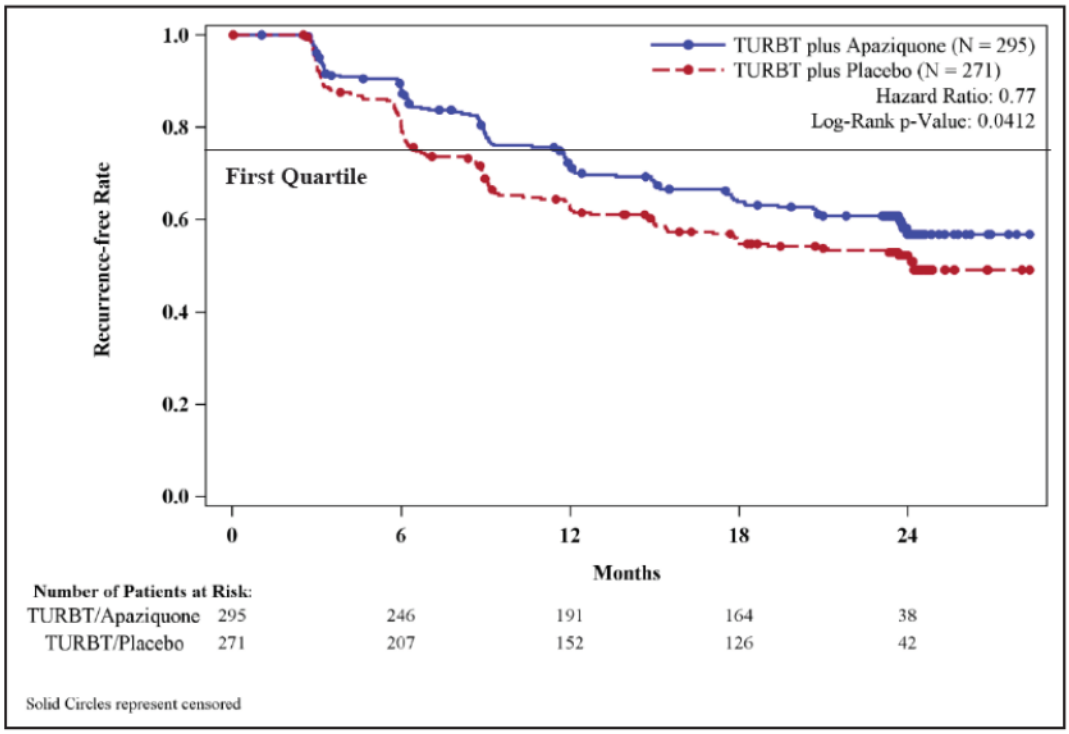
1.3.1.2 Time to Recurrence

The distribution of Time to Recurrence by the Kaplan-Meier method showed a clear divergence between the Qapzola and placebo groups over the 2-year follow-up period in both studies **(Figure 1)**. An increase in Time to Recurrence was demonstrated for Qapzola-treated patients,

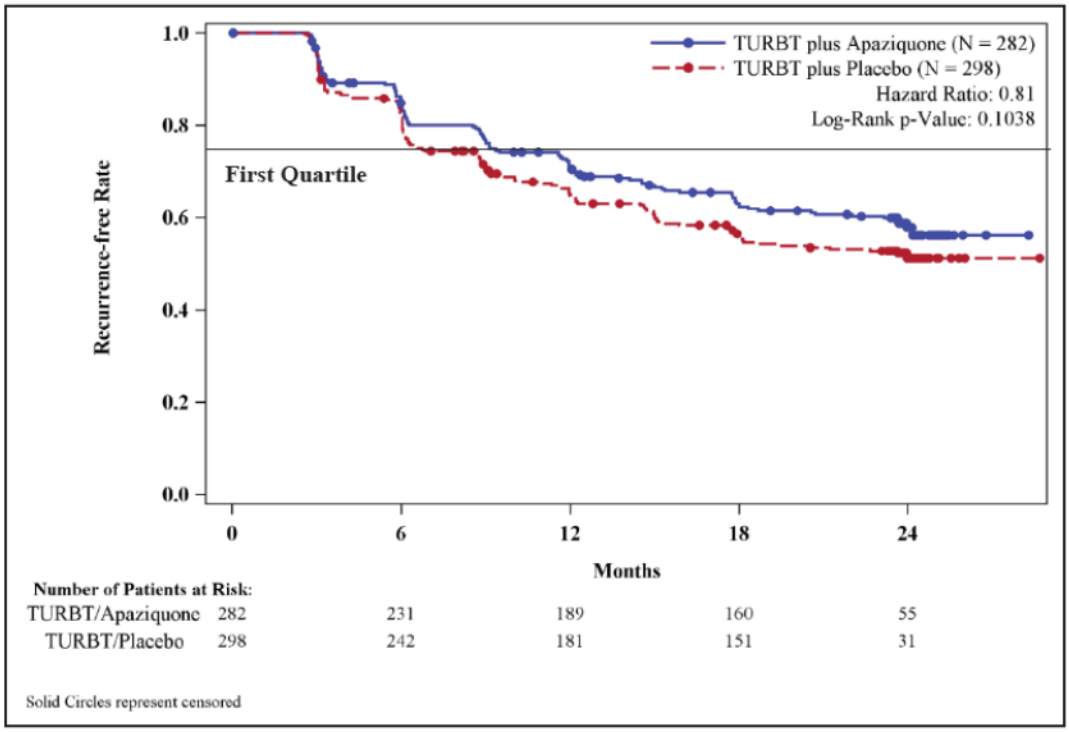
with a nominal p-value of 0.0412 in SPI-611 (Hazard ratio [HR] 0.77; 95% CI 0.59, 0.99) and 0.1038 in SPI-612 (HR 0.81; 95% CI 0.63, 1.04). When the data from the two studies are pooled, the nominal p-value was 0.0096 (HR 0.79; 95% CI 0.66, 0.94). Since fewer than 50% of patients experienced a recurrence, a median Time to Recurrence could not be calculated; however, using the first quartile (25%) of recurrence in both groups, the Time to Recurrence was 3 to 5 months longer for patients receiving Qapzola compared to placebo. The results for the ITT Population are similar for the pooled analysis.

Figure 1 Kaplan-Meier Estimates of Time to Recurrence in the Qapzola Pivotal Studies SPI-611 and SPI-612 (Ta, G1-G2 Target Population)

A. SPI-611



B. SPI-612



1.3.1.3 Other Secondary Efficacy Parameters

Other secondary efficacy endpoints supported the primary analysis in that patients treated with Qapzola had a better outcome.

1.3.1.4 Time to Instillation

The time of instillation of Qapzola post-TURBT (≤30, 31 to 90, and >90 minutes) was found to be a notable factor in the efficacy of Qapzola, with better efficacy observed when Qapzola was instilled 31 to 90 minute minutes post-TURBT. This finding was consistent in both studies:

- In **SPI-611**, there was a 20.3% absolute reduction in 2-Year Recurrence Rate for patients treated with Qapzola (n=60) compared to patients treated with placebo (n=39) (23.3% vs 43.6%; nominal $p = 0.0346$; OR 0.39; 95% CI 0.16, 0.94), representing a 46.5% relative reduction compared to placebo.
- In **SPI-612**, there was an 11.7% absolute reduction in 2-Year Recurrence Rate for patients treated with Qapzola (n=57) compared to patients treated with placebo (n=61) (33.3% vs 54.1%; nominal $p = 0.0238$; OR 0.42; 95% CI 0.20, 0.89), representing a 38.4% relative reduction compared to placebo.

The reduced efficacy of Qapzola when instilled ≤30 minutes post-TURBT may reflect the inactivation of Qapzola by red blood cells remaining in the bladder at that time due to the possible hematuria from the procedure **[12]**.

1.3.2 Clinical Safety of Qapzola

The majority of data establishing the safety of a single intravesical instillation of Qapzola in the post-TURBT setting came from the two placebo-controlled pivotal studies, SPI-611 and SPI-612 (N=808). The median duration of each study was ~2 years.

The incidence and type of adverse events (AEs) reported in SPI-611 and SPI-612 was similar for both treatment groups. Regardless of treatment group, approximately 80% of patients in each study experienced at least one treatment-emergent AE (TEAE); most TEAEs (70% to 80%) were of Grade 1 or Grade 2 severity. The most common TEAEs (occurring in approximately 10% to 20% of patients in either treatment group in either study) were dysuria, urinary tract infection, hematuria, and pollakiuria with less common TEAEs (5% to 10% of patients) being micturition urgency, bladder pain, urinary retention, procedural pain and bladder spasm.

Few patients (10% to 13%) had TEAEs the investigator considered treatment related with the incidence of these AEs being similar between Qapzola and placebo. The most common treatment-related AEs (occurring in 1% to 5% of patients) were dysuria, bladder spasm, micturition urgency, bladder pain, hematuria, urinary tract infection, and pollakiuria.

Approximately 25% of patients in SPI-611 and SPI-612 reported a serious adverse event (SAE), with the incidence and types of SAEs reported being similar between studies and between treatment groups. The most common SAEs (in <3% of patients) were congestive cardiac failure, hematuria, urinary retention, atrial fibrillation, chronic obstructive pulmonary disease, pneumonia, knee arthroplasty, and coronary artery disease, most of which may be expected in an elderly population. Two patients experienced SAEs that were considered to be possibly related to Qapzola. Both SAEs started on the day of study drug instillation, and both resolved: one patient had Grade 3 hematuria and recovered within 3 days, the other had Grade 3 acute renal failure and recovered within 18 days. Another patient who received Qapzola died of acute renal failure 624 days after Qapzola treatment; the event was assessed as not related to study treatment. Hematuria is a common presenting sign of NMIBC **[5, 13]** and is an expected consequence of the TURBT procedure.

Since there was only one instillation, there were no AEs that led to discontinuation of study drug instillation. Approximately 4% of patients discontinued from the studies due to AEs over the 2-year study period, with the incidence of these AEs being similar between studies and between treatment groups, and no individual AE occurring in more than 1% of patients. None of the AEs leading to discontinuation were assessed as related to study treatment by the Investigator.

Approximately 3% of patients had AEs that resulted in death, none of which the investigator assessed as related to study drug (Qapzola or placebo). There were no deaths reported in the immediate post TURBT instillation period (within 30 days).

Clinical laboratory assessments showed no clinically meaningful differences between patients receiving Qapzola and placebo in any hematologic, liver, kidney, or metabolic parameters and in a subgroup of patients in SPI-611 (n=191), there was no measurable effect on functional bladder capacity.

Data from the other six studies were supportive of the safety data in SPI-611 and SPI-612. Among the 245 patients in these studies, 139 received multiple instillations of Qapzola. The types of TEAEs in these patients were similar to those in SPI-611 and SPI-612, although the incidence of dysuria, hematuria, pollakiuria, and micturition urgency tended to be higher in

patients receiving multiple instillations of Qapzola (~15% to 45%) than single instillations (~3% to 15%). Treatment-related SAEs were experienced by three patients who received single instillations of Qapzola (pelvic pain, postoperative urinary retention, and hematuria) and four patients receiving multiple instillations of Qapzola (dysuria, hematuria and hemorrhage urinary tract, chemical cystitis, pollakiuria); all patients recovered. No patients in the supportive safety studies discontinued due to AEs and none died.

1.4 Study 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.

Qapzola 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 Qapzola 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 Qapzola, 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 Qapzola 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 Qapzola 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 with Qapzola was also shown to be well-

tolerated with the most common AEs commonly seen in patients with bladder cancer (eg, hematuria, dysuria, and urinary frequency).

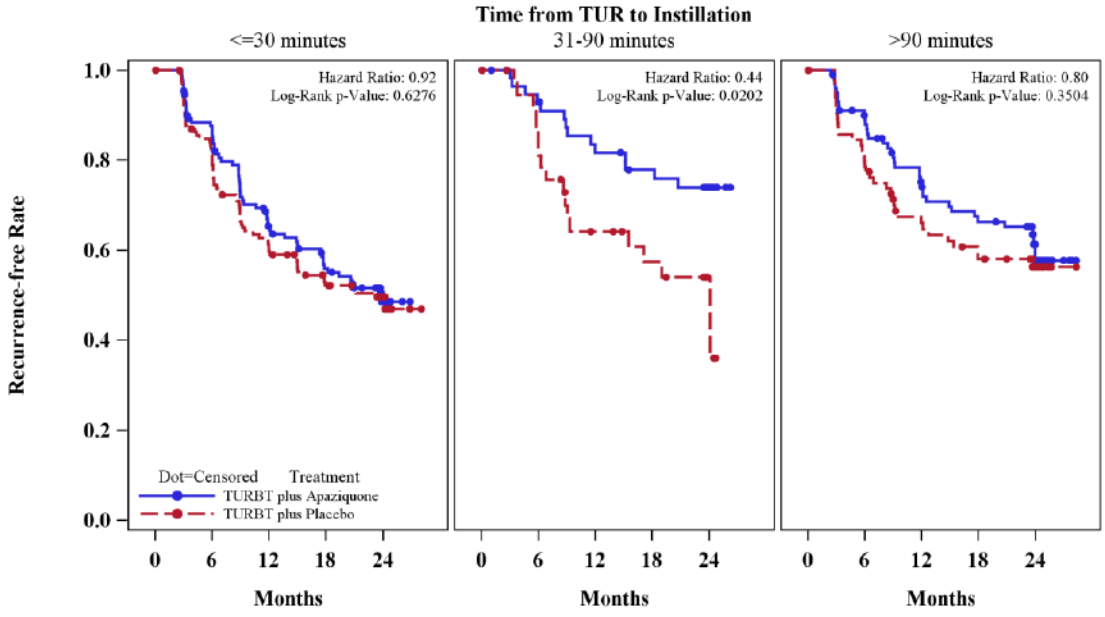
Qapzola has been shown to be inactivated by red blood cells **[12]**. Hematuria, both microscopic and macroscopic, is the most common adverse event in the immediate post-TURBT period. Therefore, any bleeding in the post-operative period following TURBT could inactivate Qapzola following its immediate, 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 Qapzola-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 Qapzola. 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 (Qapzola or placebo) (60 ± 30 minutes post-TURBT) in the new proposed Phase 3 study.

A single instillation dose of 8 mg in 50 mL Qapzola was chosen as the study treatment in the current study. The 4 mg in 40 mL dose of Qapzola was established in the Phase 1 dose-escalation study and was used in the Phase 2 and previous Phase 3 studies. Based on the data from the Phase 1 dose-escalation study, it was found that the 8 mg in 40 mL dose (0.2 mg/mL) did not show any clinically relevant safety concerns. Because the 8 mg dose of Qapzola, at a concentration of 0.2 mg/mL, was determined to be safe, the dose of 8 mg in 50 mL (0.16 mg/mL) was chosen as the dose to be used in SPI-QAP-306. As part of the safety monitoring in the study, an Independent Data Monitoring Committee (IDMC) will review the unblinded safety data from the first 30 patients to verify that the 8 mg/50 mL dose is safe.

Because of the potential for the inactivation of Qapzola by blood in the immediate post-TURBT period, the proposed Qapzola dosing is targeted to be delivered 60 ± 30 minutes post-TUBT. This dosing time window is supported by the analysis of Time to Recurrence in the previous Phase 3 single-dose studies (SPI-611, SPI-612) in patients treated 31 to 90 minutes post-TURBT. The hazard ratio for patients who were treated 31 to 90 minutes post-TURBT was 0.44 (p=0.0202, log-rank test; 95% CI 0.22, 0.90) in favor of Qapzola in SPI-611 **(Figure 2A)** and 0.55 (p=0.0344, log-rank test; 95% CI 0.31, 0.97) in favor of Qapzola in SPI-612 **(Figure 2B)**.

Figure 2 Kaplan-Meier Estimates of Time to Recurrence by Time of Instillation (Ta, G1-G2 Target Population)

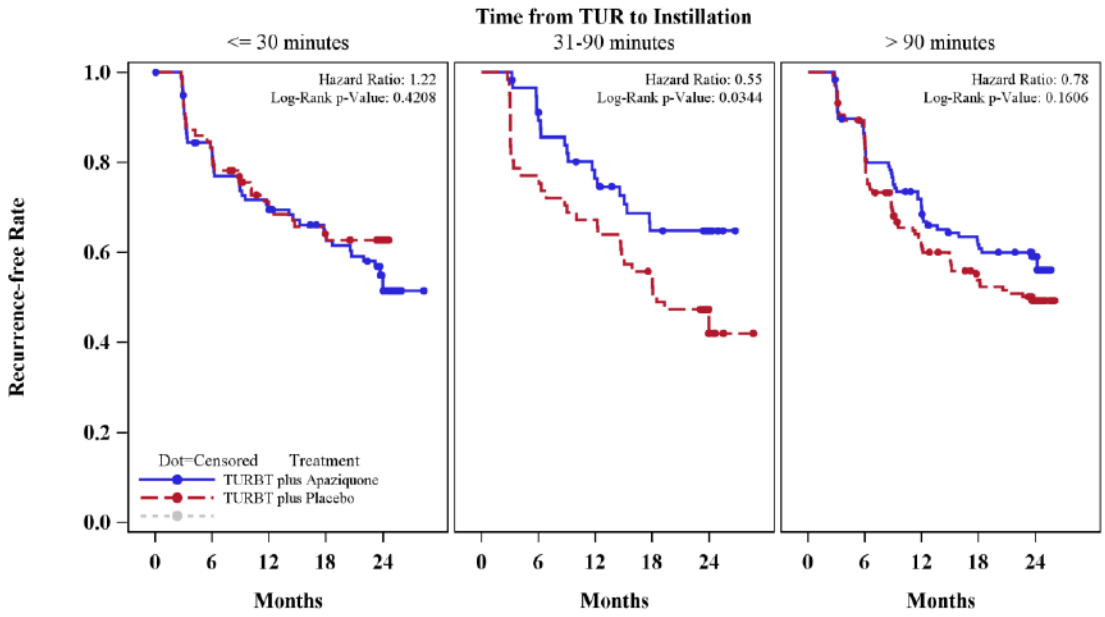
A) SPI-611



Number of Patients at Risk:

TURBT/Apaziquone	134	108	79	65	11	60	52	44	39	12	101	86	68	60	15
TURBT/Placebo	145	110	81	66	23	39	31	21	17	3	87	66	50	43	16

B) SPI-612



Number of Patients at Risk:

TURBT/Apaziquone	99	76	65	55	15	57	50	41	33	11	126	105	83	72	29
TURBT/Placebo	78	63	49	44	9	61	47	41	32	6	159	132	91	75	16

TUR=transurethral resection of bladder tumor.

2 STUDY OBJECTIVES

2.1 Primary Objective(s)

To evaluate the Time to Recurrence in patients with low- to intermediate-risk non-muscle invasive bladder cancer (NMIBC) who receive either 8 mg Qapzola or placebo post transurethral resection of bladder tumor (TURBT).

2.2 Secondary Objectives

To evaluate the following in patients with low- to intermediate-risk NMIBC who receive either 8 mg Qapzola or placebo post-TURBT:

1. 2-Year Recurrence Rate
2. Extent of Disease at Recurrence (number and location of tumors)
3. Time to Disease Progression (based on the tumor stage)
4. Safety

3 INVESTIGATIONAL PLAN

3.1 Study Design and Treatment Plan

This is a randomized, multicenter, two-arm, double-blind, placebo-controlled study of Qapzola in patients with low- to intermediate-risk NMIBC, assessed according to the 2016 American Urology Association (AUA) Guidelines. Specifically, only patients with tumor characteristics in **bold text** in the low- to intermediate-risk columns in Table 2 will be included in the study.

Table 2 2016 American Urological Association Stratification for Non-Muscle Invasive Bladder Cancer

Low Risk	Intermediate Risk	High Risk
• **Low grade solitary Ta ≤3cm*** • **PUNLMP***	• **Recurrence within 1 year, low-grade Ta*** • **Solitary low-grade Ta >3 cm*** • **Low-grade Ta, multifocal*** • **High-grade Ta, ≤3 cm (solitary tumor)*** • Low-grade T1	• High grade T1 • Any recurrent, high grade Ta • High grade Ta, >3 cm (or multifocal) • Any CIS • Any BCG failure in high-grade patient • Any variant histology • Any lymphovascular invasion • Any high-grade prostatic urethral involvement

* - histology for evaluable target population

In addition to other Screening assessments, patients will undergo an assessment of urothelial carcinoma of the bladder via cystoscopy for clinically apparent tumor of Ta histology, including PUNLMP. The qualifying cystoscopy may be performed up to 45 days prior to signing the informed consent.

Eligible patients will be randomized in a 2:1 ratio to either:

Arm 1: One dose of 8 mg Qapzola

Arm 2: One dose of placebo

Once randomized, patients will undergo TURBT on Day 1 and the study drug instillation will occur at 60 ± 30 minutes post-TURBT and will be retained for 60 minutes (±5 minutes) in the bladder. All histology specimens will be reviewed by a local pathology laboratory and all clinical treatment decisions will be based on the local pathology review. Patient target disease will be confirmed and efficacy analyses will be performed based on the pathology results. The target study population is low- to intermediate-risk patients who have Ta histology, including PUNLMP, as confirmed by a pathology laboratory. Patients whose tumor histology does not meet the criteria for eligibility, as confirmed by pathology (Non-Target Population), will be followed up for safety on Day 35 (±5 days) (Safety Follow-up Visit) and will then be discontinued from the study. If the pathology results are delayed beyond 35 days, the Safety Follow-up Visit will be conducted when the results are available for these patients.

Patients who have pathology confirmed target histology will not receive additional treatment for NMIBC during the follow-up prior to recurrence. All patients will be followed until either a confirmed tumor recurrence or the End-of-Study, whichever occurs first.

The primary analysis will be conducted once the required number of recurrence events are observed as detailed in the Statistical Methods below. The number of events needed to perform the final primary endpoint analysis was estimated based on the recurrence rate at 24 months from previous studies. The follow-up schedule is below:

- Cystoscopic examination and urine cytology every 3 months (±30 days) (calculated from date of TURBT) for 2 years for tumor recurrence and progression and then every 6 months (±60 days) until either a confirmed tumor recurrence or the End-of-Study, whichever occurs first.
- If at any time during the study there is a histologically confirmed tumor recurrence, the patient will be discontinued from the study at that time and may then be treated per the Investigator's standard of care.

The study will end (End-of-Study) when the required number of events for the primary endpoint analysis are accrued.

3.2 Study Duration

The estimated duration of the study is approximately 5 years (2.5 years accrual + approximately 2.5 years follow-up).

The total duration of the study for each patient will be approximately 5 years including:

- **Screening Period:** up to 30-days
- **Treatment:** Day 1
- **Safety Follow-up:** Day 35 (±5 days) (non-Target Population) or Month 3 Follow-up Visit (Target Population)
- **Follow-up Period:** No follow-up in non-Target Population. Until either a confirmed tumor recurrence or the End-of-Study, whichever occurs first in Target Population.

4 PATIENT POPULATION

4.1 Inclusion Criteria

1. Patient must have a clinical diagnosis of low- to intermediate-risk non-muscle invasive bladder cancer according to the 2016 American Urological Association (AUA) Guidelines
2. 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.
3. Patient is at least 18 years of age and <90 years of age at the time Informed Consent is signed.
4. 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 study treatment. Patients surgically sterilized or who are postmenopausal for at least 1 year (defined as more than 12 months since last menses) do not require contraception.
5. 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 malignancy or life-threatening systemic disease or a history of advanced, serious, life-threatening malignancy/disease within the last 5 years, except very low-risk prostate cancer
2. Patient has used any investigational drugs, biologics (vaccines, antibodies), or devices within 30 days prior to study treatment or has plans to use any of these during the course of the study
3. Patient has received any pelvic radiotherapy (including external beam and/or brachytherapy)
4. Patient has a history of allergy to red color food dye or any other component of Qapzola, placebo, or their diluents
5. Patient has had a surgical procedure 4 weeks prior to TURBT or will have other surgical procedures performed at the time of TURBT or within 4 weeks after TURBT
6. Patient has any unstable or uncontrolled medical condition that would make it potentially unsafe to undergo TURBT including a previous stroke or myocardial infarction within 6 months
7. 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 study treatment or undergo study procedures
8. Patient has a bleeding disorder or a screening platelet count $<100\times10^9$/L, or requires continuous anticoagulation or bridging anticoagulation during the procedure
9. Patient has a hemoglobin value <10 g/dL at Screening
10. Patient has ever had confirmed extravesical urothelial disease (upper tract and urethral including prostatic urethral)

11. Patient with a history of previous bladder cancer:
    - High-Risk NMIBC as classified per the 2016 AUA Guidelines
    - Bladder cancer that was muscle invasive or positive for lymph node or distant metastasis
12. Patient has received any previous intravesical therapy for bladder cancer- chemotherapy, immunotherapy, or previous exposure to Qapzola in the last 3 years
13. Patient has a tumor in the bladder diverticulum
14. Patient has a history of interstitial cystitis
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:

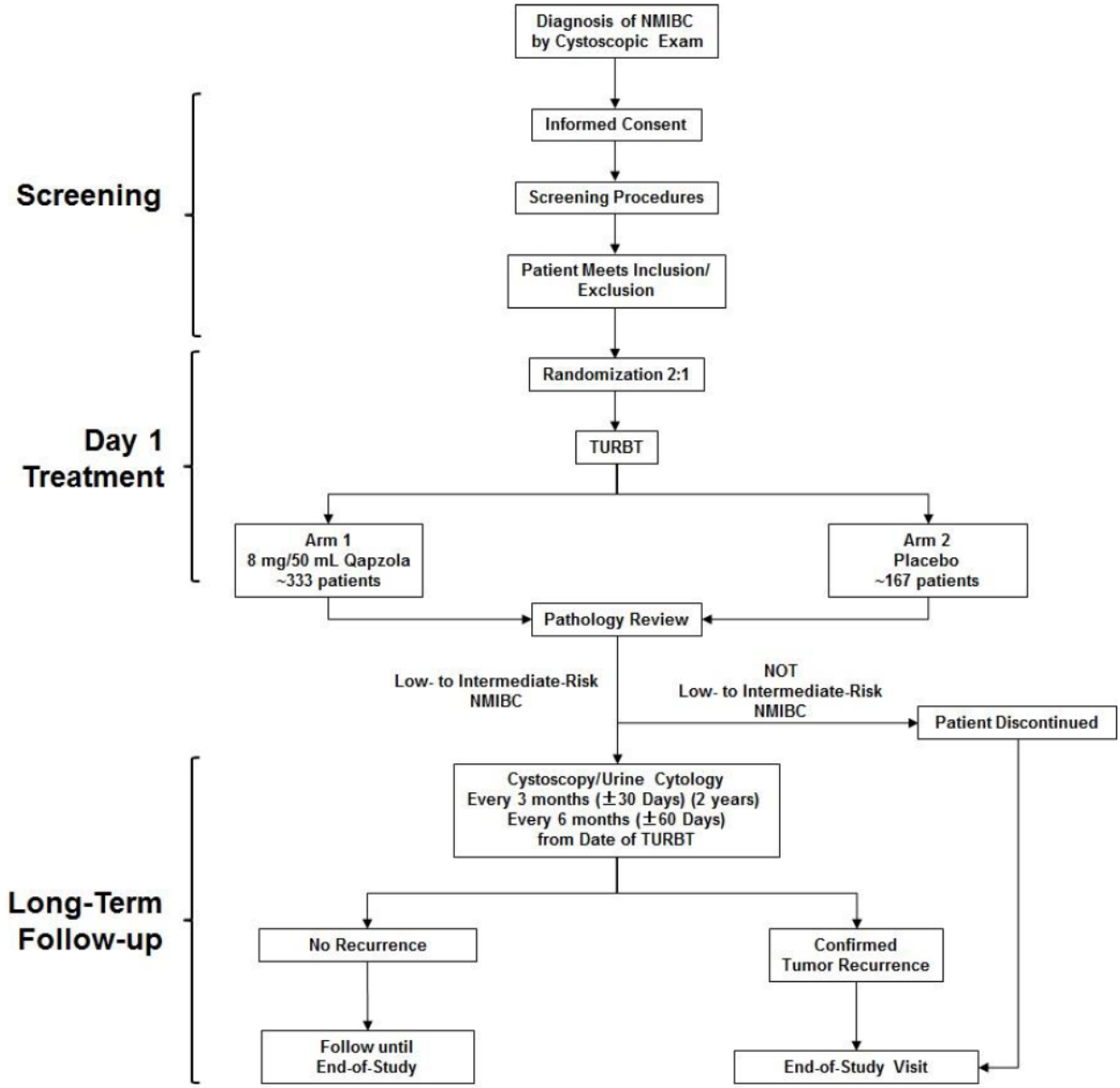
- It is determined by Day 1 pathology review that the patient has histology other than low- to intermediate-risk NMIBC
- Development of an adverse event (AE) that interferes with the patient's participation
- Patient withdrawal of informed consent
- Investigator decision
- Sponsor decision
- The patient refuses further follow-up study procedures, including cystoscopy
- The patient is lost to follow-up (missed at least two consecutive follow-up cystoscopies)
- Patient has a cystectomy
- Patient has a histologically-confirmed recurrence
- Death
- Pregnancy

The reason for the patient discontinuing study treatment or terminating from the study must be recorded on the case report form (CRF). For patients who discontinue from the study during the follow-up period or who are withdrawn, the date of last contact will be the final visit.

5 STUDY PROCEDURES

The study design diagram is presented in **Figure 3** and the Schedule of Study Assessments and Procedures is presented **Appendix 1**.

Figure 3 Study Design Diagram



5.1 Screening

Informed consent is to be obtained prior to the start of any protocol-specified assessments or procedures. However, some patients may complete cystoscopy with pathology assessment and/or urine cytology test as part of the standard of care prior to signing the informed consent. Those test results, if they are within 45 days prior to signing informed consent, could be part of eligibility assessment. In this case, there is no need to repeat same test procedure. 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. Screening includes a cystoscopic exam and urine cytology in order to assess the clinically apparent stage and grade of the bladder tumor. A cystoscopic or urine cytology exam conducted as part of the standard practice within 45 days prior to the signing of the informed consent may serve as the assessment as long as stage and grade of tumor are reported using the World Health Organization (WHO) 2004 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 CRFs, and approval for randomization has been received from Spectrum, the site will randomize the patient using a pre-specified randomization scheme. Patients must not undergo TURBT until they have been randomized. 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
- Urine cytology (Within 45 days prior to signing informed consent)
- Cystoscopic Exam (Within 45 days prior to signing informed consent)
- Complete medical history
- Vital signs (temperature, blood pressure, and heart rate)
- Demographic data
- Physical examination
- Height and weight
- Complete blood count (CBC)
- Chemistry
- 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)

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.

- Vital signs (temperature, blood pressure, and heart rate)
- Complete blood count
- Chemistry
- Randomization
- Urine dipstick just prior to drug instillation
- TURBT and packaging of pathology specimens to be sent to local pathology
- Visual inspection for gross hematuria post-TURBT but prior to drug instillation
- Qapzola or placebo administration
- Concomitant Medications
- Adverse events using NCI CTCAE Version 4.03

5.3.3 Safety Follow-up Visit: Visit 2 (Day 35 [±5 days] post-TURBT (non-Target patient population) or Visit 3 (Month 3 Follow-up Visit) (Target patient population)

- Vital signs (temperature, blood pressure, and heart rate)
- Physical examination
- Complete blood count
- Chemistry
- Urine dipstick
- Adverse events using NCI CTCAE Version 4.03
- Concomitant medications

5.3.4 Long-Term Follow-up Visits - Visits 3 through 10 (First 2 Years: Every 3 months [±30 days] Post-TURBT) and Visits 11 through 16 (Years 3-5: Every 6 months [±60 days])

- Physical exam (required at Month 3 Follow-up Visit, as needed thereafter)
- Vital signs (temperature, blood pressure, and heart rate) (required at Month 3 Follow-up Visit, as needed thereafter)
- Urine dip stick prior to cystoscopy
- Complete blood count (Month 3 Follow-up Visit only)
- Chemistry (Month 3 Follow-up Visit only)
- Urine cytology
- Cystoscopy
- Only AEs related to study procedures will be recorded until the End-of-Study
- Concomitant medications (Intravesical treatment only)

- TURBT and packaging of pathology specimens to be sent to local pathology (if necessary)

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 symptoms, findings, 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 the Safety Follow-up/Month 3 Follow-up Visit. 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, at the Treatment Visit, and the Safety Follow-up/Month 3 Follow-up 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** - 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, AST/SGOT, ALT/SGPT, alkaline phosphatase, and albumin. 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 (or up to 45 days prior to signing of informed consent), Treatment Visit 1, every 3 months (±30 days) (calculated from date of TURBT) for 2 years and then every 6 months (±60 days) until either a confirmed tumor recurrence or the End-of-Study, whichever occurs first. At Screening, if a patient has a positive cytology for a malignancy, imaging of the upper genitourinary tract should be conducted to confirm that there is no upper tract malignancies. Imaging modality can include contrast CT, MRI, or ultrasound with retrograde pyelograms. If a patient is confirmed to have a disease of upper tract or prostatic urethra, the patient is considered not eligible for the study and no other study related procedures should take place.

Similarly, at any time point during the follow-up, if a patient has a positive cytology that cannot be explained by bladder findings or bladder pathology, imaging should be conducted to confirm that there are no upper tract malignancies and that the prostatic urethra is excluded as a reservoir.

5.4.8 Cystoscopy

Cystoscopy will be performed at Screening (or up to 45 days prior to signing of informed consent), every 3 months (±30 days) from the date of TURBT for the first 2 years, and every 6 months (±60 days) until either a confirmed tumor recurrence or the End-of-Study, whichever occurs first. An operative report should contain the number, size and location of the tumors. 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. Each tumor/lesion resected during TURBT should be submitted to the local pathology lab in a separate container, noting the location, to ensure that the tumor stage and grade for each lesion is assessed. All histology specimens will be read by a local pathologist and all pathology reports must include the location, size, stage, and grade for each tumor/lesion removed according to the 2004 WHO/ISUP grading system along with the presence/absence of muscle fiber in the lesion.

Patients with significant complications from TURBT (ie, bladder perforation, ongoing bleeding) should not receive study drug. Within the administration window (60 ± 30 minutes post-TURBT), study drug administration should be delayed to allow for resolution of significant bleeding. If significant bleeding does not stop, decision to administer the drug should be left to the Study Investigator.

All clinical decisions will be made based on the local pathologist's report. Following study treatment on Day 1, pathology will be reviewed by the Study Investigator and if the patient's

tumor(s) is other than low- to intermediate-risk NMIBC, the patient will be discontinued from the study and return at Day 35 (±5 days) for a Safety Follow-up Visit.

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) Version 4.03 for AE grading, and will record the pertinent information on the CRF.

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. For all non-Target population patients, all adverse events from the time of study drug administration until Day 35 (±5 days) post-TURBT will be recorded. For Target population patients, all adverse events will be recorded from the time of study drug administration until the 3-month Follow-up Visit. Only deaths and AEs related to study procedures will be recorded from the 3 month visit until the End-of-Study.

5.4.11 Concomitant Medications

All medications administered from the time Informed Consent is signed until 35 days post TURBT will be recorded on the CRF. After 35 days, until patient discontinues from study, only additional treatment for NMIBC are to be recorded. Start and stop dates and reasons for medication use will be noted.

6 STUDY DRUG AND PHARMACEUTICAL INFORMATION

6.1 Qapzola and Placebo

Qapzola and placebo will be supplied by Spectrum.

6.1.1 Composition of Qapzola

Qapzola for intravesical instillation is a sterile, non-pyrogenic, lyophilized product supplied in two 10 mL clear glass vials. Each vial contains 4.6 mg apaziquone, 57.9 mg mannitol, and 5.8 mg sodium bicarbonate. After reconstitution, Qapzola 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 Qapzola.

6.1.3 Composition of Diluent for Qapzola and Placebo

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

The diluent for placebo is a sterile solution supplied in a two 50 mL clear Type I glass vials. Each vial contains 41.2 mL of the diluent containing 0.9% sodium chloride in 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 Qapzola 8 mg in 50 mL of dose solution or matching placebo. Reconstitution and dose preparation procedures are outlined in the Pharmacy Manual. The 50 mL dose solution of study drug is to be instilled into the bladder via an indwelling 100% Silicone Foley catheter, where it is to be retained for 60 ± 5 minutes.

6.2.2 Schedule of Study Drug Administration

A single dose of study drug on Day 1 is to be administered at 60 ± 30 minutes post-TURBT. Within the administration window (60 ± 30 minutes post TURBT), study drug administration should be delayed to allow for resolution of significant bleeding. Patients not candidates for post-operative intravesical chemotherapy after from TURBT (ie, extensive resection, bladder perforation, ongoing bleeding) should not receive study drug.

6.2.2.1 Preparation of Study Drug

Preparation of study drug dose solution should follow directions as described in the Pharmacy Manual. Equipment needed: Drug kit (Two 4.6 mg vials of Qapzola or placebo and two vials of Diluent), one 50 mL or 60 mL Luer-lok syringe, one 10 mL syringe with 0.2 mL marking, one 5-10 mL syringe, 18 gauge needle, protective clothing.

If study drug is reconstituted, and not used within 2 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.

6.2.2.2 Instillation of Study Drug

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 50 mL of the study drug should be slowly instilled into the bladder taking care not to introduce air. When instillation is complete, 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 ± 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 independent data monitoring committee (IDMC) will be established to review safety data for the first 30 treated patients in the study. The IDMC will also conduct the futility analysis of the unblinded data as described in **Section 8.1**. The details for the IDMC will be provided in a separate Charter. 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 2:1 ratio to either:

- **Arm 1:** one instillation of 8 mg Qapzola
- **Arm 2:** one instillation of placebo

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.

6.6 Randomization

After patients have been found to be eligible for inclusion in the study and prior to TURBT the site will request randomization approval from the Medical Monitor. The patient must not undergo TURBT until they have been randomized.

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.

6.7 Non-Study Treatments

6.7.1 Prior and Concomitant Medications

All medications administered from the time Informed Consent is signed until 35 days post TURBT will be recorded on the CRF. After 35 days, until patient is discontinued, only medications to treat NMIBC are to be recorded. Start and stop dates and reasons for medication use will be noted. Patients may use acetaminophen or antipyretics to manage side effects associated with TURBT and administration of study drug.

The Investigator may also prescribe standard post-operative medications.

6.7.2 Prohibited Medications

Following Day 1 treatment and prior to recurrence, patients in the Target Population should not receive other medications to treat bladder cancer. If a patient starts another therapy for bladder cancer during the follow-up period, the patient will be withdrawn from the study.

No diuretics are allowed prior to instillation on study drug instillation day. Patients should have at least a 7- to 10-day washout period for all anticoagulants, including low-dose aspirin.

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 after the last dose of study drug administration.

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. For all non-Target population patients, all adverse events from the time of study drug administration until Day 35 (±5 days) post-TURBT will be recorded. For Target population patients, all adverse events will be recorded from the time of study drug administration until the 3-month Follow-up Visit. Only deaths and AEs related to study procedures will be recorded from the 3 month visit until the End-of-Study. 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

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. For all non-Target population patients, all adverse events from the time of study drug administration until Day 35 (±5 days) post-TURBT will be recorded. For Target population patients, all adverse events will be recorded from the time of study drug administration until the 3-month Follow-up Visit. Only AEs related to study procedures and deaths will be recorded from the 3 month visit until a recurrence or the remainder of the follow-up period, whichever comes first.

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-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 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 for up to 35 days (±5 days) after treatment (**Table 3**).

Table 3 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.
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. 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, SAEs are 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

From the time the Informed Consent is signed until Day 1 of the study, only SAEs related to study procedures will be recorded. All SAEs that occur from the first dose of study drug administration until Day 35 (±5 days) post-TURBT will be recorded. All SAEs related to study procedures will be recorded for the remainder of the follow-up period and are to be reported to Spectrum within 24 hours of knowledge of the event.

SAEs 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).

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 Qapzola in pregnant women. Because the reproductive risks have not been studied in pregnant women, Qapzola 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 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 including the pre-specified power and sample size calculation as well as the methods for the primary endpoint analysis. A formal statistical analysis plan (SAP) will be finalized before database lock.

8.1 Sample Size

The enrolled patients will be randomized in a 2:1 ratio to either Qapzola or placebo. The primary endpoint is Time to Recurrence in the Target Population. The primary endpoint analysis involves a test of comparison: 8 mg Qapzola vs. placebo using 2-sided log-rank test at 5% level of significance.

The sample size calculation assumes a hazard ratio (HR) of 0.65 based on the results from previous Phase 3 studies of Qapzola and placebo comparisons overall and in the drug instillation time window 31-90 minutes post-TURBT as described in **Section 1.3.1.2** and **Section 1.3.1.4** respectively.

Approximately 500 patients will be enrolled and treated in this study. Accrual time is estimated as 24 months and follow-up time as 24 months. For the sample size calculation, the HR of 0.65 is assumed for the improvement in time to recurrence in favor of Qapzola as compared to the Placebo with a hazard rate of 0.3. In a 2:1 randomization of Qapzola and Placebo, sample sizes of 425 Target disease patients (284 in Qapzola and 141 in Placebo) will provide 85% power. This sample size is estimated to provide a total of 208 recurrence events during the follow-up duration of at least 24 months. The sample size calculation was based on PASS 14 (NCSS, LLC, Kaysville, Utah).

Since the Target population is confirmed by pathology review and this will be performed after patients are randomized and have undergone TURBT procedure, the study will account for misclassification in the Target disease population. Accounting for 15% misclassification of randomized patients, the study will enroll approximately 500 patients. However, the study will continue to enroll patients until the required number of Target disease patients are accrued.

A futility analysis will be performed during the study conduct to determine the study continuation. The futility analysis will be conducted in the Target patients once 60 events are observed. The study will be stopped for futility if the calculated z-value from the log-rank test of HR is >1.0. No adjustment for multiplicity of comparison will be made for futility analysis and the final analysis will be performed at 5% level of significance.

At the time of futility analysis, the decision will be made if additional subjects should be recruited to ensure that enough events would be accumulated at approximately 2-year follow-up from drug instillation. Based on the expected events of 208 out of 425 subjects after 2-year follow-up, it is anticipated that the first 123 subjects should have completed 2-year follow-up at the time of the futility analysis. However, if lower overall recurrence rate is observed, additional patients in the Target Population will be recruited in order to accrue the required number of events.

The futility analysis for the decision of study continuation and adjustment to sample size will be performed by the IDMC that will have access to the unblinded data. The study team will be blinded to the treatment allocation during the follow-up period.

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 2:1 to receive one instillation of 8 mg Qapzola or one instillation of placebo.

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

8.3 Analysis Populations

Four datasets will be analyzed:

- **Target (Low- to Intermediate-Risk) Population**: all randomized patients with confirmed low- or intermediate-risk NMIBC as per the AUA Guidelines. The analysis population for all efficacy endpoints will be the Target (low- or intermediate-risk NMIBC) Population based on local pathology.
- **Non-Target Population**: all randomized patients other than the Target Population defined above. No primary efficacy endpoint analysis will be provided in this population as they will not be under follow-up. Only safety analysis will be performed using this population.
- **Per-Protocol Population:** patients in the Target Population excluding patients with major protocol deviations and who received additional medications for NMIBC during the follow-up and prior to recurrence.
- **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 recurrence with any pathologically confirmed disease of ≥Ta histology or CIS post-treatment. These patients will be assessed cystoscopically and by urine cytology at 3 months (±30 days) intervals calculated from the date of TURBT for the first 2 years and then every 6 months (±60 days) for the remainder of the follow-up or until recurrence, whichever occurs first. The date of the cystoscopy or TURBT procedure when the bladder tumor was detected and which was confirmed histologically by pathology review will be used as the date of recurrence. Only the first documented recurrence will be used to assess the primary efficacy.

The disease recurrence will be determined exclusively using the pathology review of biopsied tumors when detected by the cystoscopy. The current study excludes patients with disease of upper tract or prostatic urethra. If the urine cytology is positive but the pathology review of the biopsy is negative, this may lead to the examination of upper tract disease. A urine cytology may be performed to rule out the upper tract urothelial carcinoma at any follow-up time point.

8.5.2 Primary Endpoint

- **Time to Recurrence** in patients with low- to intermediate-risk non-muscle invasive bladder cancer (NMIBC) who receive either 8 mg Qapzola or placebo post transurethral resection of bladder tumor (TURBT)

8.5.3 Secondary Endpoints

1. 2-Year Recurrence Rate
2. Extent of Disease at Recurrence (number and location of tumors)
3. Time to Disease Progression (based on the tumor stage)

8.5.4 Definitions

- **Recurrence**: any pathologically confirmed disease of ≥Ta histology or CIS post-treatment
- **Progression**: any pathologically confirmed disease of ≥T2

8.5.5 Primary Endpoint - Time to Recurrence

The Time to Recurrence is defined as time from Day 1 treatment to the date of the first histologically confirmed recurrence as described in **Section 8.5.1** above. Patients without a recurrence at the time of the primary analysis will be censored at the last available date of cystoscopy. Patients who died due to any cause before confirmed recurrence will be censored at the last available date of cystoscopy.

The primary analysis will be conducted using a hierarchical procedure of hypothesis testing at a 5% level of significance. The primary endpoint, Time to Recurrence, will be examined first, and if significant, the secondary endpoint, 2-Year Recurrence Rate, will be examined next, and if also significant, Extent of Disease at Recurrence, and Time to Disease Progression will then be examined.

The primary endpoint of Time to Recurrence will be analyzed using the Target Population as defined in **Section 8.3**. The primary analysis of Time to Recurrence will be conducted once a total of 208 recurrence events are accrued in the study. The primary endpoint analysis involves a 2-sided log-rank test of time to recurrence between two treatment groups at 5% level of significance. 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 (CI) will be estimated, together with the estimates at 6, 12, 18 and 24 months. The hazard ratio and corresponding 95% CI 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 likelihood ratio 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% CI. The model will include treatment effect, study center, low vs intermediate risk, primary vs. recurrent disease as stratification factor in addition to any other baseline or demographics factors.

In addition, the following additional sensitivity analyses of Time to Recurrence will be provided:

a. Excluding patients who miss 2 consecutive cystoscopies or lost to follow-up either prior to recurrence or prior to the date of the primary analysis – Completer analysis
b. Excluding patients who miss 2 consecutive cystoscopies or lost to follow-up either prior to recurrence or prior to patient's follow-up duration of 24 months – Completer 24 Month analysis
c. Treating patients with no recurrence who miss 2 consecutive cystoscopies or lost to follow-up prior to date of the primary analysis as recurred.

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

- Patients with Day 1 instillation that do not occur between 30 and 90 minutes post-TURBT
- Patients whose follow-up cystoscopy occurs outside the ±30-day window
- Patients who received other treatment for NMIBC prior to recurrence will be censored at the last assessment prior to the treatment

8.5.6 Secondary Endpoints

8.5.6.1 2-Year Recurrence Rate

The **2-Year Recurrence Rate** is the proportion of patients who have a confirmed recurrence before or at the 2-year follow-up visit (Visit 10) for each study arm. The treatment effect will be analyzed only if a significant treatment effect ($p<0.05$) is identified for the primary endpoint, **Time to Recurrence**. The analysis will calculate odds ratio with 95% CI and apply Cochran-Mantel-Haenszel chi-square test. The recurrence rate will also be estimated using the Kaplan-Meier product-limit method along with 95% CI. Since visits do not often occur at the specified intervals, a cut-off upper limit of 765 days from Day 1 treatment will be used for the 24 month visits.

8.5.6.2 Extent of Disease at Recurrence

Extent of disease at recurrence, including changes in number and in locations of tumors from Day 1 to recurrence, will be examined for patients with recurrence only by each treatment arm. The change in number will be summarized using quantiles. The location of all tumors will be recorded at Day 1 and at recurrence for each patient. Locations include base, dome, neck, trigone, anterior wall, posterior wall, left wall, and right wall. For each location, the number of patients (and percentage) who had tumor at that location will be summarized by at Day 1 only, at recurrence only, at both Day 1 and recurrence, and at neither. The discordance rate of each location will also be calculated.

8.5.6.3 Time to Disease Progression

Time to Progression is the time from Day 1 to the first documentation of stage progression as confirmed by pathology. Only the development of ≥T2 disease will be included in the assessment of time to disease progression. Censoring of patients with no documented progression will be the same as described for recurrence in **Section 8.5.5** above.

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 (body temperature, 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 at Screening, Day 1, and at the Safety Follow-up Visit. 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.

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 Qapzola 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 Qapzola 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 Qapzola vials will be destroyed per institution, local, and all applicable policies and procedures. After study conclusion, all unused vials of Qapzola 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. An Independent Data Monitoring Committee (IDMC) will review the unblinded safety data from the first 30 patients to verify that the 8 mg/50 mL dose is safe. 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 CRFs. The CRA is responsible for routine review of the CRFs 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 CRFs, 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:
  - Substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data;
  - Drafting the article or revising it critically for important intellectual content; and
  - 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

1. Howlader N, Noone AM, Krapcho M, Miller D, Bishop K, Altekruse SF, et al. (eds). SEER Cancer Statistics Review, 1975-2013, National Cancer Institute. Bethesda, MD, http://seer.cancer.gov/csr/1975_2013/, based on November 2015 SEER data submission, posted to the SEER web site, April 2016.
2. Leal J, Luengo-Fernandez R, Sullivan R, Witjes JA. Economic Burden of Bladder Cancer Across the European Union. Eur Urol. 2016;69(3):438-47.
3. Yeung C, Dinh T, Lee J. The health economics of bladder cancer: an updated review of the published literature. Pharmacoeconomics. 2014;32(11):1093-104.
4. Network NCC. Clinical Practice Guidelines in Oncology: Bladder Cancer (Version 2.2015): National Comprehensive Cancer Network; 2015 [August 21, 2015]. Available from: http://www.nccn.org/professionals/physician_gls/pdf/bladder.pdf.
5. Chang SS, Boorjian SA, Chou R, Clark PE, Daneshmand S, Konety BR, et al. Diagnosis And Treatment Of Non-Muscle Invasive Bladder Cancer: AUA/SUO Guideline. American Urological Association. 2016.
6. Kassouf W, Aprikian A, Black P, Kulkarni G, Izawa J, Eapen L, et al. Recommendations for the improvement of bladder cancer quality of care in Canada: A consensus document reviewed and endorsed by Bladder Cancer Canada (BCC), Canadian Urologic Oncology Group (CUOG), and Canadian Urological Association (CUA), December 2015. Can Urol Assoc J. 2016;10(1-2):E46-80.
7. Babjuk M, Böhle A, Burger M, Compérat E, Kaasinen E, Palou J, et al. Guidelines on Non-muscle-invasive Bladder Cancer (Ta, T1 and CIS) In: EAU Guidelines. Edn. presented at the EAU Annual Congress Madrid 2015. European Association of Urology, Arnhem, The Netherlands. . 2015.
8. Bellmunt J, Orsola A, Leow JJ, Wiegel T, De Santis M, Horwich A. Bladder cancer: ESMO Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2014;25 Suppl 3:iii40-8.
9. Avritscher EB, Cooksley CD, Grossman HB, Sabichi AL, Hamblin L, Dinney CP, et al. Clinical model of lifetime cost of treating bladder cancer and associated complications. Urology. 2006;68(3):549-53.
10. James AC, Gore JL. The costs of non-muscle invasive bladder cancer. Urol Clin North Am. 2013;40(2):261-9.
11. Sylvester RJ, Oosterlinck W, van der Meijden AP. A single immediate postoperative instillation of chemotherapy decreases the risk of recurrence in patients with stage Ta T1 bladder cancer: a meta-analysis of published results of randomized clinical trials. J Urol. 2004;171(6 Pt 1):2186-90, quiz 435.
12. Loadman PM, Bibby MC, Phillips RM. Pharmacological approach towards the development of indolequinone bioreductive drugs based on the clinically inactive agent EO9. Br J Pharmacol. 2002;137(5):701-9.

13. National Comprehensive Cancer Network. Clinical Practice Guidelines in Oncology: Bladder Cancer (Version 1.2016) [April 4, 2016]. Available from: http://www.nccn.org/professionals/physician_gls/pdf/bladder.pdf.

14. Hochberg Y. A sharper Bonferroni procedure for multiple tests of significance. Biometrika. 1988;75(4):800-2.

APPENDIX 1: SCHEDULE OF STUDY ASSESSMENTS AND PROCEDURES

Assessments	Screening	Randomize/ Treatment	Safety Follow-up Visit [a]	Long-Term Post-TURBT Follow-up [b]								
	Day -30 to 1	Day 1	Day 35	Month								
				3 [a]	6	9	12	15	18	21	24	Every 6 Months
	Visit 0	Visit 1	Visit 2	Visits 3-10								Visits 11+
Informed Consent (IC)	x											
Urine cytology	x [c]			x	x	x	x	x	x	x	x	x
Cystoscopy	x [c]			x	x	x	x	x	x	x	x	x
Medical history	x											
Vital signs	x	x	x	x								
Weight and height	x											
Physical examination [d]	x		x	x								
Complete Blood Count	x	x [e]	x	x								
Chemistry	x	x [e]	x	x								
Pregnancy test	x											
Urine dip stick	x	x [e,f]	x	x	x	x	x	x	x	x	x	x
TURBT and Specimen Collection		x [g]										
Randomization		x										
Qapzola or Placebo instillation [h]		x										
Concomitant medications [i]	x	x	x	x	x	x	x	x	x	x	x	x
Adverse event assessment [j]	x	x	x	x	x	x	x	x	x	x	x	x

a) Only patients who don't have pathology confirmed study-eligible NMIBC after TURBT, or patients who discontinue during follow-up, will return on Day 35 (±5 days) for the Safety Follow-up Visit. Patients in the Target Population will have the Safety Follow-up at the 3-month visit.

b) Follow-up visits for patients with Ta histology are to be conducted every 3 months (±30 days) calculated from the date of TURBT for the first 2 years and then every 6 months (±60 days) until tumor recurrence or the End-of-Study, whichever occurs first.

c) The qualifying cystoscopy and urine cytology may be performed up to 45 days prior to signing the informed consent.

d) A complete physical examination will be performed at Screening and the Safety Follow-up Visit/Month 3 Follow-up 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. If patient is on anticoagulation therapy or has bleeding disorder risk, PT/PTT test should be ordered at Screening per investigator discretion.

f) Urine dipstick to be done just prior to study drug instillation (60 ± 30 minutes) once gross hematuria is resolved.

g) Each tumor/lesion resected during TURBT should be submitted to the local pathology lab in a separate container, noting the location, to ensure that the tumor location, size, stage, and grade for each tumor/lesion, according to the 2004 WHO/ISUP grading system along with the presence/absence of muscle fiber in the lesion, is assessed.

h) Instillation of study drug (Qapzola 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 ± 5 minutes.

i) During the Follow-up Period, only medications to treat NMIBC will be recorded for concomitant medications.

j) All adverse events from the time of study drug administration until 35 days after the last dose of study treatment will be recorded. From the 3-month visit through the End-of-Study, only deaths and AEs related to study procedures will be recorded.