Apaziquone for Treatment of Patients with Non-Muscle-Invasive Bladder Cancer Following Transurethral Resection of Bladder Tumors

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Glossary of Abbreviations and Terms

Abbreviation/ Acronym	Definition
ACSNSQIP	American College of Surgeons National Surgical Quality Improvement Program
AE	Adverse Event
AHRQ	Agency for Healthcare Research and Quality
APZ	Apaziquone
AUA	American Urological Association
BCG	Bacillus Calmette–Guérin
CI	Confidence Interval
CIS	Carcinoma in situ; Tis
CR	Complete Response
CUA	Canadian Urological Association
CYP	Cytochrome P450
DLT	Dose-limiting toxicity
EAU	European Association of Urology
eCTD	Electronic Common Technical Document
EO9	Apaziquone (apaziquone)
EORTC	European Organisation for Research and Treatment of Cancer
ESMO	European Society for Medical Oncology
FDA	Food and Drug Administration
GLP	Good Laboratory Practice
HR	Hazard Ratio
HRQoL	Health-Related Quality of Life
I^2	Magnitude of Heterogeneity
IBCG	International Bladder Cancer Group
IND	Investigational New Drug
IP	Intraperitoneal
IPOC	Intravesical post-Operative Chemotherapy
ISUP	International Society of Urological Pathology
ITT	Intent-to-treat
IV	Intravenous
LLOQ	Lower Limit of Quantitation
MIBC	Muscle Invasive Bladder Cancer

Abbreviation/ Acronym	Definition
MMC	Mitomycin C
NC	Not calculable
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NCTN	National Clinical Trials Network
NDA	New Drug Application
NICE	National Institute for Health and Care Excellence
NMIBC	Non-muscle invasive bladder cancer
NR	No Response
ODAC	Oncologic Drugs Advisory Committee
OR	Odds Ratio
PBO	Placebo
PUNLMP	Papillary urothelial neoplasm of low malignant potential
RR	Relative Risk
SAE	Serious adverse event
SD	Standard Deviation
SE	Standard Error
SEER	Surveillance, Epidemiology, and End Results
SOC	System organ class
SPA	Special Protocol Assessment
T0	No evidence of tumor in the bladder
T1	Tumor invades lamina propria
T2	Tumor has spread to the muscle of the bladder wall.
T3	Tumor has grown into the perivesical tissue
Ta	Non-invasive papillary carcinoma
TEAE	Treatment-emergent adverse event
Tis	Carcinoma in situ; CIS
TURBT	Transurethral resection of bladder tumor
TUR	Transurethral resection
US	United States
WHO	World Health Organization

1 EXECUTIVE SUMMARY

1.1 Product Overview and Indication

Apaziquone (Qapzola™, EO9) has been developed by Spectrum Pharmaceuticals, Inc. over the past 14 years to answer the unmet need for a safe and effective treatment option for non-muscle invasive bladder cancer (NMIBC) after transurethral resection of bladder tumors (TURBT). Spectrum is seeking approval for the following proposed indication:

- Apaziquone is indicated for intravesical instillation post-transurethral resection of bladder tumors (post-TURBT) in patients with non-muscle invasive bladder cancer (NMIBC).

The proposed clinical dose of apaziquone is a single 4 mg dose, administered intravesically in a volume of 40 mL (0.1 mg/mL) of diluent that is instilled into the bladder 30 minutes post-TURBT and retained in the bladder for a period of 1 hour.

Apaziquone is a novel, fully synthetic, bioreductive alkylating indoloquinone. Apaziquone 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 apaziquone 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 (see **Section 2.2**).

1.2 Disease Background

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) **[7-8]**, and the European Society for Medical Oncology (ESMO) **[7-8]** 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]**.

1.3 Unmet Medical Need

Despite the consensus recommendations of the NCCN, AUA, CUA, EUA, and EMSA, few practitioners use intravesical therapy post-TURBT to treat NMIBC **[11]**. Among US urologists, 67% stated they never use intravesical therapy post-TURBT, and only 2% always use intravesical therapy post-TURBT **[12]**. Concerns about the potential for toxicity, as well as reimbursement challenges when using drugs used off-label for immediate post-operative instillation of chemotherapy (IPOC) contribute to the reluctance of physicians to adopt and comply with the consensus guidelines.

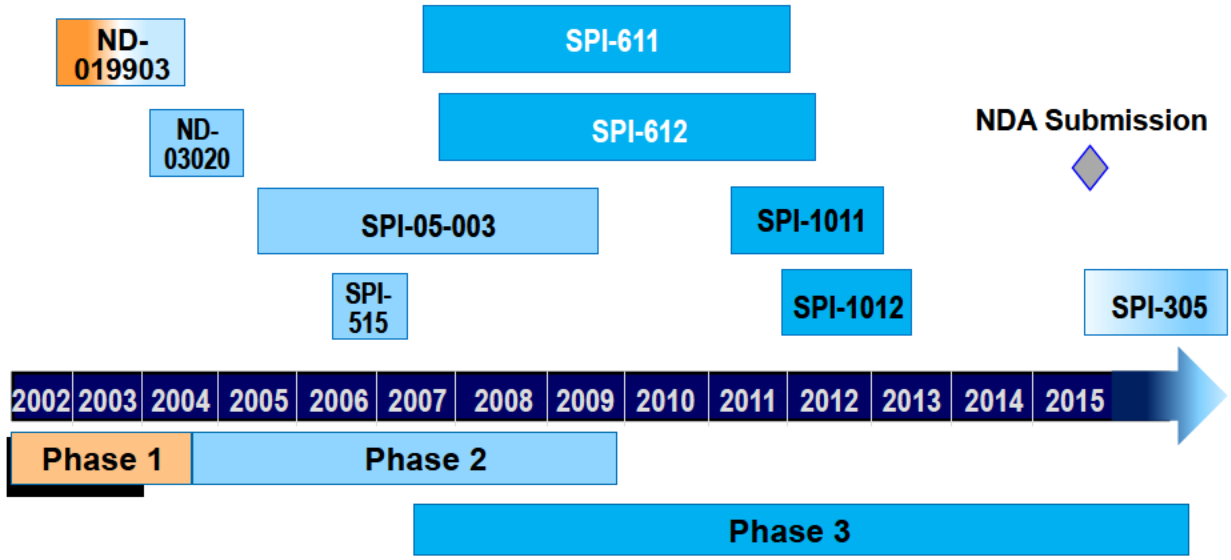
No intravesical drugs are currently approved in the US for post-TURBT treatment of low-risk NMIBC. Mitomycin C and epirubicin are used off-label but are not specifically formulated for intravesical use. They are vesicants and both have a well-documented risk for serious side effects, including extravasation. Chemical cystitis, which manifests as dysuria, increased urinary frequency, urgency, suprapubic pain, and discomfort, occurs in up to 41% of patients treated with MMC, decreased bladder capacity occurs in up to 22% of patients, and eczema-like reactions in 4% to 12% of patients; cystectomy due to severe bladder contractures has occurred in rare cases **[13-14]**. Major surgical intervention can be required to resolve symptoms resulting from extravasation of MMC in patients with unrecognized bladder perforation following TURBT as a result of chemical peritonitis **[15-18]**. The effects of epirubicin are similar to those of MMC, regarding bladder toxicity, including cystitis, dysuria, and increased urinary frequency and urgency **[13]**.

Bacillus Calmette–Guérin (BCG), which is approved for treatment of carcinoma in situ (CIS) and high-grade papillary NMIBC, has neither a utilization nor indication for IPOC due to its risk of systemic toxicity. Valrubicin is approved only for patients with NMIBC that is refractory to BCG and who are not candidates for cystectomy.

1.4 Clinical Development of Apaziquone

The clinical development program for intravesical instillation of apaziquone in the treatment of NMIBC comprised eight completed studies (Phase 1 through Phase 3) compiled over a 14-year period, as well as an additional ongoing Phase 3 study (**Figure 1**).

Figure 1 Development History for Apaziquone



ND-019903: Phase 1/2 dose-escalation and marker lesion study

ND-03020: Phase 2 marker lesion study

SPI-05-003: Phase 2 study in high-risk patients

SPI-515: Phase 2 safety study

SPI-611 and **SPI-612**: Pivotal Phase 3 single intravesical instillation studies

SPI-1011 and **SPI-1012**: Phase 3 single and multiple intravesical instillation studies (terminated early due to business reasons unrelated to safety or any other study aspects)

SPI-EOQ-13-305: Phase 3 single and multiple intravesical instillation study initiated in September 2015 and currently recruiting patients. It is expected to be completed in 5 to 6 years

The intended clinical dose of apaziquone (4 mg in 40 mL) was determined in a Phase 1/2 dose-escalation study (**ND-019903** [n=12]), which demonstrated that dysuria was the dose-limiting toxicity, occurring after intravesical instillation of apaziquone at a dose of 8 mg in 40 mL. Of note and importantly, apaziquone was not detected in the plasma of patients and does not appear to be absorbed from the bladder at doses as high as 16 mg in 40 mL (see **Section 4.3.1**). This was consistent with nonclinical studies that showed 1) minimal absorption of apaziquone after intravesical instillation in animals, and 2) rapid metabolism of apaziquone by red blood cells (see **Section 2.3.2**).

Direct evidence of the antitumor activity of apaziquone in NMIBC was provided in two marker lesion studies (**ND-019903** [n=12] and **ND-03020** [n=46]). In these studies, patients received an intravesical instillation of apaziquone (4 mg in 40 mL) once a week for 6 weeks, starting 2 to 4 weeks after TURBT. In each study, 67% of patients showed complete response to single marker tumor lesions **[19-20]**. This compared favorably to studies of other intravesical agents in which only 26% to 46% of patients reported complete response **[21-23]** (see **Section 4.3.2**).

Since a single intravesical instillation of a chemotherapeutic agent given in the post-TURBT period had been shown to significantly reduce tumor recurrence **[24]**, Spectrum planned a Phase 3 program to assess the safety and efficacy of a single instillation of apaziquone (4 mg in 40 mL) in this indication. A pilot safety study (**SPI-515** [n=20]) showed that apaziquone was well tolerated, had a very acceptable safety profile, and was not detected in the plasma of patients when given intravesically. Additionally, bladder mucosa showed re-epithelialization without any evidence of impaired wound healing, which has been seen with MMC **[25]**.

Given the positive safety profile for apaziquone in **SPI-515**, Spectrum proceeded to conduct two pivotal Phase 3 studies of apaziquone. A Special Protocol Assessment (SPA) Agreement with the FDA on the design and planned analyses of the first pivotal Phase 3 study (**SPI-611**) was issued on 28 Aug 2007. The second pivotal Phase 3 study, **SPI-612** was nearly identical in design. **SPI-611** (n=802) and **SPI-612** (n=812) were multinational (United States, Poland, and, in **SPI-612**, Canada), randomized, placebo-controlled double-blind studies whereby patients were randomized to receive either a single intravesical instillation of apaziquone (4 mg in 40 mL) or placebo (40 mL) retained for 1 hour within 6 hours post-TURBT. Patients were randomized into the study based on a visual diagnosis of NMIBC at cystoscopy and underwent TURBT, and were entered into the primary efficacy analysis based on central review of pathology. The main entry criteria in each study were age ≥18 years; a diagnosis of transitional cell carcinoma of the bladder with NMIBC, Stage Ta, Grade 1-2 (G1-G2); and ≤4 (in **SPI-611**) or ≤5 (in **SPI-612**) tumors that were ≤3.5 cm in diameter each. Patients in both studies could have had primary or recurrent disease, and could have received previous intravesical therapy, including BCG or MMC. These placebo-controlled pivotal studies provided the majority of efficacy data for apaziquone, which are described in **Section 5.2.2.3** and summarized briefly in **Section 1.5**. They also provided the majority of safety data described in **Section 6** and summarized briefly in **Section 1.6**.

Two additional Phase 3 studies (**SPI-1011** and **SPI-1012**) were initiated but terminated early based on a business decision unrelated to either patient safety or efficacy. The studies included an open-label, single-instillation phase followed by a subsequent randomized, placebo-controlled, double-blind phase, to assess the safety and efficacy of single and multiple instillations of apaziquone (4 mg in 40 mL) in patients with primary or recurrent NMIBC. A total of 66 patients (28 in the double-blind phase) were enrolled in **SPI-1011** and 47 patients (31 in the double-blind phase) in **SPI-1012**.

The safety of apaziquone is based on the above studies, as well as an additional Phase 2 study (**SPI-05-003**) conducted in high-risk patients (n=53). Overall, the clinical safety of apaziquone was evaluated using data from 1859 patients, including 1053 treated with apaziquone, who participated in the eight Sponsor-conducted clinical studies. Safety data are described and summarized in **Section 6**.

1.5 Clinical Efficacy of Apaziquone

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 apaziquone instillation 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) **[24]**. 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 apaziquone 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 apaziquone 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** (see **Section 5.2.2.2**).

1.5.1 2-Year Recurrence Rate

Fewer patients treated with apaziquone 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 apaziquone compared to 44.6% for patients treated with placebo. For **SPI-612**, the **2-Year Recurrence Rate** was 39.7% for patients treated with apaziquone 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 Apaziquone Post-TURBT (Ta, G1-G2 Target Population)

Parameter	SPI-611		SPI-612		Overall	
	APZ (n=295)	PBO (n=271)	APZ (n=282)	PBO (n=298)	APZ (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	

APZ=apaziquone; CI=confidence interval; NC=not calculable; PBO=placebo; 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.

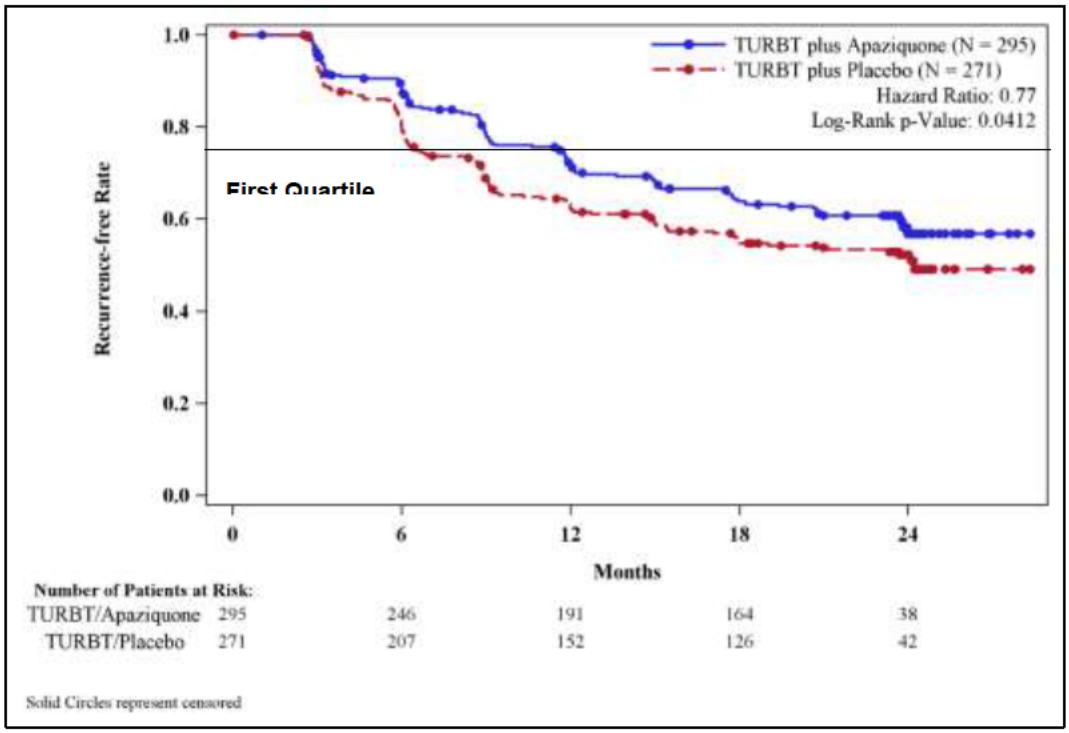
The results in the **ITT Population** were similar to those in the Ta, G1-G2 Population (see **Section 5.2.2.3.3**).

1.5.2 Time to Recurrence

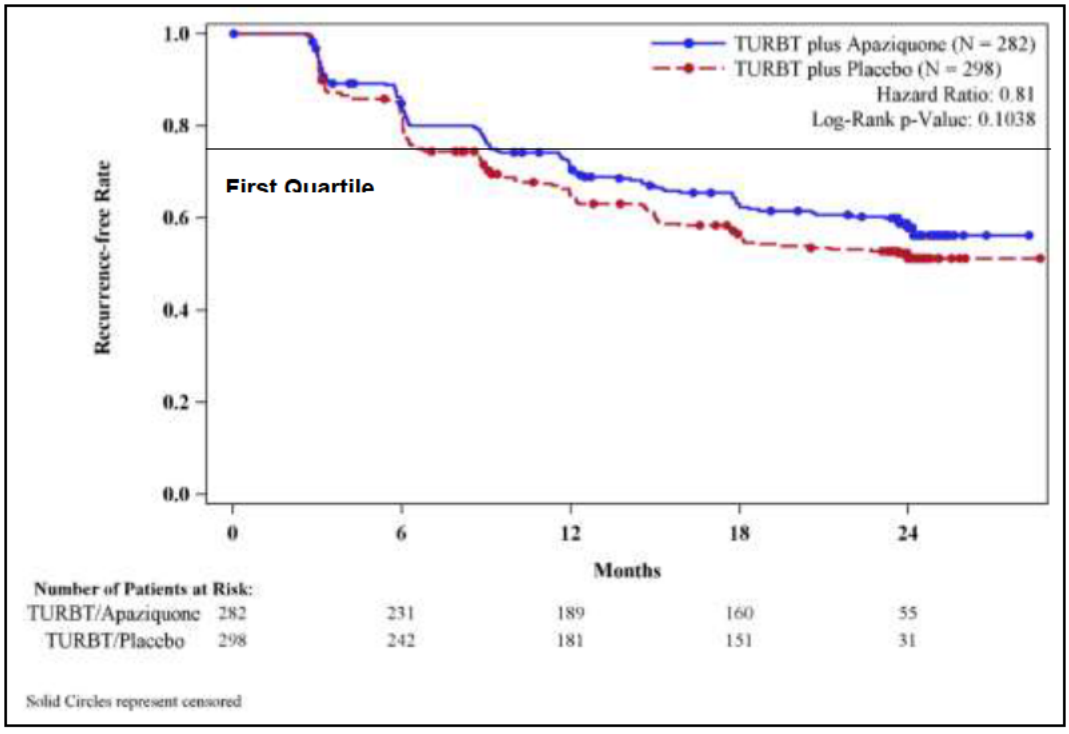
The distribution of **Time to Recurrence** by the Kaplan-Meier method showed a clear divergence between the apaziquone and placebo groups over the 2-year follow-up period in both studies **(Figure 2)**. An increase in **Time to Recurrence** was demonstrated for apaziquone-treated patients, with a nominal 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) **(Section 5.2.2.3.2)**. 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 apaziquone compared to placebo. The results for the **ITT Population** are similar for the pooled analysis (see **Section 5.2.2.3.3**).

Figure 2 Kaplan-Meier Estimates of Time to Recurrence in the Apaziquone Pivotal Studies SPI-611 and SPI-612 (Ta, G1-G2 Target Population)

A. SPI-611



B. SPI-612



1.5.3 Other Secondary Efficacy Parameters

Other secondary efficacy endpoints supported the primary analysis in that patients treated with apaziquone had a better outcome (see **Section 5.2.2.3.4**).

1.5.4 Subgroup Analyses

Spectrum performed several multivariate and subgroup analyses of efficacy endpoints (**2-Year Recurrence Rate** and **Time to Recurrence**) to identify covariates that affected the magnitude and variability of the prespecified efficacy measures. Subgroup analyses were performed for the factors identified to have effect from the multivariate analysis to examine the consistency of treatment effect. These data showed that apaziquone was favored regardless of the country that enrolled patients, the demographics of the patients, or whether the tumor was primary or recurrent, whether the patient had a single tumor or multiple tumors, and whether the tumor was Grade 1 or Grade 2 (see **Section 5.2.2.3.5**).

The time of instillation of apaziquone post-TURBT (≤30 and >30 minutes) was found to be a notable factor in the efficacy of apaziquone, with better efficacy observed when apaziquone was instilled >30 minutes post-TURBT. This finding was consistent in this subgroup analysis between the two studies:

- In **SPI-611**, there was a 10.2% absolute reduction in **2-Year Recurrence Rate** for patients treated with apaziquone (n=134) compared to patients treated with placebo (n=145) (31.1% vs 41.3%; nominal p = 0.0733; OR 0.64; 95% CI 0.39, 1.04), representing a 24.7% relative reduction compared to placebo. **Time to Recurrence** was 12.5 vs 8.3 months based on first quartile [25%] (nominal p = 0.0328; HR 0.66, 95% CI 0.45, 0.97).
- In **SPI-612**, there was an 11.7% absolute reduction in **2-Year Recurrence Rate** for patients treated with apaziquone (n=183) compared to patients treated with placebo (n=220) (38.3% vs 50.0%; nominal p = 0.0183; OR 0.62; 95% CI 0.42, 0.92), representing a 23.5% relative reduction compared to placebo. **Time to Recurrence** was 11.6 vs 6.3 months based on first quartile [25%]; (nominal p = 0.0189; HR 0.70, 95% CI 0.52, 0.95).

Additionally, there were higher improvements in **2-Year Recurrence Rate** and **Time to Recurrence** in patients treated from 31-90 minutes post-TURBT in **SPI-611** and **SPI-612**, were clinically meaningful, and were also consistent and reproducible between **SPI-611** and **SPI-612**. The reduced efficacy of apaziquone when instilled ≤30 minutes post-TURBT may reflect the inactivation of apaziquone by red blood cells remaining in the bladder at that time **[26]**.

1.5.5 Discussion of Efficacy

Each of the pivotal Phase 3 studies (**SPI-611** and **SPI-612**) was powered based on the literature available at the time of study design, particularly a meta-analysis **[24]**, which showed recurrence rates of 36.7% for TURBT plus intravesical therapy and 48.4% for TURBT over a 3.4-year median follow up, representing an absolute improvement of 11.7%. **SPI-611** and **SPI-612** were consequently designed to detect an absolute improvement in **2-Year Recurrence Rate** of 12% at minimum power (80%) and at a 5% level of significance. The individual results in the seven studies included in the meta-analysis on which sample size calculations were based **[24]** were,

however, highly variable with respect to magnitude of recurrence rates as well as the treatment effect between groups, as observed by a significant test of heterogeneity (χ^2=14, df=6, p = 0.03). The studies varied in design with respect to confounding factors such as the use of a placebo and post-operative irrigation following TURBT **[27-28]**, contributing to the heterogeneity in treatment effects. Because **SPI-611** and **SPI-612** were each powered to detect a larger effect (ie, 12%) than was demonstrated (ie, 6-7%) the studies did not achieve statistical significance for the pre-specified endpoint of **2-Year Recurrence Rate**. National and international working groups now indicate that a 6% absolute difference in the percent of patients with recurrence at 2 years, which is consistent with the treatment effect seen in **SPI-611** and **SPI-612**, is considered a reasonable magnitude of effect for a clinical trial to be considered "positive," in patients with low-risk NMIBC **[29]** (see **Section 5.2.1.4**). In view of the similar study design and patient characteristics enrolled in two studies, the integrated analysis of two studies will provide a better statistical power to the efficacy analysis to detect the recently proposed level of clinically meaningful treatment effect. In addition, an exploration of time to instillation post-TURBT showed that instillation of apaziquone >30 minutes post-TURBT may provide better efficacy due to potential for inactivation of apaziquone by red blood cells remaining in the bladder at that time.

1.6 Clinical Safety of Apaziquone

The majority of data establishing the safety of a single intravesical instillation of apaziquone 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 (see **Section 6.2.2**). 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 (see **Section 6.2.3**).

Few patients (10% to 13%) had TEAEs the investigator considered treatment related with the incidence of these AEs being similar between apaziquone and placebo (see **Section 6.2.2**). 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 (see **Section 6.2.3.1**).

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 apaziquone. 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 (see **Section 6.2.3.3**). Another patient who received apaziquone died of acute renal failure 624 days after apaziquone treatment; the event was

assessed as not related to study treatment. Hematuria is a common presenting sign of NMIBC **[4-5]** and is an expected consequence of the TURBT procedure.

No patients had 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 (see **Section 6.2.3.4**).

Approximately 3% of patients had AEs that resulted in death, none of which the investigator assessed as related to study drug (apaziquone or placebo). There were no deaths reported in the immediate post TURBT instillation period (within 30 days). (see **Section 6.2.4**).

Clinical laboratory assessments showed no clinically meaningful differences between patients receiving apaziquone and placebo in any hematologic, liver, kidney, or metabolic parameters (see **Section 6.2.6**) and in a subgroup of patients in **SPI-611** (n=191), there was no measurable effect on functional bladder capacity (see **Section 6.2.8**).

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 apaziquone. 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 apaziquone (~15% to 45%) than single instillations (~3% to 15%). Treatment-related SAEs were experienced by three patients who received single instillations of apaziquone (pelvic pain, postoperative urinary retention, and hematuria) and four patients receiving multiple instillations of apaziquone (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 (see **Section 6.3**).

1.7 Benefit/Risk for Apaziquone

Spectrum has worked closely with the FDA over the past 10 years in the development program for apaziquone, including two landmark placebo-controlled pivotal trials conducted in the largest number of patients ever treated in the intended patient population. While **SPI-611** and **SPI-612** did not meet their pre-specified primary endpoint, the data from the pivotal and supportive studies support the safety and effectiveness of apaziquone for the treatment for low-risk NMIBC. These studies and data include:

- Two marker lesion studies demonstrating clear antitumor activity of apaziquone in NMIBC.
- An outstanding safety profile and lack of toxicity for apaziquone in all studies, representing a clear advantage over other available therapy (MMC, epirubicin) given by single intravesical instillation.
- Efficacy data that were consistent between the pivotal studies, **SPI-611** and **SPI-612**, showing a clinically meaningful benefit (6.7%).
- A favorable impact on **Time to Recurrence** in one of the studies, delaying the need for repeat TURBT and number of subsequent TURBT.

Given the clinically meaningful efficacy, minimal inconvenience from a single instillation, and lack of toxicity, these data support a positive benefit/risk profile for apaziquone given as a single 1-hour intravesical instillation at a dose of 4 mg in 40 mL of diluent post TURBT.

No drugs are currently approved in the US for the treatment of low-risk NMIBC. As such, chemotherapeutic agents such as MMC and epirubicin, which are recommended by various national and international organizations for immediate intravesical therapy in the treatment of low-risk NMIBC are being used "off-label" and are not specifically formulated for intravesical use. BCG, which is approved for the treatment of CIS and high-grade papillary NMIBC, and not indicated in the immediate postoperative setting for low-risk NMIBC because of the risk of systemic adverse effects.

In the US, there are currently ~600,000 patients with bladder cancer, and ~75% (~450,000) have NMIBC. At least half of these patients (~225,000) will relapse and require additional treatment and surgeries in two years. These are elderly patients, often with co-morbidities, who face multiple surgeries with exposure to anesthesia. They risk having their bladders damaged, repaired, or even removed—a risk that is potentially increased by the reluctance on the part of urologists to use currently available therapies (MMC, epirubicin) due to toxicity. These patients also face considerable expense associated with repeat treatments.

Spectrum believes that the approval of apaziquone by the FDA, coupled with efforts by Spectrum to educate practitioners about the benefits of this treatment, could significantly improve the adherence to recommended treatment guidelines that support instillation of a chemotherapeutic agent post-TURBT. Greater use of intravesical chemotherapy in the US has the potential to substantially reduce the economic and humanistic burdens of NMIBC—one study estimated that over a 2-year period, about 8,000 recurrences could be avoided if all patients received intravesical chemotherapy, resulting in an aggregate cost savings of $30 million **[30]**.

Following discussions with FDA, Spectrum has initiated another large placebo-controlled Phase 3 study designed to further assess the safety and efficacy of apaziquone in low-risk NMIBC. The study is not expected to be complete until at least 2021. In the meantime, adoption of this treatment strategy—giving tens of thousands of patients each year timely access to an effective and well-tolerated therapy—would prevent tumor recurrence in thousands of patients a year, bringing significant relief to the patient and substantial savings to the overall cost of managing this disease. It is reasonable to consider approval for a single post-TURBT intravesical instillation of apaziquone for low-risk NMIBC in order to reduce the tremendous personal and societal burden of this highly recurrent disease.

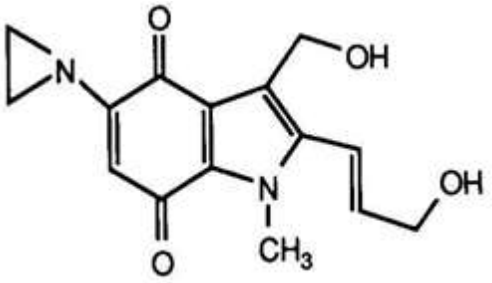
2 INTRODUCTION

Apaziquone has been developed by Spectrum Pharmaceuticals, Inc. for intravesical instillation post-TURBT in patients with NMIBC to help fill the unmet need for safe and effective treatment options for NMIBC. More potent against bladder cancer cell lines *in vitro* than MMC and other chemotherapeutic agents, systemic absorption of apaziquone after intravesical administration in this setting is minimal, reducing the likelihood of drug:drug interactions with concomitant medications or potential systemic side effects. **[4]**.

2.1 Product Description

Apaziquone (3-hydroxymethyl-5-aziridinyl-1-methyl-2-[1H-indole-4,7-dione]-propenol) (**Figure 3**) is a novel, fully synthetic bioreductive alkylating indoloquinone with potent antitumor activity that has been demonstrated both *in vitro* and *in vivo* in several tumor models, including bladder cancer.

Figure 3 Structure of Apaziquone



For intravesical instillation, apaziquone is supplied as a sterile, non-pyrogenic lyophilized product containing 4 mg apaziquone, 50 mg mannitol as a bulking agent, and 5 mg sodium bicarbonate as a pH adjuster. Prior to instillation, apaziquone is reconstituted in a diluent that contains propylene glycol, sodium bicarbonate, and disodium ethylene diaminetetraacetic acid disodium salt (Na_2-EDTA).

The final concentration of apaziquone after reconstitution in 40 mL diluent is 0.1 mg/mL.

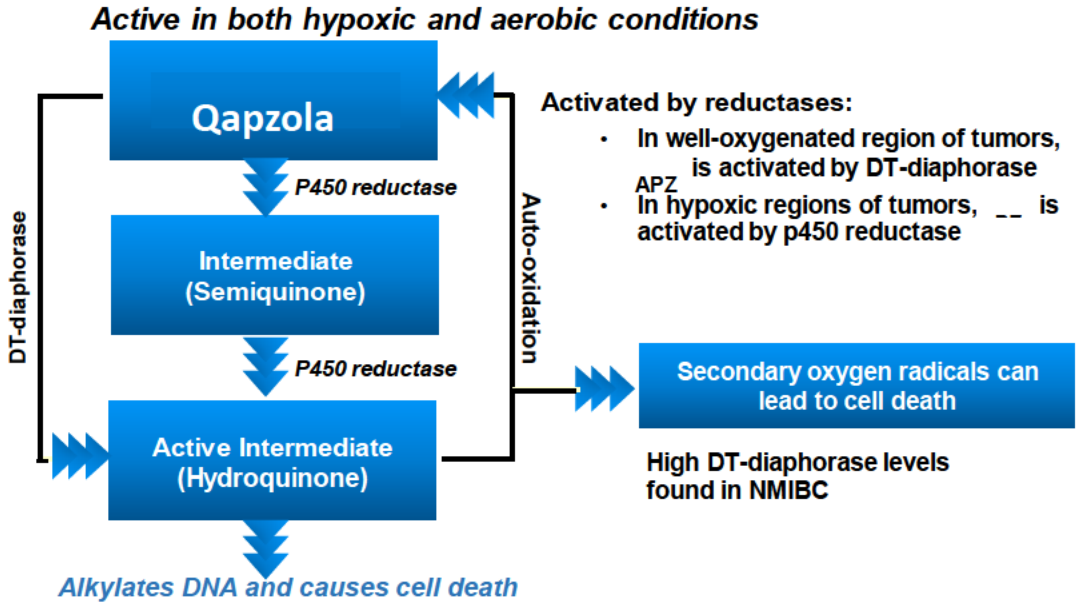
2.2 Mechanism of Action

Apaziquone is a pro-drug that is enzymatically reduced by the enzyme DT-diaphorase (DTD), also called NAD(P)H:quinone oxidoreductase-1, and other reductases to generate cytotoxic species. The basic mechanism of activation of apaziquone is believed to be similar to that of other indolequinones, involving reduction by cellular enzymes that transfer one or two electrons, forming a semiquinone and a hydroquinone, respectively **[31]**.

Oxidation of the semiquinone under aerobic conditions results in a redox cycle that can cause cell death by forming reactive oxygen species or depleting reducing nucleotides (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. A diagram of the two alternative pathways of apaziquone activation is shown in **Figure 4**.

Apaziquone is converted to several inactive metabolites, the major one being 3-hydroxymethyl-5-β-hydroxyethylamino-2-(1H-indole-4,7-dione)prop-β-en-α-ol (EO5a) that is a hydrolysis product with an opened aziridine ring. A degradation product seen only in urine is 3-hydroxymethyl-5-β-chloroethylamino-2-(1H-indole-4,7-dione)prop-β-en-α-ol (EO9-Cl), a chlorine adduct of apaziquone.

Figure 4 Mechanism of Action of Apaziquone



2.3 Overview of Nonclinical Program

The nonclinical development program for apaziquone included evaluation of the pharmacology, pharmacokinetics, and toxicology of the drug with a focus on intravesical administration. Intravenous (IV) and intraperitoneal (IP) administration studies were also conducted.

2.3.1 Nonclinical Pharmacology

Apaziquone has the following important features as a cancer chemotherapeutic agent:

- High potency against a broad spectrum of tumor lines, including human bladder cancer **[32-34]**. The *in vitro* potency of apaziquone is 30- to 100-fold higher than that of MMC.
- Bioreductive activation by one- and two-electron transfer enzymes [31]
- Enhancement of cytotoxicity under low-oxygen conditions [35-38]
- Enhancement of cytotoxicity at low pH **[32, 39-41]**

Because apaziquone demonstrates high *in vitro* potency and is rapidly eliminated after systemic administration (see **Section 2.3.2**), apaziquone is ideally suited for local delivery to superficial tumors in the bladder by intravesical instillation.

Pharmacology studies of apaziquone conducted on behalf of the Sponsor have included a comparison of the effect of intravesical apaziquone, MMC, and placebo on murine bladder cancer cell lines in an animal model; the effectiveness of different apaziquone formulations in a

rat bladder urothelial cell carcinoma model **[42]**; and an *in vitro* pharmacodynamic interaction study of apaziquone with hexyl aminolevulinate (Hexvix), a photosensitizing agent used to enhance detection of NMIBC.

These studies showed that:

- Apaziquone demonstrated antitumor activity after intravesical administration in animal models of bladder cancer.
- An apaziquone concentration of 0.1 mg/mL was optimal based on median survival time in mice bearing orthotopic bladder cancer tumors, and had comparable activity to 1.0 mg/mL MMC.
- Hexvix did not affect the anticancer activity of Apaziquone.

2.3.2 Nonclinical Pharmacokinetics

Published studies of the nonclinical pharmacokinetics of Apaziquone after IV administration in mice and rats indicated that Apaziquone has a short half-life ($t_{½}$) (≤3 minutes) **[26, 43]**. Unlike MMC, which was relatively stable in murine whole blood ($t_{½}$>120 minutes), apaziquone was rapidly metabolized by murine whole blood ($t_{½}$=15.6 minutes) and red blood cells ($t_{½}$=14.5 minutes) **[26]**.

Nonclinical pharmacokinetic studies conducted on behalf of the Sponsor included nonclinical pharmacokinetics of apaziquone after single or repeated intravesical instillation, determined as part of the toxicology studies conducted in dogs, and *in vitro* studies to determine protein binding, metabolism, and inhibition and induction of cytochrome P450 (CYP) enzymes by apaziquone in human serum, plasma, and subcellular fractions.

These studies indicated that:

- Following intravesical administration, systemic exposure to apaziquone was minimal in dogs, and most often was below the lower limit of quantification (LLOQ), even at a total dose that was seven times higher than the intended clinical dose of apaziquone in humans (4 mg) and 16 times higher than the intended clinical concentration in humans (0.1 mg/mL).
- Apaziquone metabolites were not detected in plasma following intravesical instillation of apaziquone.
- *In vitro*, apaziquone is a moderate inhibitor of CYP 1A2, 2B6, and 2E1 and a weak inhibitor of 2A6, 2C8, 2C9, 2C19, 2D6, and 3A4. Because of the minimal systemic absorption of apaziquone, as well as its short half-life and rapid metabolism in whole blood, these interactions are not expected to be clinically relevant.

2.3.3 Nonclinical Toxicology

The nonclinical toxicology program for apaziquone included both IV and IP studies in rodents and intravesical studies in dogs and pigs to support the intended route of administration in humans. These studies included three single-dose IV studies in mice and rats; two repeat-dose IV studies in mice and rats; three repeat-dose IP studies in mice and rats; a single-dose study by intravesical instillation in dogs; a repeat-dose study by intravesical instillation in dogs (Good Laboratory Practice [GLP]); a cardiovascular safety study of apaziquone administered by

intravesical instillation in telemetered dogs (GLP); a single-dose study by intravesical administration in pigs (GLP); two *in vitro* genotoxicity studies (GLP); and two local tolerance studies (GLP).

These studies indicated that:

- Apaziquone, given by the IV and IP routes, with plasma concentrations greater than is achieved by intravesical instillation, was safely administered and well tolerated at less than lethal doses in mice and rats. Reversible red cell depression was the primary toxic effect.
- Given the minimal systemic exposure to apaziquone after intravesical instillation in dogs, systemic toxicity after intravesical exposure was also minimal and much less than that observed after IV or IP administration in mice and rats.
- In a single-dose intravesical instillation study, toxicity after a 1-hour intravesical instillation of apaziquone in dogs (at up to seven times the intended clinical dose in humans) and pigs (at up to 20 times the intended clinical dose in humans) was largely restricted to the bladder at lower doses, and bladder, kidney, and ureters at higher doses, without substantial systemic exposure.
- Single dose intravesical instillation of apaziquone, retained for 1 hour in dogs, caused acute cystitis, an expected finding given this route of administration with a cytotoxic agent.
- After repeat-dose intravesical instillation in dogs (1-hour retention), 0.0125 mg/mL and 0.05 mg/mL apaziquone given once weekly for 6 weeks was not associated with mortality and resulted in a limited number of clinical observations that were not considered to be adverse. At a higher dose (0.2 mg/mL), three deaths from renal failure observed were attributed to urinary tract complications resulting from reflux of apaziquone into the ureters and not due to systemic absorption.
- The proposed clinical dose of apaziquone is 4 mg, administered intravesically in a volume of 40 mL (0.1 mg/mL).
- There were no ophthalmic findings at any dose and no changes in electrocardiogram (ECG) at any dose.
- Apaziquone had no cardiovascular effects in dogs following repeated intravesical instillation at the maximum tolerated dose (MTD) in dogs.
- Apaziquone has positive genotoxic potential *in vitro* and like other anti-cancer drugs, might have the potential of embryo-fetal toxicity.
- Apaziquone did not produce signs of dermal toxicity at the proposed clinical concentration of 0.1 mg/mL.

2.4 Summary

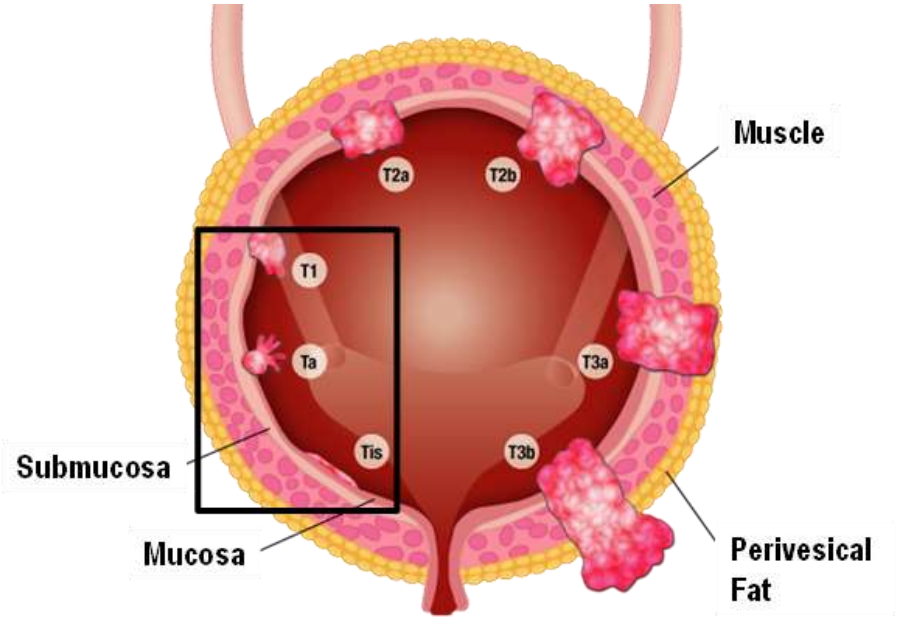
Nonclinical studies support the use of apaziquone in patients with low-risk NMIBC, given by postoperative intravesical instillation. One-hour retention of apaziquone instilled into the urinary bladder demonstrated sufficient local exposure to provide a potent anticancer effect. The lack of systemic exposure observed during intravesical instillation and retention, followed by draining of bladder contents, resulted in apaziquone being tolerated with only mild to moderate local effects.

3 DISEASE BACKGROUND AND MEDICAL NEED

3.1 Disease Background and Pathology

As noted in **Section 1.2**, the majority of patients (70%) with newly diagnosed bladder cancer will have NMIBC, with ~77,000 patients expected to be newly diagnosed this year. The recommended management of these patients depends on the stage and grade of the disease. Initial staging is based on clinical examination and followed by cystoscopic biopsy and resection (TURBT) under anesthesia. The resected tissues are then histologically examined leading to a final pathologic diagnosis **[4]**. NMIBC may present as single or multiple superficial papillary tumors confined to the mucosa (Stage Ta), may invade the submucosa (lamina propria) but not reach the bladder wall muscle (T1), or be noninvasive, carcinoma in situ (CIS), also termed noninvasive flat carcinoma (Tis). Muscle invasive bladder cancer is represented by higher-stage disease (T2 and T3) that is not amenable to intravesical therapy (**Figure 5**).

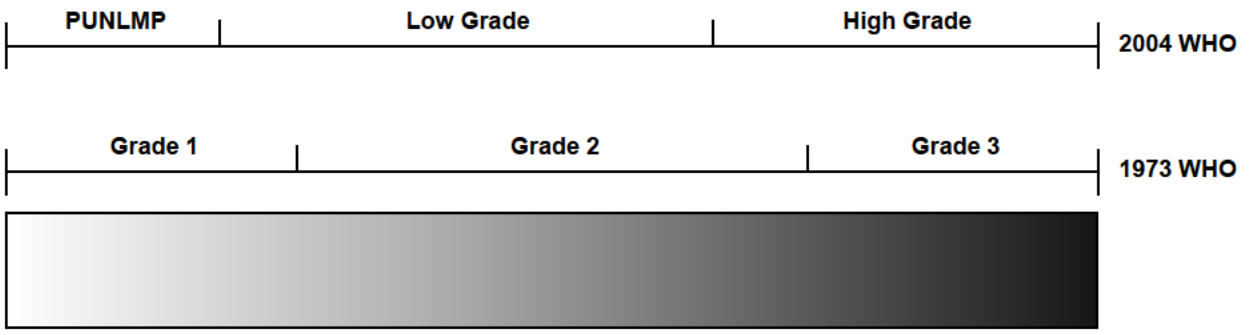
Figure 5 Bladder Cancer Staging



Ta, T1, Tis=nonmuscle-invasive bladder cancer; T2a, T2b, T3a, T3b=muscle-invasive bladder cancer

Grading of NMIBC tumors is by one of two classification systems. The first, in which tumors are graded on a scale of 1 (well differentiated) to 3 (poorly differentiated), was introduced by the World Health Organization (WHO) in 1973. The second, in which tumors are graded as papillary urothelial neoplasm of low malignant potential (PUNLMP), and low-grade or high-grade papillary urothelial carcinoma, was introduced by the WHO and the International Society of Urological Pathology (ISUP) in 2004 **(Figure 6)**.

Figure 6 Stratification of Bladder Tumors According to Grade (WHO 1973 and WHO/ISUP 2004)



PUNLMP = papillary urothelial neoplasm of low malignant potential; WHO = World Health Organization
Grade 1 = well differentiated; Grade 2 = moderately differentiated; Grade 3 = poorly differentiated
Source: Babjuk et al 2015 [8].

In the pivotal studies conducted by Spectrum (see Section 5.2), the target population was patients with Ta, G1-G2 disease (WHO/ISUP low grade). In patients newly diagnosed with NMIBC, the majority (70% to 75%) will present at Stage Ta (**Table 2**). Although the survival rate for the majority of patients with NMIBC is favorable [5], the probability of tumor recurrence is high, with 50% of patients with low-grade Ta disease expected to have a recurrence within 5 years (**Table 2**) [4]. There is also a 10% to 20% risk of progression to MIBC [5]. Rates of recurrence, as well as progression to MIBC, are important surrogate endpoints for overall prognosis, as these are major determinants of long-term outcome [5].

Table 2 Stages of Newly Diagnosed NMIBC and Probability of Recurrence in 5 Years by Stage

Non-Muscle Invasive Bladder Cancer Stage	Proportion of New NMIBC Cases	Probability of Recurrence in 5 years	
		Low Grade[a]	High Grade[a]
Ta	70% to 75%	50%	60%
T1	20% to 25%	50%	50% to 60%
Tis	5% to 10%	50% to 90%	

NMIBC = non muscle-invasive bladder cancer; Ta = noninvasive papillomas or carcinomas confined largely to the mucosa; T1 = tumors that invade the submucosa (lamina propria); Tis = noninvasive flat carcinoma, carcinoma in situ.

[a] WHO/ISUP 2004 criteria

Source: The National Comprehensive Cancer Network 2016 [4].

The AUA categorizes risk for recurrence and/or progression as 'low,' 'intermediate,' and 'high,' depending on tumor stage, size, and grade, as well as other factors (Table 3). Based on these categorizations, the **Ta, G1-G2 Target Population** in the pivotal studies conducted by Spectrum (see **Section 5.2**) included patients with low- or intermediate-risk disease.

Table 3 2016 AUA Risk 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 • 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

BCG=Bacillus Calmette–Guérin; CIS=carcinoma in situ; PUNLMP = papillary urothelial neoplasm of low malignant potential; Ta = noninvasive papillomas or carcinoma confined largely to the mucosa; T1 = tumors that invade the submucosa (lamina propria); Tis = noninvasive flat carcinoma, carcinoma in situ.
Source: Chang et al 2016 [5].

Because of the risk of tumor recurrence, patients with NMIBC require frequent follow-up and retreatment, resulting in significant morbidity and healthcare expense **[44]**. Similar to other cancer populations, due to frequent follow up and surgical procedures for diagnosis as well as treatment, reduced quality of life and changes in mental health (eg, depression and anxiety) may arise as patients learn to cope with their disease and treatment outcomes **[45]**.

3.2 Current Management of NMIBC

3.2.1 Treatment Guidelines

The latest guidelines for treatment of NMIBC were issued in 2016 by the NCCN **[4]** and the AUA **[5]**. These guidelines, along with European **[7-8]** and Canadian guidelines **[6]** for the treatment of NMIBC, recommend management of NMIBC depending on the stage and grade of disease or risk category **(Table 4)**. The fact that these organizations have slightly different definitions for risk categories and treatment algorithms demonstrates the natural development within this field.

Table 4 Summary of National and International Recommendations for Treatment of NMIBC

Organization (Date)	Recommendation	Level of Evidence
NCCN (2016) [4]	• Low-grade Ta tumors: TURBT with immediate intravesical therapy. MMC is the most commonly used drug. • High-grade Ta tumors: TURBT with immediate intravesical therapy. Adjuvant BCG at 3-4 weeks is preferred over MMC. • T1 tumors (most of which are high grade and have a higher risk of recurrence and progression): repeat TURBT with adjuvant intravesical therapy (BCG orMMC) at 3-4 weeks, or early cystectomy. • Tis: intravesical BCG once a week for 6 weeks.	Category 2A: Based on lower level evidence, there is uniform NCCN consensus that the intervention is appropriate
AUA (2016) [5]	• Low- or intermediate-risk bladder cancer: single postoperative instillation of intravesical chemotherapy (eg, MMC or epirubicin) within 24 hours of TURBT should be considered. • High-risk patient with newly diagnosed CIS, high-grade T1, or high-risk Ta urothelial carcinoma: 6-week induction course of BCG	Grade B, Moderate recommendation: Benefits > risks/burdens. Net benefit is moderate. Applies to most patients in most circumstances but better evidence could change confidence
EAU (2015) [8]	• Low- or intermediate-risk tumor: TURBT with single instillation of chemotherapy (if no perforation, no extensive resection, no bleeding with clots after TURBT) • Intermediate-risk tumors: immediate instillation of chemotherapy followed by 1-year BCG or chemotherapy • High-risk tumors: intravesical BCG for 1-3 years	Grade A
CUA (2015) [6]	• Low-risk tumors: TURBT with MMC, epirubicin, or doxorubicin within 6 hours (and up to 24 hours)	Grade B
ESMO (2014) [7]	• TURBT followed by immediate post-operative MMC • Intravesical instillations (MMC or BCG) according to risk group	Category 1A: Evidence from at least one large randomized, controlled trial of good methodological quality (low potential for bias) or meta-analysis of well-conducted randomized trials without heterogeneity Strong evidence for efficacy with a substantial clinical benefit, strongly recommended

AUA = American Urological Association; BCG = Bacillus Calmette–Guérin; CIS = carcinoma in situ; CUA = Canadian Urological Association; ESMO = European Society for Medical Oncology; EAU, European Association of Urology; MMC=mitomycin C; NCCN = National Comprehensive Cancer Network; T1 = tumors that invade the submucosa (lamina propria); Ta = noninvasive papillomas or carcinomas confined largely to the mucosa; Tis = carcinoma *in situ*; TURBT = transurethral resection of bladder tumor.

In general, there is consensus among the guidelines for treatment of NMIBC that show:

- Patients at low risk and some at intermediate risk may only need a single dose of perioperative intravesical chemotherapy to improve their risk of recurrence.
- Some patients at intermediate risk may benefit from further adjuvant intravesical chemotherapy to prevent recurrences.
- Patients at high risk have not shown a benefit with perioperative intravesical chemotherapy, and intravesical immunotherapy (BCG) is recommended for this patient population. BCG is given only after the bladder has healed from TURBT and has no place in the postoperative setting.

In 2015, the Agency for Healthcare Research and Quality (AHRQ) summarized efficacy data from studies comparing TURBT plus intravesical chemotherapy with TURBT alone, including studies using single, adjuvant, and maintenance therapy **[46]**. Overall, the AHRQ found moderate evidence for MMC to reduce tumor recurrence (relative risk 0.71; 95% CI: 0.57, 0.89; magnitude of heterogeneity [I^2]=72%), with no effect on tumor progression. Similar findings were noted for epirubicin (relative risk 0.63; 95% CI, 0.53, 0.75; I^2 = 64%).

BCG, which was approved in 1989 (Tice) and 1990 (TheraCys) for treatment of patients with CIS and high-grade papillary NMIBC, has remained the standard of care for these patients for nearly three decades **[29]**. BCG is not recommended for low-grade Ta tumors given the very low risk of disease progression **[47]** and risk of systemic adverse effects, especially during the first 2 weeks after TURBT, when the risk of systemic absorption is highest **[13]**. The AHRQ found a low level of evidence for BCG to decrease tumor recurrence (relative risk 0.56; 95% CI, 0.43, 0.71; I^2 = 0%) and progression (relative risk: 0.39; 95% CI, 0.24, 0.64; I^2=40%).

There were no clear differences in estimates of effectiveness of intravesical therapies in subgroups defined by tumor stage, grade, size, multiplicity, recurrence status, or DNA ploidy. None of the trials analyzed by the AHRQ evaluated how estimates of effectiveness of intravesical therapy vary in subgroups defined by patient characteristics, such as age, sex, race/ethnicity, performance status, and comorbidities. As described in **Section 5.2.2.3.5**, Spectrum conducted several subgroup analyses to determine which patients may benefit most from treatment with intravesical apaziquone.

3.2.2 TURBT

TURBT is the initial step in the diagnosis and treatment of low-grade Ta tumors. TURBT is an invasive procedure, conducted under general or regional anesthesia. Aside from the inherent surgical risks associated with the resection, which include infection, bleeding, perforation, and urethral injury, medical complications arising from anesthesia are also important considerations as most of these patients are elderly and are likely to have medical comorbidities **[4]**.

TURBT can have significant impact on a patient's HRQoL. For example, in a prospective study conducted in Danish patients undergoing TURBT for NMIBC, more than half of the 121 respondents had substantial voiding problems **(Table 5)**, which lasted from several days to 8 months after TURBT and with small to substantial impact on daily activities; one third of patients reported emotional concerns following TURBT **[48]**.

Table 5 Impact of TURBT for NMIBC on HRQoL

Symptom/Emotional Concern	Percentage of Respondents[a] with "Quite a Bit" or "Very Much" of Symptom/Emotional Concern
Symptom	
Pollakiuria	74
Nocturia	58
Urge	56
Dysuria	45
Sleep disturbances because of voiding problems	36
Difficulties in leaving their homes because of voiding problems	35
Incontinence	9
Emotional Concern	
Concerned about their health in the future	34
Concerned about the results from the operation	36
Concerned about treatments in the future	31
Concerned about the repeated treatments	29

HRQoL = health=related quality of life; NMIBC = non muscle-invasive bladder cancer; TURBT = transurethral resection of the prostate.
a) Percentage based on at total of 121 respondents
Source: Mogensen 2016 [48]

Cystoscopy, which is an invasive procedure and causes pain and discomfort in about one third of patients [49], is routinely used to follow patients after TURBT to monitor for recurrence and determine whether and when to repeat intervention is necessary. Even in patients who adapt and tolerate repeated TURBT procedures, report that their general HRQoL remains adversely affected [48, 50]. Indeed, among long-term elderly survivors of bladder cancer, patients with an intact bladder had an inferior HRQoL compared to patients who had their bladder removed because of cancer. This may be due to the repetitive invasive cystoscopies and TURBT procedures those with an intact bladder had to endure [51].

According to The American College of Surgeons National Surgical Quality Improvement Program (ACSNSQIP), the duration of the TURBT procedure can also have significant impact on the incidence of postoperative complications [52]. In the ACSNSQIP review of 10,599 TURBT procedures, the postoperative complication rate was 4.0% for TURBTs lasting 30 minutes or less, increasing to 11.3% for TURBTs lasting 90 minutes or more (OR: 2.5, 95% CI: 1.8, 3.5; $p < 0.001$), though these percentages probably do not capture minor complications such as postoperative retention and significant bleeds not requiring transfusion. Renal insufficiency, urinary tract infection, sepsis or septic shock, pulmonary embolism/deep-venous thrombosis, reintubation or failure to wean, myocardial infarction, and death were significantly more likely to occur with longer duration of procedure, irrespective of patient age, comorbidities, tumor size,

and functional status. The authors were unable to differentiate between initial and subsequent TURBT procedures in this analysis.

Delaying, or even preventing, the need for a repeat TURBT by reducing the risk of tumor recurrence and/or increasing the time to tumor recurrence could have a substantial impact on a patient's well-being. In this respect, it has been estimated that for every 100 patients treated with an intravesical chemotherapeutic agent after TURBT, 11.7 future TURBTs can be prevented **[24]**. There can also be considerable cost-saving in preventing recurrence and the need for repeat TURBT. Another study estimated that over a 2-year period, about 8,000 recurrences could be avoided if all patients received intravesical chemotherapy, resulting in an aggregate cost savings of $30 million **[30]**.

3.2.3 Intravesical Therapy Post TURBT

TURBT alone can eradicate low-grade Ta, but because of the high risk of recurrence **(Table 2)**, the NCCN recommends that strong consideration be given to the instillation of intravesical therapy within 24 hours of TURBT **[4]**, as reflected in current treatment guidelines **(Table 4)**. Instillation of intravesical therapy within this time frame following TURBT is important because there is a greater than two-fold higher relative risk of NMIBC recurrence for patients when chemotherapy is delayed to the day after TURBT **[53-54]**. Recent meta-analyses, however, have suggested that immediate intravesical therapy, within 2 hours after TURBT, improves efficacy **[28]**.

Evidence for the benefit of a single intravesical instillation of a chemotherapeutic agent given within 24 hours of TURBT has been derived from meta-analyses of individual clinical studies that have compared effects of TURBT alone (or with placebo) with those of a single instillation of chemotherapeutic agents given post-TURBT and incorporated into all treatment guidelines **[24, 27-28]**.

The first of these meta-analyses, which included seven randomized trials (N=1,476) assessed whether one intravesical instillation of chemotherapy (epirubicin in three trials, MMC in two trials, thiotepa in one trial, and pirarubicin in one trial) within 24 hours after TURBT decreased the risk of recurrence in patients with Stage Ta and T1 NMIBC **[24]**. After a median follow-up period of 3.4 years:

- 36.7% (267/728) of patients receiving one postoperative intravesical instillation of a chemotherapeutic agent experienced a recurrence
- 48.4% (362/748) of patients who received TURBT alone experienced a recurrence

Although the treatment effect varied due to size and rigor of study design between agents tested, as observed by a significant test of heterogeneity (X^2 14, df 6, $p = 0.03$), this represented a relative decrease of 39% in the risk of recurrence with chemotherapy (OR 0.61, 95% CI 0.49, 0.75; $p < 0.0001$). Among the chemotherapeutic agents, only thiotepa did not have a measurable benefit over TURBT alone.

A second meta-analysis, which included 13 studies (N=2,548) investigated whether postoperative intravesical chemotherapy prolonged recurrence-free interval **[27]**. Nine of the 13 studies used MMC (five studies) or epirubicin (four studies), with peplomycin, thiotepa, THP-doxorubicin, and gemcitabine used in the other four studies. Overall:

- A single intravesical instillation of the chemotherapeutic agent increased the recurrence-free interval by 38% (HR: 0.62; 95% CI, 0.50, 0.77; $p < 0.001$; [I^2]: 69%)
- The beneficial effect persisted regardless of tumor risk (lower or higher) and was not different for MMC or epirubicin.

A subgroup analysis examined whether using an intravesical instillation placebo (water or saline) had an impact on recurrence free interval over TURBT alone. When stratified by placebo use:

- Nine trials without placebo demonstrated a 44% reduction in recurrence-free interval (HR: 0.56; 95% CI, 0.41–0.76; $p < 0.001$; I^2: 75%)
- Four trials that used placebo demonstrated a 25% reduction in recurrence-free interval (HR: 0.75; 95% CI, 0.61–0.91; $p = 0.004$; I^2: 4%).

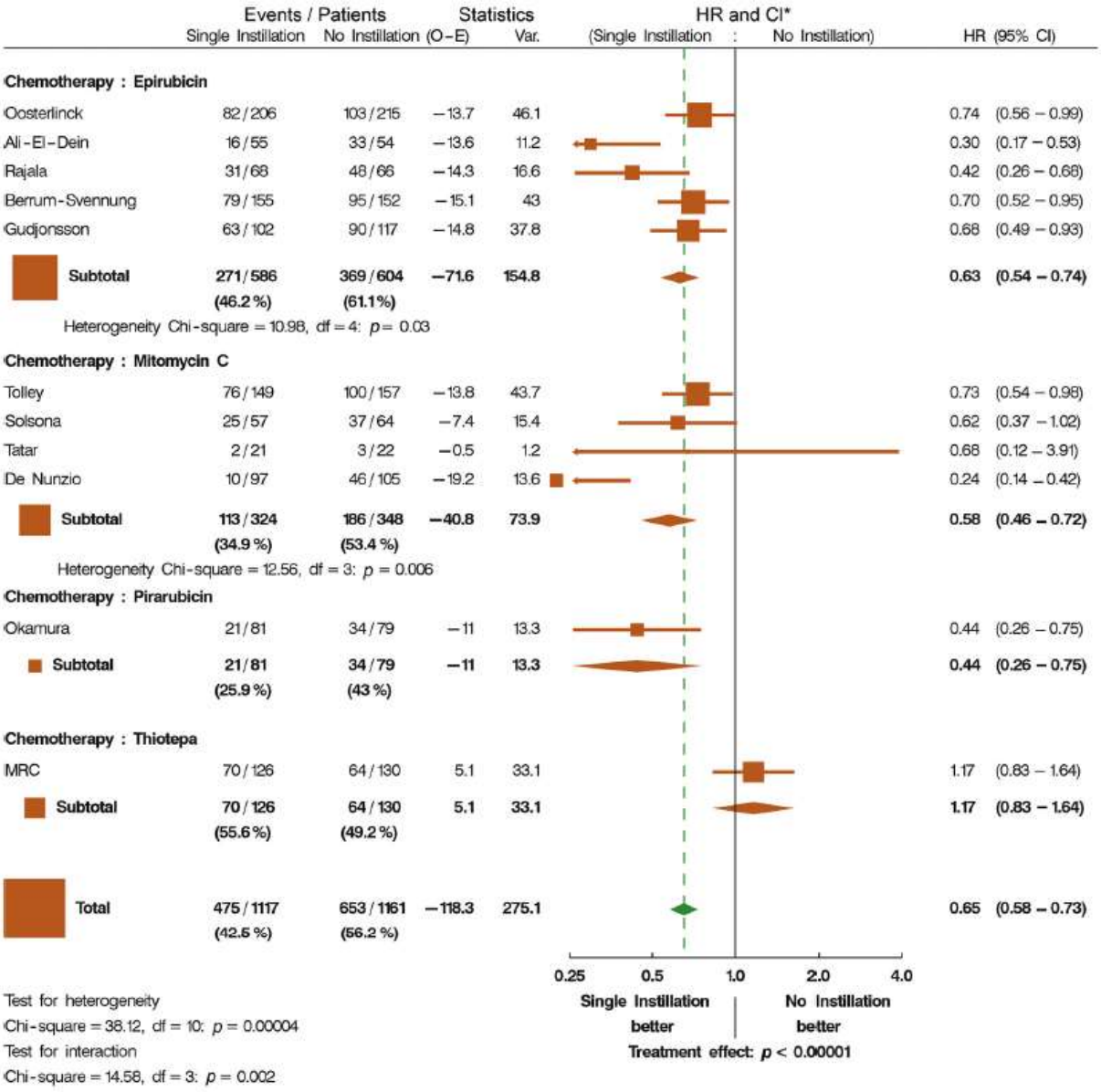
Thus, placebo instillation increased the **Time to Recurrence** over TURBT alone. Whatever the mechanism for this placebo effect (eg, mechanical lavage of circulating tumor cells, tumor cell lysis, or simply a reflection of better quality studies), this is an important finding considering that the pivotal studies of apaziquone included a matching placebo as the control arm, and thus smaller differences between apaziquone and placebo may be expected than if apaziquone had been compared to TURBT alone (ie, without placebo) (see **Section 5.2**).

In the most recent meta-analysis, Sylvester et al (2016) **[28]** included a total of 13 eligible studies, and individual patient data were presented for 11 of the studies randomizing 2278 eligible patients (1161 to TURBT and 1117 to a single instillation of epirubicin, MMC, pirarubicin, or thiotepa after TURBT). Overall, the meta-analysis showed that:

- A total of 1128 (49.5%) of the patients experienced a recurrence, including:
  - 475 (42.5%) who received a single instillation of chemotherapeutic after TURBT
  - 653 (56.2%) who received TURBT (alone or with placebo).
- The 5-year recurrence rates were 44.8% (95% CI, 41.6, 48.0) and 58.8% (95% CI, 55.7, 61.9), respectively.
- The difference in time to first recurrence between treatments was statistically significant in favor of immediate instillation of the chemotherapeutic agent, with a reduction of 35% in the relative risk of recurrence (HR: 0.65; 95% CI, 0.58, 0.74; $p < 0.001$).

Forest plots of time to first recurrence, stratified by chemotherapy and study, are shown in **Figure 7**.

Figure 7 Forest Plot of Time to First Recurrence after Single Intravesical Instillation of Chemotherapy with TURBT versus TURBT (Alone or with Placebo)



TURBT = transurethral resection of bladder tumor.

Source: Sylvester et al 2016 [28]

The studies included in the above meta-analysis as shown in **Figure 7** included a wide range of drugs, study designs, sample sizes, and control treatment groups, as well as other study design characteristics. Based on the significant heterogeneity ($p \leq 0.03$), the treatment effect observed varied between intravesical treatments and between studies of different sample size. The treatment effect observed were also impacted by the size and rigor of the study design. Therefore, the true magnitude of treatment effect of immediate instillation of intravesical therapy post-TURBT over TURBT alone was not well understood.

3.3 Challenges with Current Treatment Options for NMIBC

3.3.1 Toxicity

There are no drugs currently specifically approved for intravesical instillation post-TURBT in patients with low- to intermediate-risk NMIBC. Neither MMC nor epirubicin, which are recommended by the NCCN and AUA for low-grade Ta/low-intermediate risk NMIBC have an approved indication, and BCG is specifically contraindicated in this setting.

Safety analyses conducted by the AHRQ **[46]** provide limited data with respect to the safety of TURBT plus intravesical MMC and epirubicin when compared with TURBT alone **[46]**. The AHRQ noted the following:

- One trial (n=121) found no difference between TURBT plus a single instillation of MMC versus TURBT in the risk of chemical cystitis (3.5% vs. 1.6%).
- A single instillation of MMC was associated with a lower risk of local AEs than multiple instillations.
- A single instillation of epirubicin 80 mg (up to four repeat instillations for recurrence) was associated with an increased risk of chemical cystitis versus placebo (12% vs. 1.9%; relative risk 6.29, 95% CI 2.22 to 17.8).
- A single instillation of epirubicin 100 mg versus no intravesical therapy was associated with differences in risk of dysuria (5.9% vs. 0%; relative risk 8.74, 95% CI 0.48 to 159) and fever (0% vs. 0.9%; relative risk 0.32, 95% CI 0.01 to 7.80), but the differences were not statistically significant.

The safety of intravesical instillation of MMC was studied in the perioperative setting to TURBT in a retrospective study of 116 control-matched cases **[55]**. Compared to controls, patients receiving MMC were younger ($p = 0.04$) and more likely to have invasive disease (ie, T1 or greater) (23% vs. 15%, $p = 0.02$). Complications were more frequent among patients who were treated with MMC (34.5% vs. 19.8%, OR 2.89, 95% CI 1.43, 5.81). The most common complication among MMC patients that required medical management was dysuria (17%). Major complications, including dysuria, chemical cystitis, and gross hematuria, were more common among MMC patients (5.2% vs. 0.9%).

Others **[13-14]** have reported that, in clinical trials, the most common AE associated with MMC instillation is chemical cystitis (in up to 41% of patients), which manifests as dysuria, frequency, urgency, suprapubic pain, and discomfort. Decreased bladder capacity (in up to 22% of patients) has also been reported, as have eczema-like cutaneous reactions (4% to 12%). Cystectomy due to severe bladder contracture and myelosuppression from systemic absorption have occurred in rare cases. Major surgical intervention can be required to resolve symptoms resulting from extravasation of MMC **(Figure 8)** in patients with unrecognized bladder perforation following TURBT **[15-18]** as a result of chemical peritonitis. One report described extravasation of MMC after it was instilled in six patients with unrecognized bladder perforation following TURBT **[15]**. The effects of extravasation included pelvic pain refractory to simple analgesia, urinary retention, severe lower urinary tract symptoms, recurrent urinary tract infections, and in one patient, development of a fibrotic pelvic mass. Three of the six patients required major surgical intervention.

Figure 8 Cystectomy after MMC

Macroscopic image of the cystectomy piece from a 77-year old man who experienced bladder perforation after TURBT with subsequent extravasation of MMC. The perforation with necrotic borders can be observed.

Source: Panach-Navarrete 2015 [17]

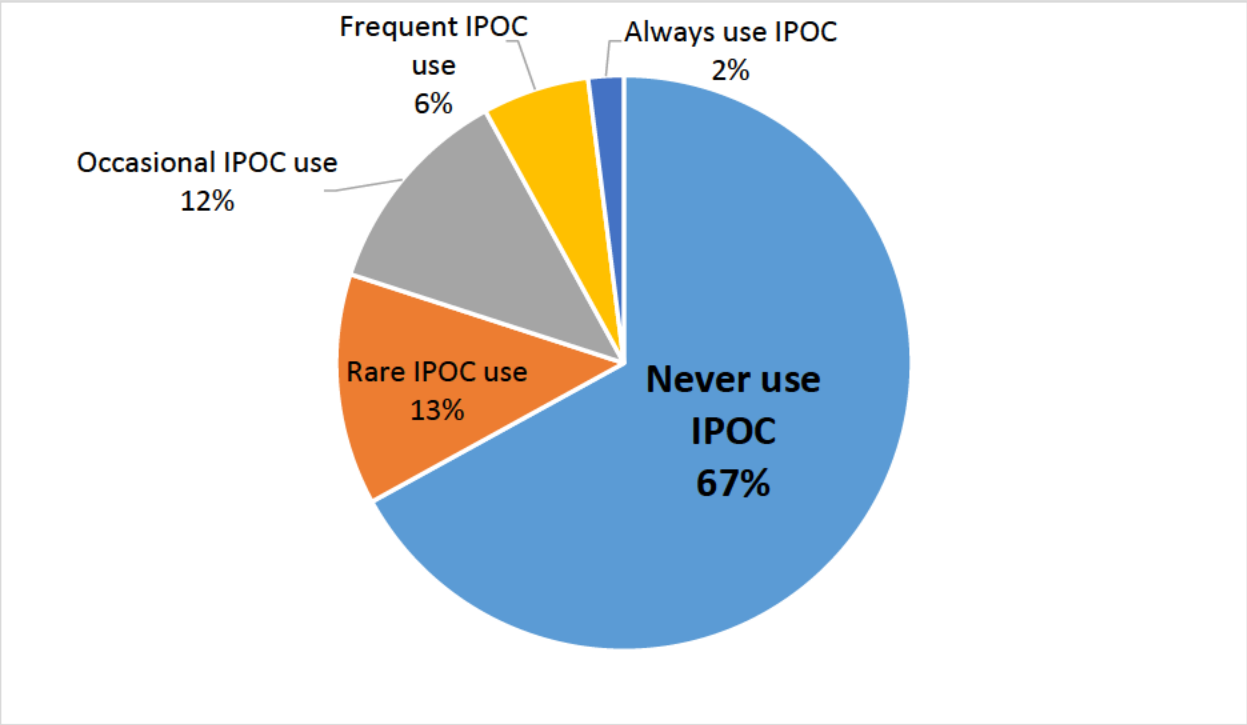
The effects of epirubicin are similar to those of MMC, with local toxicity, including cystitis, dysuria, and increased urinary frequency and urgency **[13]**. As noted by the NCCN **[4]** and others **[29]**, local and systemic side effects of BCG can range from mild fever, hematuria, hepatitis, cystitis, and tuberculosis to life-threatening BCG sepsis **[13]**. In safety analyses conducted by the AHRQ, side effects of BCG included granulomatous cystitis or irritative symptoms (27% to 84% of patients), macroscopic hematuria (21% to 72%), and fever (27% to 44%).

Although BCG is recognized as an effective intravesical treatment for NMIBC and is recommended as a first-line treatment in high-grade/high-risk NMIBC and CIS, because of its considerable side effects and the risk of systemic absorption, it is contraindicated in the post-operative setting and only administered as adjuvant intravesical chemotherapy to prevent recurrences.

3.3.2 Underutilization

Despite the evidence that intravesical instillation of a chemotherapeutic agent post-TURBT reduces recurrences and the consensus recommendations made by the NCCN and AUA, many practitioners do not regularly utilize this intervention to treat their patients with NMIBC. One study of claims data from 1997 to 2004 reported on 16,748 patients with newly diagnosed bladder cancer, found that 14,677 (88%) patients underwent cystoscopic biopsy or TURBT and of these only 49 (0.33%) patients received same-day intravesical instillation of chemotherapy **[11]**. In a survey of US urologists, 67% stated they never use intravesical therapy post-TURBT, and only 2% routinely used intravesical therapy post-TURBT **(Figure 9) [12]**.

Figure 9 Use of Intravesical Instillation of Chemotherapy with TURBT by US Urologists



IPOC = intravesical postoperative chemotherapy; TURBT = transurethral resection of bladder tumor; US = United States.
Source: Cookson et al 2012 [12].

The most commonly cited reasons for the lack of compliance with the recommendations to administer intravesical therapy post-TURBT amongst US urologists were cost, challenge of administering chemotherapy in the operating or recovery room, possibility of serious side effects with current treatments, and the belief that decreasing small superficial bladder cancer recurrences is not clinically important **[12]**. Others have cited a reluctance to give chemotherapy until histological confirmation of pathology, as well as uncertainty of tumor invasiveness, pharmacy logistical issues, suspected or possible bladder perforation, toxicity, lack of evidence of efficacy, and lack of an FDA approved product in the indication **[56]**.

In addition, it was found that urologist perception of recurrence risk did not always match guidelines (eg concomitant CIS was assigned a lower risk of recurrence than multifocality, grade or T stage) **[12]**, suggesting that educational efforts are needed in this area. Notably, the rate of IPOC use was higher in patients treated by physicians with fellowship training in urological oncology (31.2% vs 13.8%, $p<0.02$) **[12]**.

3.4 The Unmet Medical Need in Bladder Cancer

Given the current challenges in the management of NMIBC, including rising incidence, especially among the elderly, high recurrence rates, and concerns regarding global supplies of current therapies, new approved therapies for the indication are urgently needed **[29, 57]**. This is especially true for low-grade Ta/low-risk NMIBC, which appears to be increasing in prevalence (from 5.52 per 100,000 population in 1998 to 9.09 per 100,000 population in 2006; $p < 0.0001$) **[58]**.

Currently, all drugs administered by intravesical instillation in the immediate post-TURBT setting, including MMC and epirubicin, are used off label, and given the limited efficacy and the potential for moderate to severe toxicity appear to contribute to the reluctance of physicians to adopt using these drugs in the immediate post-operative setting. Despite the obvious need for new, and better studied, therapies, the Bladder Cancer Task Force and the NCI recently acknowledged the lack of trials in the NMIBC space within the National Clinical Trials Network (NCTN) **[29]**. The reason for this is many fold, including lack of consensus on trial endpoints and appropriate control arms. In addition, there is a lack of recommendations on appropriate clinical trial designs founded on evidence-based literature, current clinical practice guidelines, and expert consensus, which may change during the conduct of a long-term trial. There has also been a call to establish realistic efficacy thresholds to ensure that new and novel therapies receive realistic review by regulatory bodies. For example, in patients with low-risk NMIBC, an absolute reduction of 6% in the percent of patients with recurrence at 2 years has been proposed as a reasonable treatment effect for a clinical trial to be considered 'positive' **[29]**.

To help meet the acknowledged large unmet medical need for the treatment of low-grade Ta/low-risk NMIBC, Spectrum has conducted a development program for apaziquone, specifically to assess its safety and efficacy as an intravesical instillation post-TURBT in patients with NMIBC. This development program, described in **Section 4**, has shown that apaziquone provides clinically relevant efficacy on tumor recurrence and recurrence rates in patients with Ta, G1-G2 NMIBC. Apaziquone, by providing clinically meaningful reductions in tumor recurrence (as measured by **2-Year Recurrence Rate**) and increases in **Time to Recurrence** (see **Section 5)** has demonstrated the clinical efficacy and benefit of single intravesical instillation post-TURBT. Furthermore, the safety profile of apaziquone is favorable, intravesical administration does not lead to systemic absorption, and it is well tolerated (see **Section 6**). Thus apaziquone has the potential to increase utilization of this treatment modality, improve compliance with guideline recommendations, reduce the need for repeat TURBT, reduce costs, and lead to increased patient well-being and improved health related QoL.

4 OVERVIEW OF CLINICAL PROGRAM

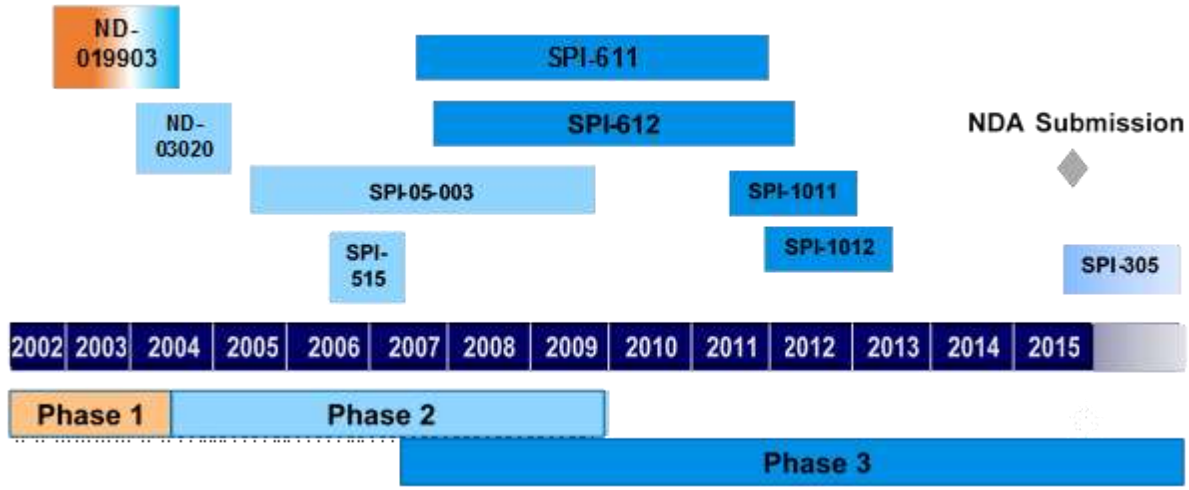
4.1 Clinical Development History

Apaziquone was first synthesized in 1987 and the initial preclinical and clinical development was performed by the New Drug Development Office of the EORTC. In the early clinical program conducted in the 1990s, which included four Investigator-initiated studies (two Phase 1 and two Phase 2), apaziquone was given by IV administration to patients with various types of cancer, but showed no significant antitumor activity **[59-60]**; this was demonstrated to be attributed to its short plasma half-life and inactivation in blood.

Intravesical administration of apaziquone circumvents drawbacks of the short half-life of apaziquone after IV administration and its rapid metabolism in the blood. Given the inactivation of apaziquone in blood after IV administration, Spectrum initiated its own clinical development program for intravesical administration of apaziquone in 2002. Spectrum's clinical program focused on the potential of apaziquone as a treatment option to reduce recurrence rates and prolong the **Time to Recurrence** in patients with NMIBC.

The overall clinical development program for intravesical instillation of apaziquone post-TURBT in the treatment of NMIBC comprised eight studies (Phase 1 through Phase 3) spanning an approximate 10-year period, with one additional Phase 3 study currently ongoing (**Figure 10**).

Figure 10 Development History for Apaziquone



ND-019903: Phase 1/2 dose-escalation and marker lesion study

ND-03020: Phase 2 marker lesion study

SPI-05-003: Phase 2 study in high-risk patients

SPI-515: Phase 2 safety study

SPI-611 and **SPI-612**: Pivotal Phase 3 single intravesical instillation studies

SPI-1011 and **SPI-1012**: Phase 3 single and multiple intravesical instillation studies (terminated early due to business reasons unrelated to safety or any other study aspects)

SPI-EOQ-13-305: Phase 3 single and multiple intravesical instillation study initiated in September 2015 and currently recruiting patients. It is expected to be completed in 5 to 6 years

4.2 Regulatory History

As shown in **Table 6**, key milestone interactions with the FDA included:

- Special Protocol Agreement with FDA on the design and planned analyses of the pivotal Phase 3 study (**SPI-611**) (28 Aug 2007); **SPI-612** was a nearly identically designed Phase 3 study
- Fast-track Designation granted for the investigation of apaziquone in NMIBC to prolong the time to disease recurrence (10 Jul 2009)
- Pre-NDA Meeting with FDA to discuss **SPI-611** and **SPI-612** study results, and FDA recommendation to start an additional Phase 3 study (11 Dec 2012)
- Special Protocol Agreement on a new Phase 3 apaziquone study in patients with NMIBC, **SPI-EOQ-13-305** (13 Aug 2015)
- NDA submitted to the FDA (11 Dec 2015)
- Participated in the NDA Orientation Meeting (05 Feb 2016)
- Responses to FDA Information Requests re: NDA Review (January 2016 – Present)
- Co-hosted the FDA Pre-approval Inspection (11 May 2016 to 17 May 2016)
- Hosted the NDA Mid-Cycle Communication Teleconference with the FDA (18 May 2016)
- Late cycle review meeting scheduled (1 September 2016)
- ODAC meeting scheduled (14 September 2016)

Table 6 Key Milestone Interactions with FDA for the Apaziquone Development Program

Date	Interactions with FDA
19 Jan 2006	**Pre-IND Meeting** Held with FDA – The Agency specified that a pilot study of immediate administration after TURBT (**SPI-515**) would need to be performed prior to initiating the Phase 3 study
13 Mar 2006	**IND 073572 submitted** for apaziquone
13 April 2006	FDA determined that the **SPI-515** study is safe to proceed from a chemistry and pharmacology/toxicology standpoint
15 May 2006	Updated **SPI-515** protocol submitted to the Agency
10 Jan 2007	**SPA Request** submitted for **SPI-611**
5 Feb 2007	**Special Protocol Assessment (SPA) Type A face-to-face Meeting** to discuss the design and analysis of **SPI-611** for registration of apaziquone as a surgical adjuvant instilled in the early postoperative period in patients undergoing TURBT for NMIBC
28 Aug 2007	FDA agreed that the design and planned analysis of **SPI-611** adequately address the objectives necessary to support a regulatory application; **SPI-612** was a nearly identically designed Phase 3 study [submitted 11 Jun 2007]
10 Jul 2009	FDA granted **Fast Track Designation** for NMIBC to prolong the time to disease recurrence
11 Dec 2012	**Type B pre-NDA Meeting** to discuss planned NDA submission for apaziquone for use as a single intravesical instillation post-TURBT to reduce the risk of recurrence
18 Apr 2013	**SPA Request** submitted for **SPI-EOQ-13-305** [eCTD sequence 0128]
May 2013 – Jul 2015	SPA Negotiations

Date	Interactions with FDA
13 Aug 2015	FDA agreed that the design and planned analysis of **SPI-EOQ-13-305** adequately addresses the objectives necessary to support a regulatory application
11 Dec 2015	NDA submitted to the FDA
January 2016 – Present	Responses to FDA Information Requests re: NDA Review
11 May 2016 to 17 May 2016	Co-hosted the FDA Pre-approval Inspection
18 May 2016	Hosted the NDA Mid-Cycle Communication Teleconference with the FDA.
1 September 2016	Late cycle review meeting scheduled
14 September 2016	ODAC meeting scheduled

eCTD = electronic common technical document; FDA = Food and Drug Administration; IND = Investigational New Drug; NDA = New Drug Application; NMIBC = non muscle-invasive bladder cancer; ODAC = Oncologic Drugs Advisory Committee; SPA = Special Protocol Assessment.

In the pre-NDA meeting in 2012, the FDA recommended conducting an additional study before submitting the NDA. While the FDA did not recommend submitting the NDA at that time, the FDA stated that if it were submitted the NDA would be filed and discussed before ODAC. Because of several factors, including the nature of the FDA feedback and competing business priorities, Spectrum did not immediately file an NDA after the 2012 meeting. However, several considerations led Spectrum to reconsider filing the NDA based on the results of **SPI-611** and **SPI-612**. Spectrum received strong support and advice from expert urology consultants who considered the results to be compelling and clinically meaningful. In addition, the evolving literature on NMIBC, and updated risk stratification and treatment guidelines for NMIBC, also suggested that the effects of apaziquone demonstrated in the pivotal studies were clinically meaningful, especially in view of its lack of significant toxicity. Spectrum also recognized that the studies were underpowered to detect with statistical significance a reasonable magnitude of effect of apaziquone compared to placebo. This is further discussed in **Section 5.2.1.4**. Spectrum believes that the results of additional evaluations, along with the remarkable consistency of results between **SPI-611** and **SPI-612**, show that apaziquone has both clinically meaningful efficacy (detailed in **Section 5**) and excellent safety profile (detailed in **Section 6**), resulting in a positive benefit-risk profile (detailed in **Section 7**). Consequently, Spectrum submitted the NDA in December 2015.

4.3 Development Milestones

4.3.1 Dose Selection for Phase 3 Studies

The intended clinical dose of apaziquone (4 mg in 40 mL) was determined in a Phase 1/2 dose-escalation study (**ND-019903** [n=12]). Over a 6-week period, six patients received intravesical apaziquone, starting at a dose of 0.5 mg/40 mL and escalating to 16 mg/40 mL or until a dose-limiting toxicity (DLT) was observed. Pharmacokinetic sampling was also performed in this study.

The study showed:

- The most frequent DLT was dysuria, which was observed in three patients at 8 mg/40 mL and two patients at 16 mg/40 mL.
- Hematuria was observed in one patient at 8 mg/40 mL and two patients at 16 mg/40 mL.
- None of the patients treated with 4 mg/40 mL apaziquone experienced dysuria or hematuria.

To confirm the finding that the MTD for apaziquone was 4 mg in 40 mL of diluent, this dose was administered to six additional patients weekly for 6 weeks. The 4 mg in 40 mL dose was safe and well tolerated; no patients experienced dysuria or hematuria, or any other DLTs at this dose. Importantly, apaziquone could not be detected in the plasma of patients given apaziquone at doses up to 16 mg in 40 mL, ie, four times the intended clinical dose of 4 mg in 40 mL diluent.

4.3.2 Proof of Mechanism: Marker Lesion Studies

The primary proof of anti-tumor efficacy for apaziquone came from the Phase 2 component of **ND-019903** as well as a second marker lesion study (**ND-03020**). Marker lesion studies involve removing all but one bladder tumor (the marker lesion), administering treatment, and evaluating the effect of treatment on the marker lesion at 12 weeks. Marker lesion studies are designed to provide direct evidence of the antitumor activity of an intravesical agent in NMIBC.

The two studies, conducted in Europe (the United Kingdom and the Netherlands), were the earliest clinical studies of intravesical apaziquone in NMIBC:

- **ND-019903**, a Phase 1/2 intrapatient dose-escalation (0.5 to 16 mg in 40 mL) and marker lesion study of apaziquone (4 mg in 40 mL) (n=12)
- **ND-03020**, a Phase 2 marker lesion study of apaziquone (4 mg in 40 mL) (n=46)

The studies included patients with primary or recurrent Stage Ta-T1, G1-G2 NMIBC. Patients with NMIBC underwent TURBT, during which all but one bladder tumor was removed. Apaziquone (4 mg in 40 mL) was then administered once a week for 6 weeks, starting 2 to 4 weeks after TURBT and the effects on the marker lesion evaluated 2 weeks after the final instillation of apaziquone.

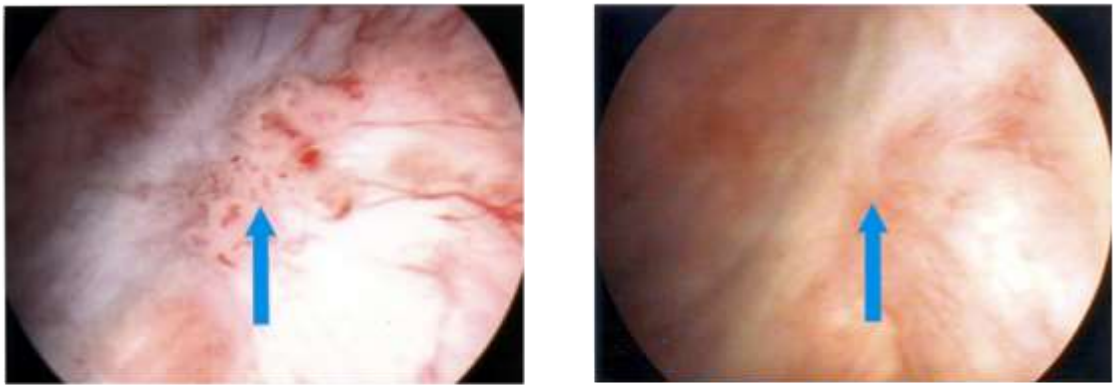
Apaziquone demonstrated clear anti-tumor activity in each study. Overall, 8 of 12 (67%) patients in **ND-019903** and 31 of 46 (67%) in **ND-03020** exhibited a complete response (disappearance) of the marker lesion **[19-20]**. This is illustrated in **Figure 11**, which shows the same region of the bladder before and after treatment with apaziquone. The remaining patients in these studies, at the follow up cystoscopy, had persistence of the marker lesion tumor that was stable and progression was not reported. The results for apaziquone, which showed that 67% of patients in each study had complete response, compared favorably to published data indicating 26% to 46% of patients achieved complete response with other agents used for intravesical administration in similarly designed clinical studies **[21-23]**. Other key findings obtained from the marker lesion studies included the following:

- The dose of 4 mg in 40 mL (0.1 mg/mL) was well tolerated in both studies.
- At the 12-month follow-up, only one patient had a recurrence (**ND-019903**).
- No patients progressed in either study.

Figure 11 Complete Cystoscopic Response after Intravesical Apaziquone (ND-03020)

Response	N (%)	95% CI
Complete Response	31 (67)	51 to 80
NR (Stable marker lesion)	15 (33)	20 to 49

No patient had progressive disease



Before Apaziquone Treatment

After Apaziquone Treatment
(Complete Response)

Van der Heijden, et al. 2006.

NR=no response (ie, stable marker lesion)

Source: Van der Heijden et al (2006) [20]

4.3.3 Pilot Safety Study of Intravesical Instillation of Apaziquone within 6 hours of TURBT

Following the positive results of the two marker lesion studies and the publication of the first meta-analysis showing that a single intravesical instillation of a chemotherapeutic given in the immediate post-TURBT period could significantly reduce tumor recurrence **[24]**, Spectrum planned two Phase 3 studies (**SPI-611** and **SPI-612**) to assess the safety and efficacy of a single intravesical instillation of apaziquone retained within the bladder for 1 hour when given in the immediate post-TURBT period (ie, within 6 hours). Before initiating the Phase 3 studies, at the request of the FDA **(Table 6)**, an open-label pilot safety study was conducted:

- **SPI-515** assessed the safety, tolerability, and pharmacokinetics of a single intravesical instillation of apaziquone at the intended clinical dose (4 mg in 40 mL) administered within 6 hours of TURBT in patients with Stage Ta or T1, G1 or G2 NMIBC (n=20)

Key findings from **SPI-515** were that:

- Apaziquone could not be detected in the plasma of patients given apaziquone at the intended clinical dose.
- Intravesical instillation of apaziquone within 6 hours after TURBT was well tolerated with a relatively benign safety profile in patients with NMIBC. The most frequently reported AEs were dysuria (7 patients, 35%), abdominal pain lower (5 patients, 25%),

hematuria (3 patients, 15%), and urinary retention and urinary tract infection (2 patients each, 10%).

- The bladder mucosa showed re-epithelialization without evidence of impaired wound healing or ulceration at the 12-week follow-up cystoscopy.

Given the positive safety findings for apaziquone in **SPI-515**, Spectrum proceeded to conduct the two pivotal Phase 3 studies of apaziquone (**SPI-611** and **SPI-612**).

4.3.4 Pivotal Phase 3 Studies (SPI-611 and SPI-612)

The two pivotal Phase 3 studies (**SPI-611** and **SPI-612**) enrolled a total of 1614 patients with or clinically diagnosed low risk NMIBC. This is the largest study ever conducted to assess the safety and efficacy of intravesical instillation in the immediate post-TURBT period.

SPI-611 and **SPI-612** were of nearly identical design. The major differences between the studies were 1) the number of tumors in eligible patients was increased from ≤4 tumors in **SPI-611** to ≤5 tumors in **SPI-612**, and 2) functional bladder capacity was assessed in a subgroup of patients in **SPI-611** but not in **SPI-612**.

Both studies were multinational, randomized, placebo-controlled, double blinded studies that randomized patients to receive either a single 1-hour intravesical instillation of apaziquone (4 mg in 40 mL) or matching placebo (40 mL) within 6 hours post-TURBT and utilized central pathology review:

- **SPI-611** randomized 802 patients and was conducted between 25 Apr 2007 and 19 Jan 2012 at 72 sites in the US and 7 sites in Poland.
- **SPI-612** randomized 812 patients and was conducted between 28 Aug 2007 and 25 Jan 2012 at 23 sites in the US, 30 sites in Canada, and 20 sites in Poland.

The design features, demographic and baseline characteristics, and efficacy results from the studies are described in **Section 5.2**. Safety results are described in **Section 6.2**.

4.3.5 Supportive Phase 3 Studies (SPI-1011 and SPI-1012)

Prior to completion of the pivotal studies, **SPI-611** and **SPI-612**, Spectrum initiated **SPI-1011** (in September 2011), followed by **SPI-1012** (in January 2012). The studies were identically designed Phase 3 studies that included an open-label, single-instillation phase followed by a subsequent randomized, placebo-controlled, double-blind phase, to assess the safety and efficacy of single and multiple instillations of apaziquone (4 mg in 40 mL) in patients with primary or recurrent NMIBC.

Based on internal business decisions not related to safety or any other study related issues, **SPI-1011** was terminated in March 2013 and **SPI-1012** was terminated in April 2013. At the time of study termination, 66 patients were enrolled in **SPI-1011**, and 47 patients in **SPI-1012**. These patients comprised the Safety Population for these studies. Of the enrolled patients, a total of 28 patients in **SPI-1011** and 31 patients in **SPI-1012** with confirmed Stage Ta histology had received a single instillation of apaziquone and continued in the randomized double-blind phase to receive up to six weekly instillations of either apaziquone (**Multiple-Instillation Group**) or placebo (**Single-Instillation Group**). These patients comprised the Randomized Population for these studies.

4.3.6 Study SPI-EOQ-13-305

Following discussions with the FDA, Spectrum is enrolling another large-scale Phase 3 study (**SPI-EOQ-13-305**) designed to assess and confirm the clinical benefit of apaziquone intravesical instillation, based on the reported results of **SPI-611** and **SPI-612** to guide the study design. The study is currently recruiting patients but is not expected to be completed until 2021 (NCT02563561).

SPI-EOQ-13-305 is a Phase 3, randomized, multicenter, multi-arm, placebo-controlled, double-blind study of apaziquone in patients with NMIBC who receive TURBT. The planned enrollment is 1869 patients (623 per treatment group). This sample size is estimated to provide 519 evaluable patients per treatment group to achieve 80% power to detect superiority. The entry criteria for **SPI-EOQ-13-305** include patients with NMIBC aged 18 years and older with ≤4 Ta, G1-G2 tumors, ≤3.5 cm in diameter, all of which must have been fully resected at TURBT. Patients in **SPI-EOQ-13-305** will not be eligible for study participation if they have received any prior intravesical chemotherapy, immunotherapy, or had previous exposure to apaziquone.

SPI-EOQ-13-305 will assess the safety and efficacy of a single instillation and multiple instillations of apaziquone (or placebo) post-TURBT. Based on the results of **SPI-611** and **SPI-612** apaziquone (or placebo) will be given at 60±30 minutes post-TURBT, instead of the 6-hour window that was allowed in **SPI-611** and **SPI-612**. **SPI-EOQ-13-305** was therefore designed as a 3-arm study:

- Arm 1: the initial apaziquone instillation will be followed by a second instillation of apaziquone 2 weeks later.
- Arm 2: the initial apaziquone instillation will be followed by an instillation of placebo 2 weeks later.
- Arm 3: the initial placebo instillation will be followed by a second instillation of placebo 2 weeks later.

The primary outcome measure of the study is to evaluate the **Time to Recurrence** with either one instillation of 4 mg apaziquone or two instillations of 4 mg apaziquone separated by 2 weeks relative to placebo instillation following TURBT. Secondary outcome measures are to evaluate the 1-Year Recurrence Rate, **2-Year Recurrence Rate**, Time to Progression, and AEs.

4.4 Summary

Spectrum has conducted a robust and well-designed clinical development program for apaziquone, including two large, randomized, placebo-controlled, Phase 3 studies (**SPI-611** and **SPI-612**). These two Phase 3 studies together comprise the largest clinical studies completed in the setting of intravesical chemotherapeutic agents for the treatment of NMIBC. Spectrum has initiated enrollment in another large Phase 3 study designed to confirm the reproducibility and further assess the clinical benefit of apaziquone in this setting. To delay submission of the apaziquone NDA until **SPI-EOQ-13-305** study has been completed would delay the approval of apaziquone for at least 5 years or more and potentially deprive thousands of patients of a safe and effective therapy for NMIBC. Without an approved agent in this indication, these patients will either continue to be exposed to the off-label use of agents with less favorable safety and

tolerability profiles or denied access to the recognized beneficial impact of post-TURBT intravesical therapy that provides an incremental efficacy over TURBT on recurrence rates.

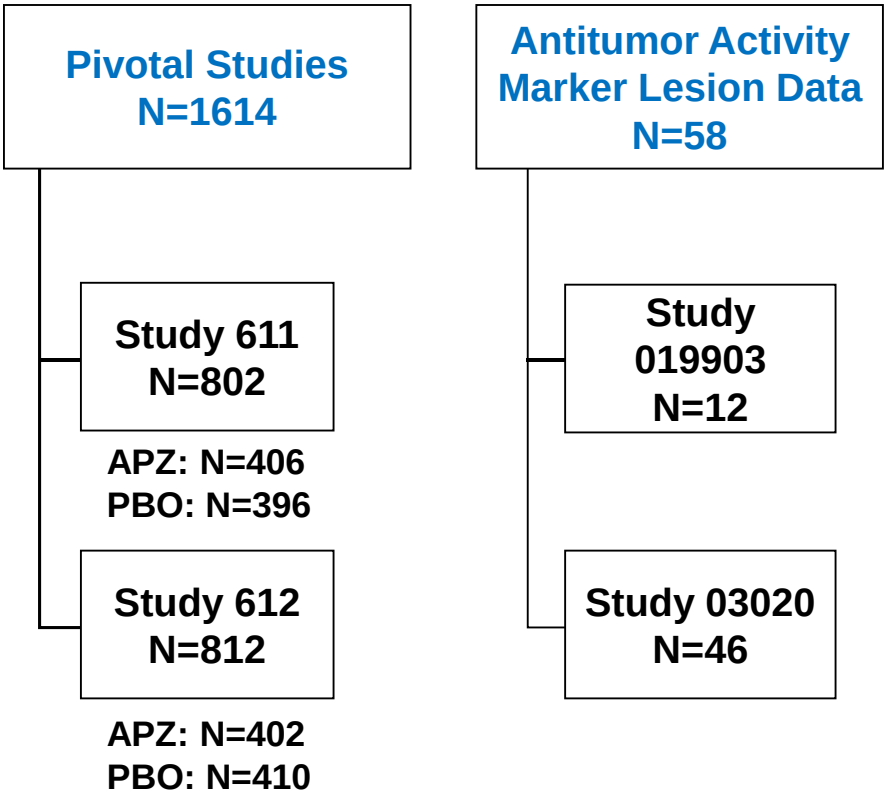
Spectrum believes that the current pending NDA provides positive data from Phase 1 through Phase 3 studies that support the safe and effective use of apaziquone for NMIBC as an adjunct to TURBT. An approved product would provide patients with a product with an excellent safety profile compared to the current unapproved products.

5 CLINICAL EFFICACY RESULTS

5.1 Overview of Studies

The clinical efficacy of apaziquone was evaluated using data from 1672 patients, including 866 patients treated with apaziquone, who participated in four Sponsor-conducted clinical studies. The initial demonstration of efficacy and antitumor activity was provided by one Phase 1/2 study and one Phase 2 marker-lesion study (**ND-019903** and **ND-03020**, respectively), which are discussed in **Section 4.3.2**. The majority of efficacy data are from two pivotal clinical studies, **SPI-611** and **SPI-612**, which compared the efficacy of a single intravesical instillation of apaziquone (n=808) with placebo (n=806) in the post-TURBT setting on tumor recurrence rates at 2 years. These studies are discussed in **Section 5.2**.

Figure 12 Studies Assessing the Clinical Efficacy of Apaziquone



5.2 Single-Dose Pivotal Phase 3 Studies (SPI-611 and SPI-612)

SPI-611 and **SPI-612** were Phase 3, randomized, double-blind, placebo-controlled, single-instillation studies. Synopses for **SPI-611** and **SPI-612**, which provide additional study details, are located in **Appendix 1** and **Appendix 2**, respectively.

5.2.1 Study Methodology

5.2.1.1 Patient Eligibility Criteria

The two studies had nearly identical patient inclusion criteria, with the main entry criteria being age ≥18 years and a diagnosis of transitional cell carcinoma of the bladder with clinically

apparent low-intermediate risk NMIBC, Stage Ta, G1-G2 and ≤4 tumors (**SPI-611**) or ≤5 tumors (**SPI-612**) tumors that were ≤3.5 cm in diameter each. Note that while patients were enrolled into the study based on visual diagnosis and assessment at cystoscopy, the target population for the primary efficacy analysis was determined by histological confirmation of Stage Ta, G1-G2 from the central pathology laboratory. Thus, patients with higher stage disease (T1, Tis) were also enrolled and received study drug, but were not included in the efficacy analyses for the prespecified **Ta, G1-G2 Target Population**; they were, however, included in the ITT analyses. In both studies, bladder cancer could have been primary or recurrent and patients may have received prior intravesical therapy with MMC or BCG.

The only other difference between the two studies was that functional bladder capacity, as a safety measure, was evaluated in a subset of patients in **SPI-611** and not in **SPI-612**.

5.2.1.2 Study Objectives

The primary objective of **SPI-611** and **SPI-612** was to assess the **2-Year Recurrence Rate** of bladder cancer in randomized patients with low-grade (Ta, G1-G2) NMIBC who underwent TURBT followed by apaziquone instillation versus those who underwent TURBT followed by placebo instillation. Secondary efficacy objectives were to evaluate:

- **Time to First Recurrence** in patients with Ta, G1-G2 bladder cancer who received TURBT plus apaziquone versus those who received TURBT plus placebo
- **Progression** to higher stage or grade
- **Number of Recurrences per Patient**
- **Disease-free Interval**
- **Disease-free Survival**
- **Overall Survival**

The definitions for all the efficacy variables that supported these objectives are presented in **Table 7**.

Table 7 Description of Efficacy Variables Used in Pivotal Apaziquone Clinical Trials

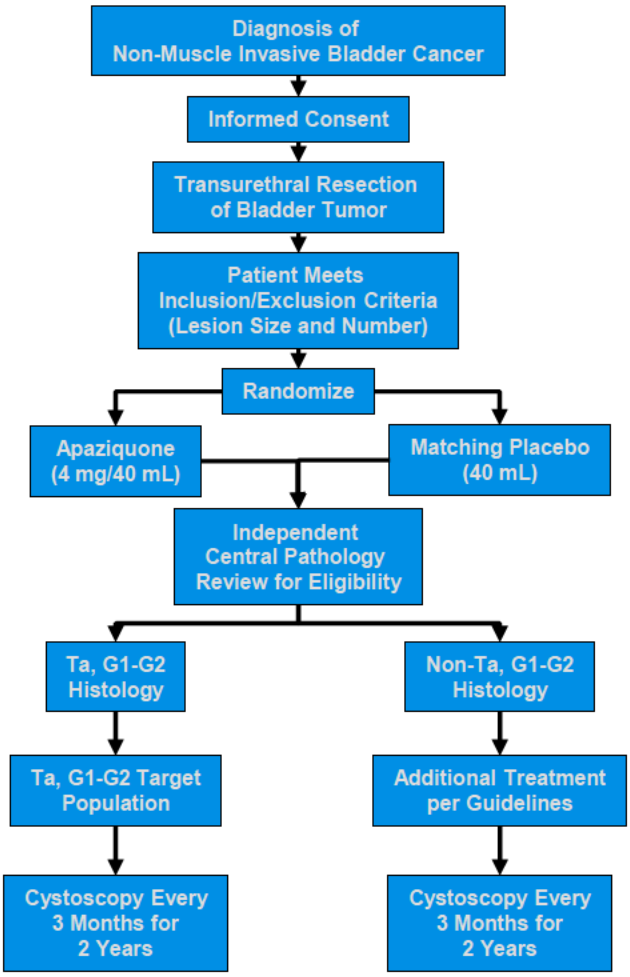
Variable	Definition
Recurrence	Appearance of new, histologically confirmed, bladder tumor while on study.
Recurrence Rate	The proportion of patients with histologically confirmed recurrence of the bladder tumor at any time after randomization and on or before **Year 2**. The first recurrence was used for **Recurrence Rate**.
Time to Recurrence	Time from randomization to the first histologically confirmed recurrence of the bladder tumor. **Time to Recurrence** of patients without recurrence was censored at the date of last negative cystoscopy.
Progression	Appearance of histologically confirmed bladder cancer with a higher grade or higher stage when compared with the histology of **Baseline** bladder cancer. Date of the first observation of histologically confirmed progression was used as the date of progression.
Progression Rate	The proportion of patients with histologically confirmed progression of the bladder tumor at any time after randomization and on or before **Year 2**.

Variable	Definition
Time to Progression	Time from randomization to the first histologically confirmed progression to a higher stage or higher grade of the bladder tumor. **Time to Progression** of patients without progression was censored at the last negative cystoscopy.
Disease-Free Interval	The number of months from randomization to histologically confirmed progression to higher stage or grade of the patient's bladder tumor or death from any cause. (This definition was requested by FDA as part of the Special Protocol Assessment agreement.)
Disease-Free Survival	The number of months from randomization to histologically confirmed recurrence of the patient's bladder tumor or death from any cause.
Overall Survival	Time from randomization to death from any cause. **Overall Survival** of living patients was censored at the date of study completion or discontinuation.

5.2.1.3 Study Design

Figure 13 provides an overview of the design of **SPI-611** and **SPI-612**. In each study, eligible patients were randomized in a 1:1 ratio to receive either apaziquone or placebo of identical appearance using a permuted block design that was not stratified by prognostic factors. Patients were randomized within each center with a block size of four. Patient numbers were assigned sequentially at each site, and study drug was shipped to the sites in blocks of four to ensure balance at each site.

Figure 13 Study Design of Pivotal Apaziquone Clinical Trials: SPI-611 and SPI-612



Eligible patients, as assessed by cystoscopy, had a TURBT during **Visit 1** (**Day 0**) after which they were randomized to receive either apaziquone (4 mg) or placebo instilled in a volume of 40 mL into the bladder within 6 hours of the TURBT. After a 60-minute retention, study drug was drained from the bladder. Depending upon each site's standard operating procedures, the specimens from the TURBT were examined by a local pathologist, and all clinical decisions were made based on the local pathologist's report. A postoperative follow-up examination was performed at Visit 2 (Week 3; 21±10 days post-TURBT).

An independent central pathology laboratory, blinded to the treatment assignments, performed definitive histologic assessment for eligibility for inclusion in the primary efficacy population (**Ta, G1-G2 Target Population:** patients with tumors with Ta, G1-G2 histology ≤3.5 cm, ≤4 tumors). Patients with tumors other than Ta, G1-G2 who received study drug were included in the **ITT Population** (which included all randomized patients regardless of central pathology confirmation of Ta, G1-G2 histology). In both studies (**SPI-611** and **SPI-612**):

- Patients with confirmed Ta, G1-G2 disease received no further treatment and were followed by cystoscopy every 3 months through Year 2 for assessment of tumor recurrence (**Visit 3** through **Visit 10**).

- Patients with histology other than Ta, G1-G2 could receive further treatment in accordance with the treatment guidelines and local standards of care that were in effect at the time; these patients were also followed up by cystoscopy every 3 months through **Year 2** for tumor recurrence (**Visit 3** through **Visit 10**).

All patients were scheduled to be followed for 2 years.

5.2.1.4 Discussion of Efficacy Endpoints and Statistical Considerations

Spectrum initially proposed **Time to Recurrence** as the primary endpoint for **SPI-611** and **SPI-612** and this was the primary endpoint in the initial protocol and early protocol amendments for **SPI-611** (before any patients were enrolled). However, the FDA, after consultation with Division of Reproductive and Urologic Products experts, recommended **2-Year Recurrence Rate** as the primary efficacy endpoint in **SPI-611** and **SPI-612**, and Time to First Recurrence as the key secondary efficacy variable (Meeting Minutes 5 Feb 2007). Spectrum accepted these recommendations.

The powering and sample size calculation for the statistical test of hypotheses for the treatment effect of apaziquone over placebo were based primarily on the treatment effect observed in a meta-analysis conducted by Sylvester et al, 2004 **[24]**, which, as previously discussed **(Section 3.2.3)** demonstrated recurrence rates of 48.4% for TURBT alone and 36.7% for TURBT plus intravesical therapy, an absolute difference of 11.7%, representing a decrease of 39% in the odds of recurrence with chemotherapy (OR 0.61, 95% CI 0.49, 0.75; $p < 0.0001$). **SPI-611** and **SPI-612** were consequently designed to detect an absolute improvement of **2-Year Recurrence Rate** of 12% at a 5% level of significance, and were each powered at 80%.

It is important to note, however, that there were significant challenges of determining what is clinically meaningful treatment effect to be used to calculate the sample size for the **Ta, G1-G2 Target Population**, summarized as follows:

- There was a lack of published data on **2-Year Recurrence Rate** for single immediate intravesical instillation over placebo.
- The heterogeneity in the results of the individual studies reported in meta-analysis meant that a precise estimation of treatment effect in recurrence rate was not available.
- There was an absence of preliminary efficacy studies of apaziquone for single immediate intravesical instillation prior to the initiation of the Phase 3 studies.

The data presented in the meta-analysis on which sample size calculations were based **[24]** was for recurrence in patients with a median follow up of 3.4 years, not 2 years, which was the duration of **SPI-611** and **SPI-612**. There was also significant heterogeneity in the studies included in the meta-analysis ($p = 0.03$) (**Section 3.2.3**). The largest study (~400 patients) included in the meta-analysis **[61]** reported a lower absolute improvement of 9.2% in recurrence for the chemotherapeutic (epirubicin) compared to placebo post-TURBT, over a median duration of 5.5 years.

SPI-611 and **SPI-612**, which initiated enrollment in the second and third quarters of 2007, respectively, were not adequately powered to show this treatment effect. In addition, as noted in **Section 3.2.3**, placebo itself and/or the use of post-operative irrigation have since been suggested

to have significant effect compared to TURBT alone, reducing the difference between active drug and control (ie, TURBT alone or TURBT plus placebo) in recurrence-free interval **[27-28]**.

Following the pre-NDA meeting in 2012, Spectrum continued the evaluation of data from **SPI-611** and **SPI-612**. Spectrum performed several multivariate and subgroup analyses of efficacy endpoints to determine if any of the baseline demographics, disease status or the treatment administration parameters affected the magnitude and variability of the prespecified efficacy measures. These analyses were performed in **SPI-611** first and the same methodology was applied to **SPI-612** once the former analysis was complete.

5.2.1.5 Pooling of Data

When **SPI-611** and **SPI-612** were designed, there was little information in the literature for estimating the statistical power. Based on the continuing updates in the published literature on use of IPOC in NMIBC, Spectrum proposes that the reasonable estimates of treatment effect in 2-year recurrence is less than hypothesized difference of 12% in recurrence rate and the studies as designed were underpowered. Therefore, Spectrum judged that combining data from the two pivotal studies was reasonable although not pre-specified and conducted analyses based on the pooled data. The reasoning for combining the data included:

- The studies were identical in design with a minimal difference in exclusion criteria.
- The primary endpoint was the same in both studies, including independent central pathology
- All study sites were in one of three countries: the US and Poland in **SPI-611** and the US, Poland, and Canada in **SPI-612**. Thus, there was relatively the same distribution of countries and sites in each study.
- Importantly, both studies started within a short time of each other (**SPI-611** enrolled the first patient on 25 Apr 2007 and **SPI-612** on 28 Aug 2007) and both ended at the same time (**SPI-611** on 19 Jan 2012 and **SPI-612** on 25 Jan 2012). Therefore, with the studies were independent of each other, no information and lessons learned from one study were incorporated in to the other.

Essentially, the two studies provided an expansion of sample size from each study alone. Further justification for pooling the data from the studies was based on the results of each study:

- Patients in both randomized studies had similar demographic characteristics.
- The baseline tumor/disease characteristics were comparable between studies, including numbers of patients with primary/recurrent tumors, prior intravesical therapy, median size of tumor, and number of tumors at baseline.
- All patients in each study were dosed similarly and were compliant with the protocol; the follow-up duration was similar in both studies.
- The results of primary and secondary endpoint analyses including, subgroup analyses, were of similar magnitude and direction of differences.

5.2.2 Study Results

5.2.2.1 Patient Disposition

In **SPI-611**, most patients were enrolled at study sites in the US (94%) and the remainder of patients were at sites in Poland (6%). In **SPI-612**, the majority of patients (54%) were enrolled by Canadian sites, 21% by US sites and the remainder (25%) by Polish sites (**Table 8**).

Table 8 Study Site Distribution in the Apaziquone Pivotal Studies (SPI-611 and SPI-612)

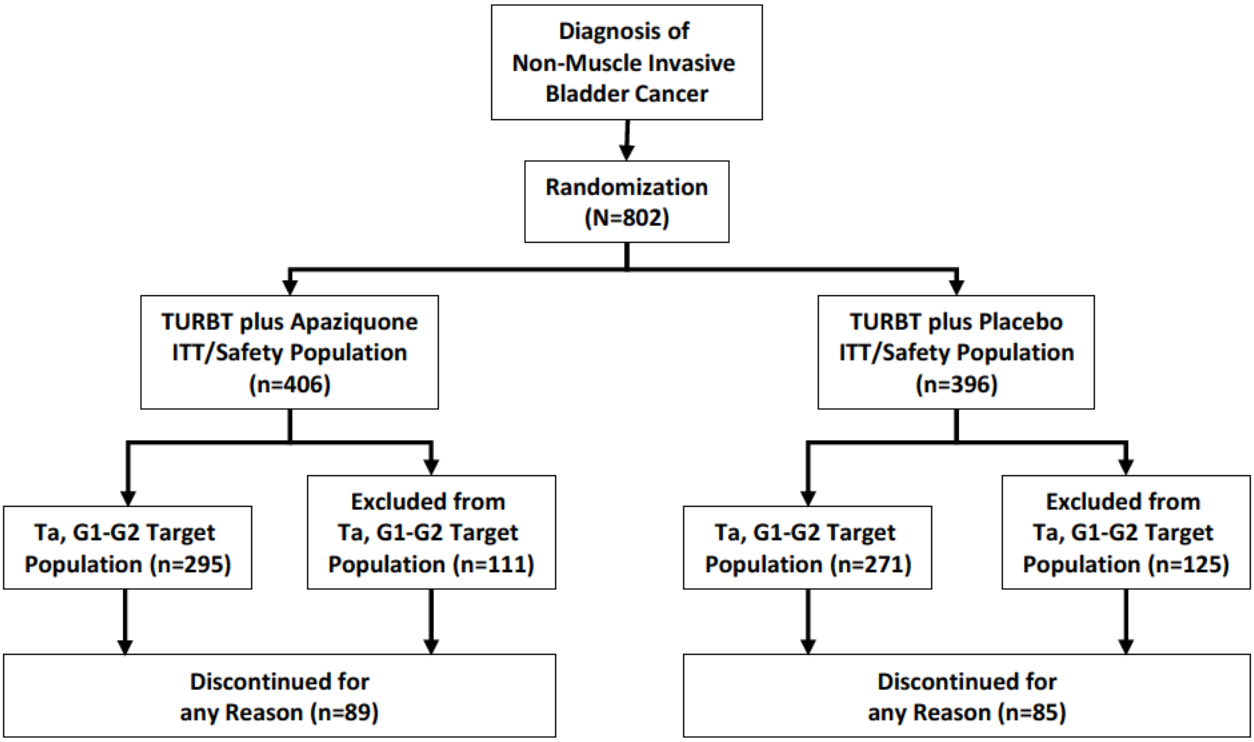
Study Number	Country	Sites, n	Patients, n (%)
SPI-611	United States	72	756 (94.3)
	Poland	7	46 (5.7)
SPI-612	United States	23	167 (20.6)
	Canada	30	438 (53.9)
	Poland	20	207 (25.5)

In **SPI-611**, 802 patients were enrolled and received a single dose of either apaziquone (406 patients) or placebo (396 patients). All of these patients were included in the **ITT Population**. In the **Apaziquone Treatment Group**, 295 patients were included in the **Ta, G1-G2 Target Population** with 111 patients excluded for one of the following factors: more than four lesions, lesions >3.5 cm, or following central pathology review, lesions were categorized as other than Ta, G1-G2 histology. In the **Placebo Treatment Group**, 271 patients were included in the **Ta, G1-G2 Target Population** with 125 patients excluded for the same reasons as above (**Figure 14A**).

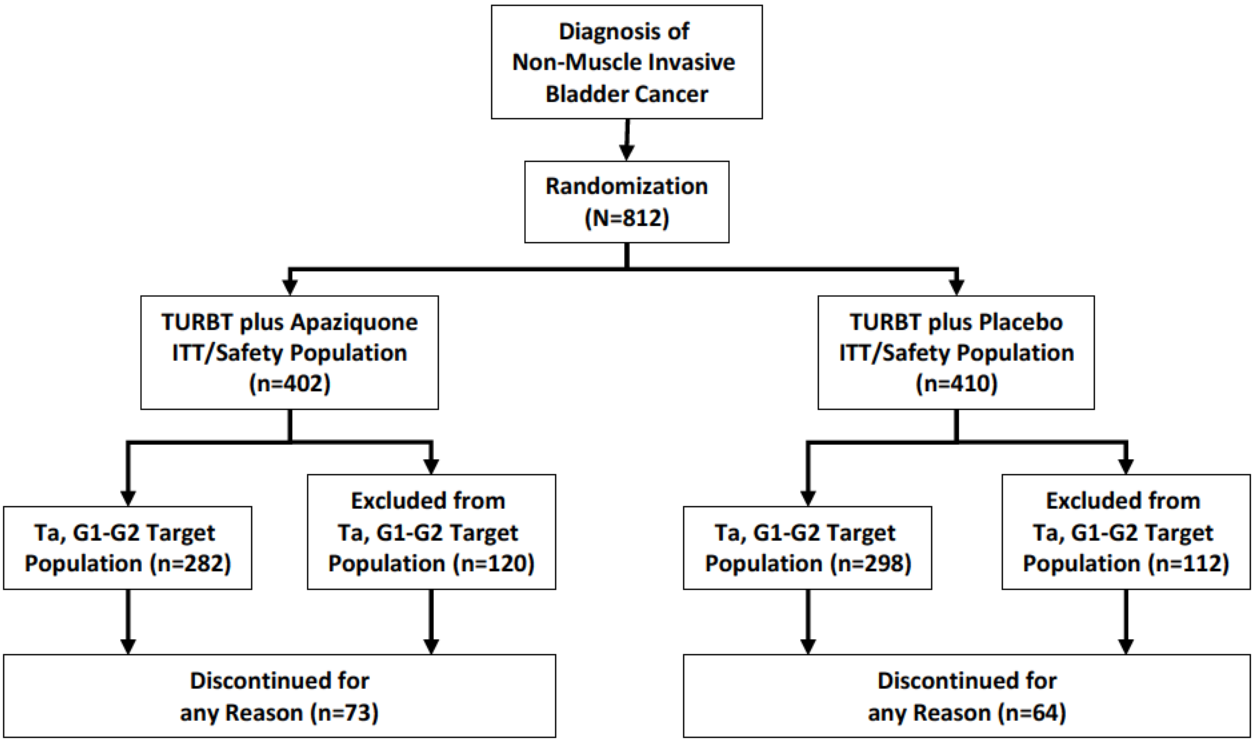
In **SPI-612**, 812 patients were enrolled and received a single dose of either apaziquone (402 patients) or placebo (410 patients) (**Figure 14B**). All of these patients were included in the **ITT Population**. Although patients with up to five lesions were allowed to be enrolled in the study, in order to combine data from both studies for the integrated analyses, only patients with up to four lesions were included in the **Ta, G1-G2 Target Population**. In the **Apaziquone Treatment Group**, 282 patients were included in the **Ta, G1-G2 Target Population**, with 120 patients excluded, and in the **Placebo Treatment Group**, 298 patients were included and 112 patients excluded.

Figure 14 Patient Disposition in the Apaziquone Pivotal Studies (SPI-611 and SPI-612)

A) SPI-611



B) SPI-612



5.2.2.2 Demographics and Baseline Characteristics

The demographics of the patient populations for **SPI-611** and **SPI-612** were consistent between studies with no notable differences between treatment groups. Additionally, the **Ta, G1-G2 Target Population** (**Table 9**) was not different demographically from the **ITT Population** (**Table 10**). Overall, most of the patients in both studies were male (~70%), White (~97%), and ≥65 years old (~60%). These demographics are consistent with the population of patients in the US with the highest incidence of bladder cancer and resulting mortality.

Table 9 Patient Demographics in Apaziquone Pivotal Studies (Ta, G1-G2 Target Population)

Characteristic/ Category	SPI-611		SPI-612		Overall	
	APZ (n=295)	PBO (n=271)	APZ (n=282)	PBO (n=298)	APZ (n=577)	PBO (n=569)
Gender, n (%)						
Male	210 (71.2)	199 (73.4)	203 (72.0)	208 (69.8)	413 (71.6)	407 (71.5)
Female	85 (28.8)	72 (26.6)	70 (28.0)	90 (30.2)	164 (28.4)	162 (28.5)
Race, n (%)						
White	287 (97.3)	263 (97.0)	275 (97.5)	289 (97.0)	562 (97.4)	552 (97.0)
Black or African American	6 (2.0)	5 (1.8)	5 (1.8)	2 (0.7)	11 (1.9)	7 (1.2)
Asian	0	2 (0.7)	2 (0.7)	6 (2.0)	2 (0.3)	8 (1.4)
Other	2 (0.7)	1 (0.4)	0	1 (0.3)	2 (0.3)	2 (0.4)
Age, years						
Mean (SD)	66.9 (11.29)	67.7 (10.62)	66.6 (11.94)	65.9 (11.81)	66.8 (11.60)	66.7 (11.28)
Median	68	68	67	67	67	68
Minimum, Maximum	29, 90	32, 94	24, 94	22, 89	24, 94	22, 94
Age Group, years, n (%)						
<65	123 (41.7)	105 (38.7)	114 (40.4)	125 (41.9)	237 (41.1)	230 (40.4)
≥65 to ≤75	94 (31.9)	97 (35.8)	97 (34.4)	110 (36.9)	191 (33.1)	207 (36.4)
>75	78 (26.4)	69 (25.5)	71 (25.2)	63 (21.1)	149 (25.8)	132 (23.2)
Smoking Status, n (%)						
Current	70 (23.7)	55 (20.3)	87 (30.9)	68 (22.8)	157 (27.2)	123 (21.6)
Former	173 (58.6)	152 (56.1)	138 (48.9)	155 (52.0)	311 (53.9)	307 (54.0)
Never	52 (17.6)	64 (23.6)	57 (20.2)	75 (25.2)	109 (18.9)	139 (24.4)

APZ=apaziquone; PBO=placebo; SD=standard deviation.

Table 10 Patient Demographics in Apaziquone Pivotal Studies (ITT Population)

Characteristic/ Category	SPI-611		SPI-612		Overall	
	APZ (n=406)	PBO (n=396)	APZ (n=402)	PBO (n=410)	APZ (n=808)	PBO (n=806)
Gender, n (%)						
Male	298 (73.4)	294 (74.2)	297 (73.9)	302 (73.7)	595 (73.6)	596 (73.9)
Female	108 (26.6)	102 (25.8)	105 (26.1)	108 (26.3)	213 (26.4)	210 (26.1)
Race, n (%)						
White	392 (96.6)	383 (96.7)	392 (97.5)	400 (97.6)	784 (97.0)	783 (97.1)
Black or African American	11 (2.7)	9 (2.3)	5 (1.2)	2 (0.5)	16 (2.0)	11 (1.4)
Asian	1 (0.2)	3 (0.8)	5 (1.2)	7 (1.7)	6 (0.7)	10 (1.2)
Other	2 (0.5)	1 (0.3)	0	1 (0.2)	2 (0.2)	2 (0.2)
Age, years						
Mean (SD)	67.5 (10.92)	68.2 (10.72)	66.9 (11.60)	66.5 (11.83)	67.2 (11.26)	67.3 (11.32)
Median	68	68	68	68	68	68
Minimum, Maximum	29, 90	32, 94	24, 94	22, 89	24, 94	22, 94
Age Group, years, n (%)						
<65	159 (39.2)	146 (36.9)	157 (39.1)	164 (40.0)	316 (39.1)	310 (38.5)
≥65 to ≤75	140 (34.5)	139 (35.1)	144 (35.8)	146 (35.6)	284 (35.1)	285 (35.4)
>75	107 (26.4)	111 (28.0)	101 (25.1)	100 (24.4)	208 (25.7)	211 (26.2)
Smoking Status, n (%)						
Current	95 (23.4)	80 (20.2)	116 (28.9)	97 (23.7)	211 (26.1)	177 (22.0)
Former	236 (58.1)	238 (60.1)	204 (50.7)	218 (53.2)	440 (54.5)	456 (56.6)
Never	75 (18.5)	78 (19.7)	82 (20.4)	95 (23.2)	157 (19.4)	173 (21.5)

APZ=apaziquone; PBO=placebo; SD=standard deviation.

The bladder cancer history for patients was also similar between studies and treatment groups and between the **Ta, G1-G2 Target Population** (Table 11) and the **ITT Population**. Most patients had primary tumors (>60%). In the **Ta, G1-G2 Target Population** patients with recurrences had up to 32 positive cystoscopies and one to three intravesical treatments prior to study enrollment. BCG and MMC were the most common previous intravesical therapies. Previous BCG therapy was more common in patients in **SPI-611** than **SPI-612**, possibly due to the higher percentage of patients from the US.

Table 11 Baseline Bladder Cancer History in the Apaziquone Pivotal Studies (Ta, G1-G2 Target Population)

Characteristic/ Category	SPI-611		SPI-612		Overall	
	APZ (n=295)	PBO (n=271)	APZ (n=282)	PBO (n=298)	APZ (n=577)	PBO (n=569)
Disease History, n (%)						
Primary	188 (63.7)	165 (60.9)	173 (61.3)	187 (62.8)	361 (62.6)	352 (61.9)
Recurrent	107 (36.3)	106 (39.1)	109 (38.7)	111 (37.2)	216 (37.4)	217 (38.1)
Number of Positive Cystoscopies for Patients with Prior Recurrences						
n	107	106	109	111	216	217
Mean (SD)	3.2 (3.65)	2.8 (2.47)	3.2 (4.01)	3.0 (3.53)	3.3 (3.83)	2.9 (3.05)
Median	2	2	2	2	2	2
Minimum, Maximum	0, 22	0, 18	0, 32	0, 26	0, 32	0, 26
Number of Prior Intravesical Therapies						
n	52 (17.6)	41 (15.1)	46 (16.3)	38 (12.8)	98 (17.0)	79 (13.9)
Mean (SD)	1.3 (0.47)	1.3 (0.52)	1.2 (0.45)	1.3 (0.61)	1.3 (0.46)	1.3 (0.56)
Median	1	1	1	1	1	1
Minimum, Maximum	1, 2	1, 3	1, 3	1, 3	1, 3	1, 3
Prior Intravesical Therapies, n (%)						
BCG	43 (14.6)	35 (12.9)	23 (8.2)	17 (5.7)	66 (11.4)	52 (9.1)
Mitomycin C	23 (7.8)	12 (4.4)	17 (6.0)	20 (6.7)	40 (6.9)	32 (5.6)
Other	2 (0.7)	7 (2.6)	14 (5.0)	12 (4.0)	16 (2.8)	19 (3.3)

APZ=apaziquone; BCG=Bacillus Calmette–Guérin; Max=maximum; Min=minimum; PBO=placebo ; SD=standard deviation.

At Baseline, most patients (~60%) had a single lesion. The number of lesions in each patient in the **Ta, G1-G2 Target Population** ranged from one to four, and the median number of lesions across both studies and between groups was one. All patients with five or more lesions were excluded from the **Ta, G1-G2 Target Population**. In the **ITT Population**, lesion size ranged from 0.2 cm to 5.5 cm in **SPI-611** and 0.2 cm to 5.0 cm in **SPI-612** and the median lesion size was 1.5 cm in both treatment groups in both studies. In patients in the **Ta, G1-G2 Target Population**, patients with lesion sizes >3.5 cm were excluded and lesions sizes ranged from 0.2 cm to 3.5 cm **(Table 12)**.

Table 12 Baseline Tumor Characteristics in Apaziquone Pivotal Studies (Ta, G1-G2 Target Population)

Characteristic/ Category	Ta, G1-G2 Population					
	SPI-611		SPI-612		Overall	
	APZ (n=295)	PBO (n=271)	APZ (n=282)	PBO (n=298)	APZ (n=577)	PBO (n=569)
Total Number of Lesions						
Mean (SD)	1.6 (0.87)	1.5 (0.82)	1.7 (0.92)	1.7 (0.93)	1.6 (0.90)	1.6 (0.88)
Median	1	1	1	1	1	1
Min, Max	1, 4	1, 4	1, 4	1, 4	1, 4	1, 4
Number of Lesions, n (%)						
1	191 (64.7)	181 (66.8)	167 (59.2)	181 (60.7)	358 (62.0)	362 (63.6)
2	51 (17.3)	54 (19.9)	65 (23.0)	53 (17.8)	116 (20.1)	107 (18.8)
3	42 (14.2)	26 (9.6)	31 (11.0)	49 (16.4)	73 (12.7)	75 (13.2)
4	11 (3.7)	10 (3.7)	19 (6.7)	15 (5.0)	30 (5.2)	25 (4.4)
5	0	0	0	0	0	0
Lesion Size (Largest), cm						
Mean (SD)	1.7 (0.93)	1.7 (0.95)	1.6 (0.86)	1.6 (0.85)	1.7 (0.90)	1.6 (0.90)
Median	1.5	1.5	1.5	1.5	1.5	1.5
Min, Max	0.2, 3.5	0.2, 3.5	0.3, 3.5	0.2, 3.5	0.2, 3.5	0.2, 3.5

APZ=apaziquone; G1-G2=Grade 1/2; Max=maximum; Min=minimum; PBO=placebo; SD=standard deviation.

5.2.2.3 Efficacy

5.2.2.3.1 Primary Efficacy Variable: Two-Year Recurrence Rate (Ta, G1-G2 Target Population)

In **SPI-611**, the **2-Year Recurrence Rate** was 38.0% for apaziquone-treated patients compared to 44.6% for patients treated with placebo, representing a 6.7% absolute reduction in **Recurrence Rate** for apaziquone vs placebo. In **SPI-612**, the **2-Year Recurrence Rate** was 39.7% vs 46.3% for apaziquone versus placebo, respectively, representing a 6.6% absolute reduction. Although clinically meaningful, these absolute differences were not statistically significant in the individual studies. In the integrated analysis from the two clinical studies, the resulting 6.7% difference was statistically significant (nominal p=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.

The relative reduction in **2-Year Recurrence Rate** seen in **SPI-611** and **SPI-612** for the **Ta, G1-G2 Target Population** was consistent between studies (15.0% and 14.2%, respectively) and in the integrated analysis (14.7%) **(Table 13)**.

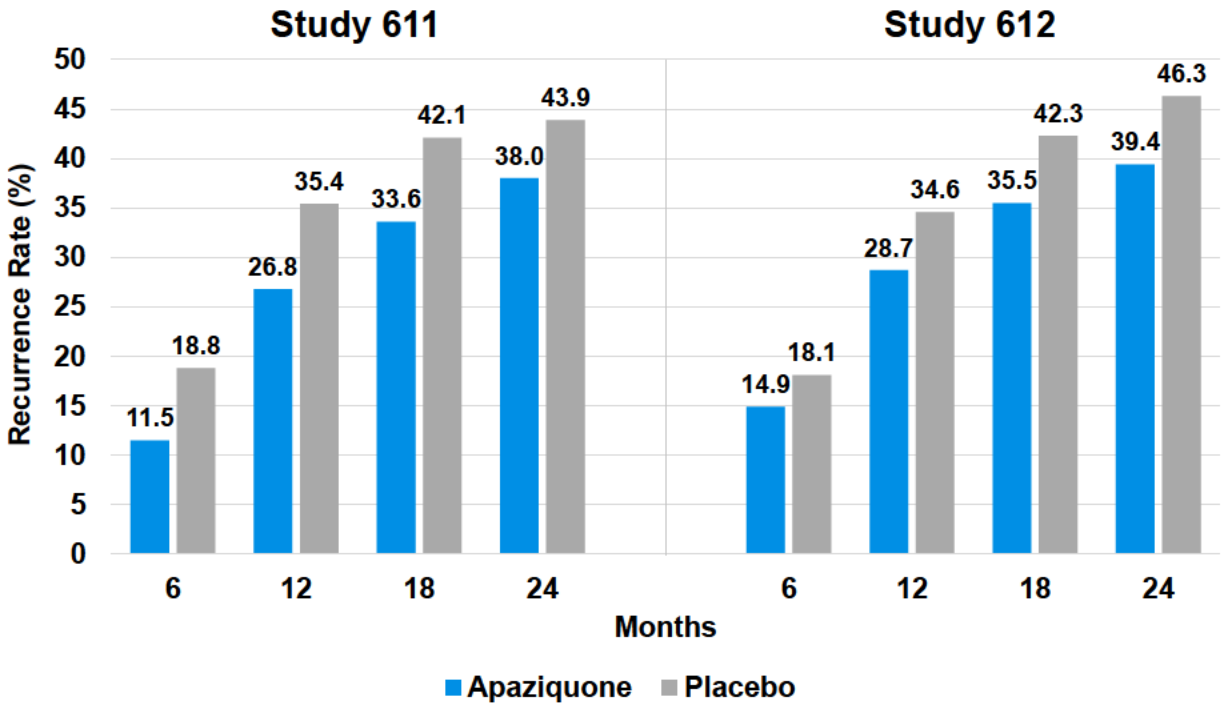
Table 13 Two-Year Recurrence Rate and Time to Recurrence after a Single Post-TURBT Intravesical Instillation of Apaziquone (Ta, G1-G2 Target Population)

Parameter	SPI-611		SPI-612		Overall	
	APZ (n=295)	PBO (n=271)	APZ (n=282)	PBO (n=298)	APZ (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)
2-Year Recurrence Rate						
(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[h]	
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	
Time to Recurrence (months)						
Mean (SE)[d]	18.3 (0.47)	16.7 (0.55)	18.1 (0.50)	16.7 (0.50)	18.2 (0.34)	16.8 (0.37)
Median (95% CI)[d]	NC	24.2 (17.8, NC)	NC	NC	NC	24.2 (19.0, NC)
Minimum, Maximum [e]	2.4, 24.0	2.7, 24.2	2.7, 24.2	2.6, 24.0	2.4, 24.2	2.6, 24.2
Hazard Ratio (95% CI)[f]	0.77 (0.59, 0.99)		0.81 (0.63, 1.04)		0.79 (0.66, 0.94)	
Nominal p-value [g]	0.0412		0.1038		0.0096	

APZ=apaziquone; CI=confidence interval; NC=not calculable; PBO=placebo; 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) Kaplan-Meier (product-limit) estimate.
(e) For patients with event.
(f) Cox proportional hazards model.
(g) Log-rank test.
(h) Nominal p-value.

The overall improvement in recurrence rates in the apaziquone groups compared to the placebo groups in these two pivotal studies (**SPI-611** and **SPI-612)** were consistent over the 2-year follow-up period at 6, 12, 18, and 24 months within and between each study **(Figure 15)**.

Figure 15 Overall Recurrence Rates at 6, 12, 18, and 24 Months by Study and Treatment



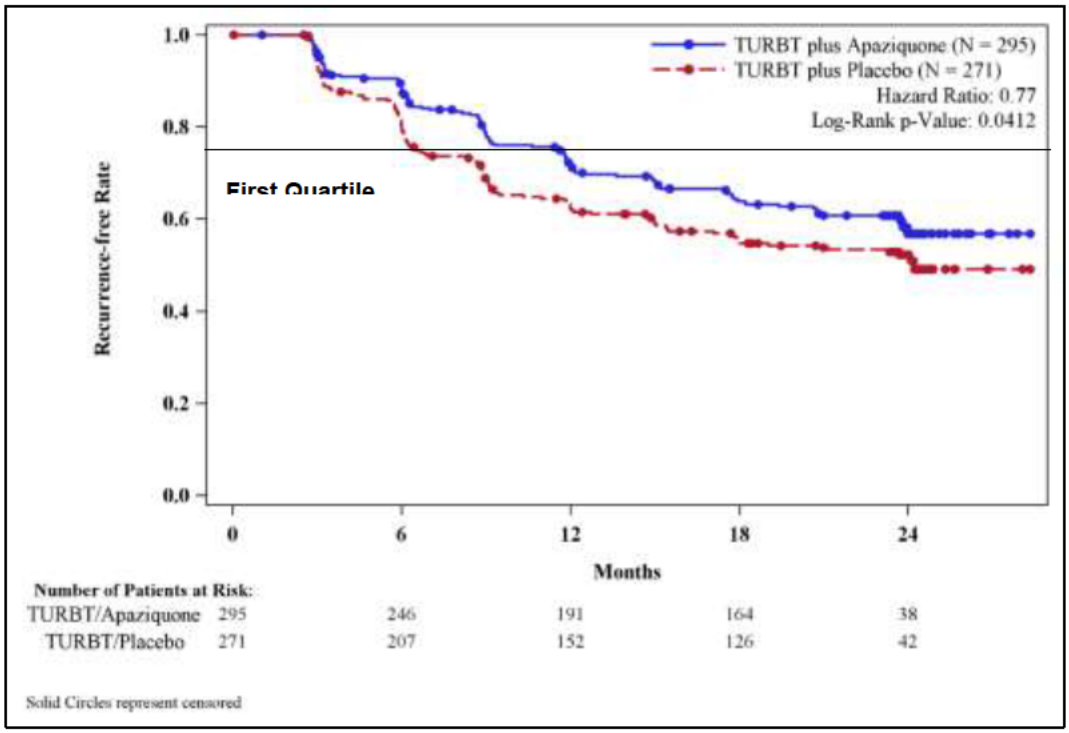
Note: The 6, 12, 18 and 24 month data were calculated based on 183, 366, 548 and 731 days, respectively.

5.2.2.3.2 Key Secondary Efficacy Variable: Time to Recurrence (Ta, G1-G2 Target Population)

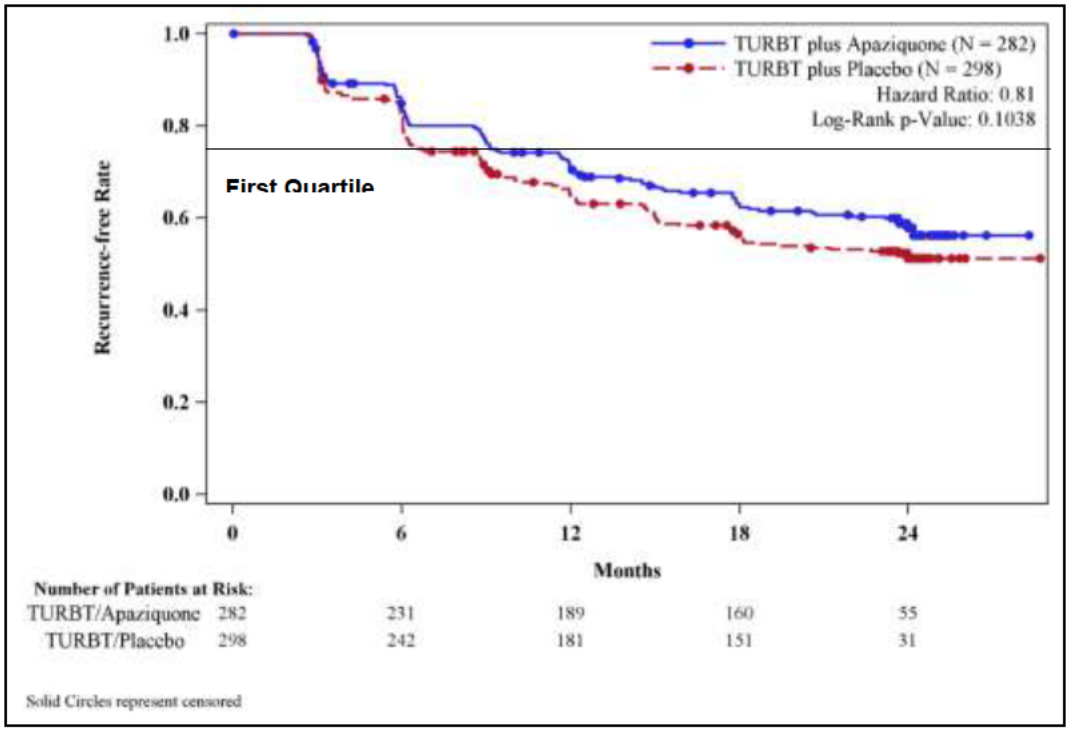
Time to Recurrence, defined as time from randomization to date of first histologically confirmed recurrence of the patient's bladder tumor, was the key secondary endpoint in the studies. The distribution of **Time to Recurrence** by the Kaplan-Meier method showed a clear divergence between apaziquone and placebo over the 2-year follow-up period in both studies (**SPI-611** and **SPI-612**), demonstrating an improvement in the **Time to Recurrence** for apaziquone-treated patients in the **Ta, G1-G2 Target Population** in **SPI-611** (HR 0.77, 95% CI 0.59, 0.99; nominal $p = 0.0412$) (**Figure 16A**) with a similar magnitude of effect in **SPI-612** (HR 0.81,95% CI 0.63, 1.04; nominal $p = 0.1038$) (**Figure 16B**) and for the two studies combined (HR 0.79, 95% CI 0.66, 0.94; nominal $p = 0.0096$) (**Table 13**, **Figure 16C**).

Figure 16 Kaplan-Meier Estimates of Time to Recurrence in the Apaziquone Pivotal Studies SPI-611 and SPI-612 (Ta, G1-G2 Target Population)

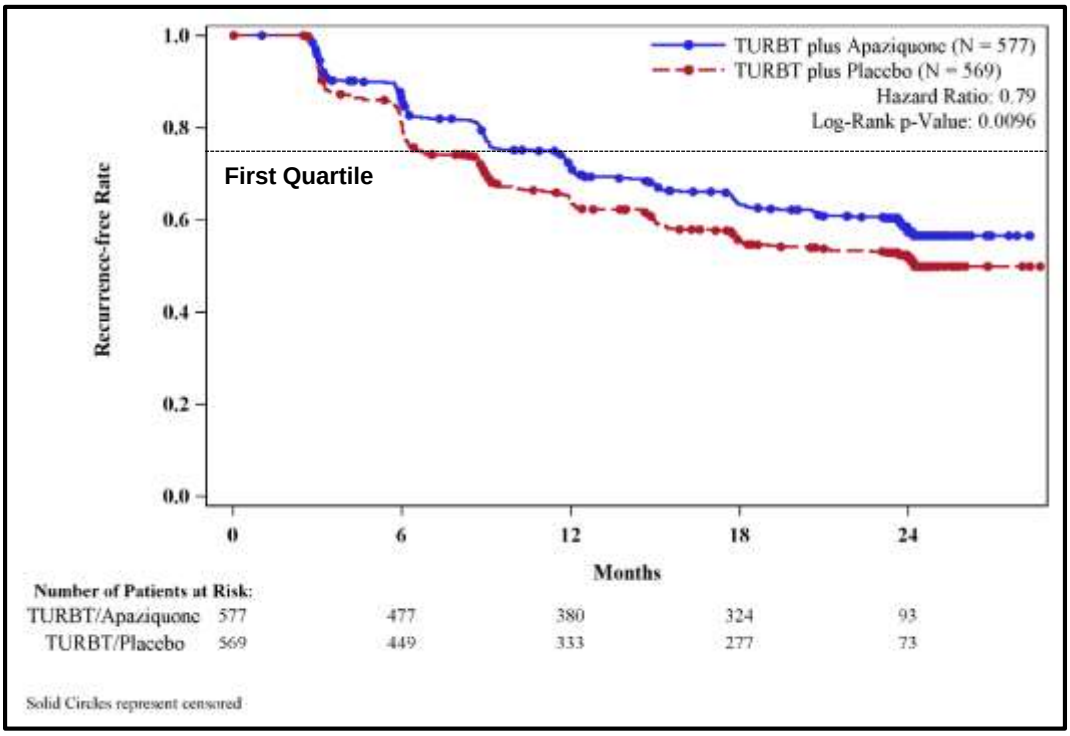
A. SPI-611



B. SPI-612



C. SPI-611 + SPI-612



TURBT=transurethral resection of bladder tumor.

5.2.2.3.3 Efficacy in the ITT Population

The results in the **ITT Population** were similar to the results obtained in the **Ta, G1-G2 Target Population** in both studies **(Table 14)**. In **SPI-611**, the **2-Year Recurrence Rate** was 36.9% in apaziquone-treated patients compared to 42.2% in patients treated with placebo, representing a 12.6% relative reduction for apaziquone vs placebo. In **SPI-612**, the **2-Year Recurrence Rate** was 40.0% vs 46.1%, representing a 13.2% relative reduction. The absolute reduction in **2-Year Recurrence Rate** seen in **SPI-611** and **SPI-612** for the **ITT Population** was 5.2% and 6.0%, respectively, and 5.7% when the studies were combined (nominal p = 0.0206; OR 0.79; 95% CI 0.65, 0.96). **Time to Recurrence** was also in favor of apaziquone in the integrated analysis (nominal p = 0.0237; HR 0.84; 95% CI 0.72, 0.98).

Table 14 Two-Year Recurrence Rate and Time to Recurrence after a Single Post-TURBT Intravesical Instillation of Apaziquone (ITT Population)

Parameter	SPI-611		SPI-612		Overall	
	APZ (n=406)	PBO (n=396)	APZ (n=402)	PBO (n=410)	APZ (n=808)	PBO (n=806)
Patients with Recurrence [a], n (%)	150 (36.9)	167 (42.2)	161 (40.0)	189 (46.1)	311 (38.5)	356 (44.2)
2-Year Recurrence Rate						
(95% CI)[b]	(32.2, 41.8)	(37.3, 47.2)	(35.2, 45.0)	(41.2, 51.1)	(35.1, 41.9)	(40.7, 47.7)
Nominal p-value [c]	0.1304		0.0821		0.0206	
Difference (95% CI)	-5.2 (-12.0, 1.5)		-6.0 (-12.8, 0.8)		-5.7 (-10.5, -0.9)	
Odds ratio (95% CI)	0.80 (0.61, 1.07)		0.78 (0.59, 1.03)		0.79 (0.65, 0.96)	
Relative Change (%)	-12.6		-13.2		–12.9	
Time to Recurrence (months)						
Mean (SE)[d]	18.3 (0.42)	17.0 (0.45)	17.7 (0.43)	16.7 (0.43)	18.0 (0.30)	16.9 (0.31)
Median (95% CI)[d]	NC	NC	NC	NC	NC	NC
Minimum, Maximum [e]	2.4, 24.1	2.6, 24.2	1.7, 24.2	1.7, 24.0	1.7, 24.2	1.7, 24.2
Hazard Ratio (95% CI)[f]	0.84 (0.67, 1.05)		0.84 (0.68, 1.04)		0.84 (0.72, 0.98)	
Nominal p-value [g]	0.1169		0.1058		0.0237	

APZ=apaziquone; CI=confidence interval; ITT=intent-to-treat; NC=not calculable; PBO=placebo; 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) Kaplan-Meier (product-limit) estimate.
(e) For patients with event.
(f) Cox proportional hazards model.
(g) Log-rank test.

5.2.2.3.4 Other Secondary Efficacy Results

Secondary efficacy endpoints for the **Ta, G1-G2 Target Populations** in **SPI-611** and **SPI-612** generally supported the primary analysis that patients treated with apaziquone had a better outcome:

- **Progression Rate at 2 Years:** Data were consistent between studies and showed that fewer patients treated with apaziquone than with placebo progressed at 2 years (10.2% vs 14.4% in **SPI-611** and 10.3% vs 12.4% in **SPI-612**).
- **Time to Progression:** The median time to progression could not be calculated for either group in either study because the progression rate was low.
- **Overall Survival:** Median survival could not be calculated for either treatment group in either study. Fewer patients treated with apaziquone than with placebo died (8 patients

[2.7%] vs 10 patients [3.7%] in **SPI-611** and seven patients [2.5%] vs 11 patients [3.7%] in **SPI-612**). None of the deaths in either study were due to bladder cancer or study-related treatment. Additional details are presented in **Section 6.2.4**.

- **Disease-Free Interval:** The median **Disease-Free Interval** could not be calculated in either treatment group from either study.
- **Disease-Free Survival:** The median **Disease-Free Survival** could not be calculated for apaziquone but was calculated for placebo. In **SPI-611** the disease-free survival was 23.7 months (95% CI: 15.4, not calculable; nominal p=0.0381 vs apaziquone, log-rank test) and in **SPI-612** was 24.0 months (95% CI: 17.7, not calculable; nominal p = 0.0651).
- **Number of Recurrences within 2 Years:** The mean Number of Recurrences per patient at 2 Years was numerically lower in the apaziquone group in both studies compared with placebo (0.6 vs 0.9 in both studies).

It is important to note that the study was designed to assess the recurrence rate at the 2-year endpoint and the data analyzed for progression, disease free survival, and overall survival were censored due to the time-bound endpoint.

5.2.2.3.5 Subgroup Analyses

Following the pre-NDA meeting in 2012, Spectrum continued the evaluation of data from **SPI-611** and **SPI-612**. Spectrum performed several multivariate analyses for, and subgroup analyses of, the primary and key secondary efficacy endpoints (**2-Year Recurrence Rate** and **Time to Recurrence**) to identify covariates that may have affected the magnitude and variability of the prespecified efficacy measures. Subgroup analyses were performed for the factors identified from the multivariate analysis to examine the consistency of treatment effect across the various subgroups.

Subgroup analyses included country of enrollment, demographics of patients, whether the tumor was primary or recurrent, number of tumors at Baseline, Grade 1 or Grade 2 tumors, previous intravesical treatment, and time to instillation post-TURBT. Additional subgroup analyses were conducted for subjects' risk level (low, intermediate, and high), based on the 2016 AUA guideline for risk classification **(Table 3)**. Forest plots were constructed for odds ratios for **2-Year Recurrence Rate** and hazard ratios for **Time to Recurrence**. The consistency of results in all of the subgroup analyses supports the clear effect of apaziquone in reducing the recurrence.

5.2.2.3.5.1 Baseline Characteristics

Data were largely consistent within each study and between the two pivotal studies for both **2-Year Recurrence Rate** and **Time to Recurrence**. Apaziquone was favored in the analyses independent of the country that enrolled patients, demographics of patients, whether the tumor was primary or recurrent, whether the patient had a single tumor or multiple tumors, and whether the tumor was Grade 1 or Grade 2 **(Figure 17, Figure 18)**.

Figure 17 Odds Ratios (95% CI) for 2-Year Recurrence Rate by Study and Baseline Characteristics (Ta, G1-G2 Target Population)

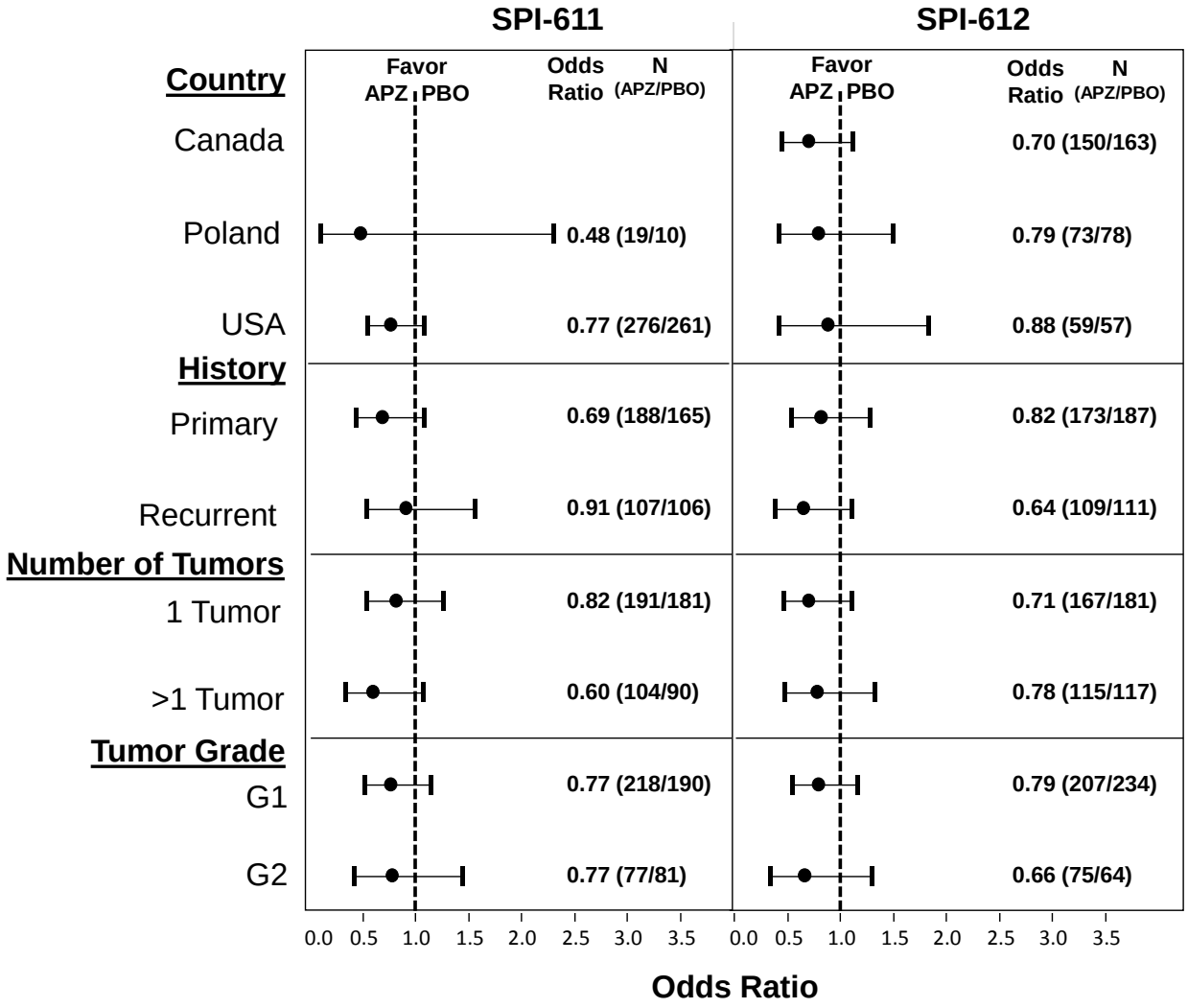
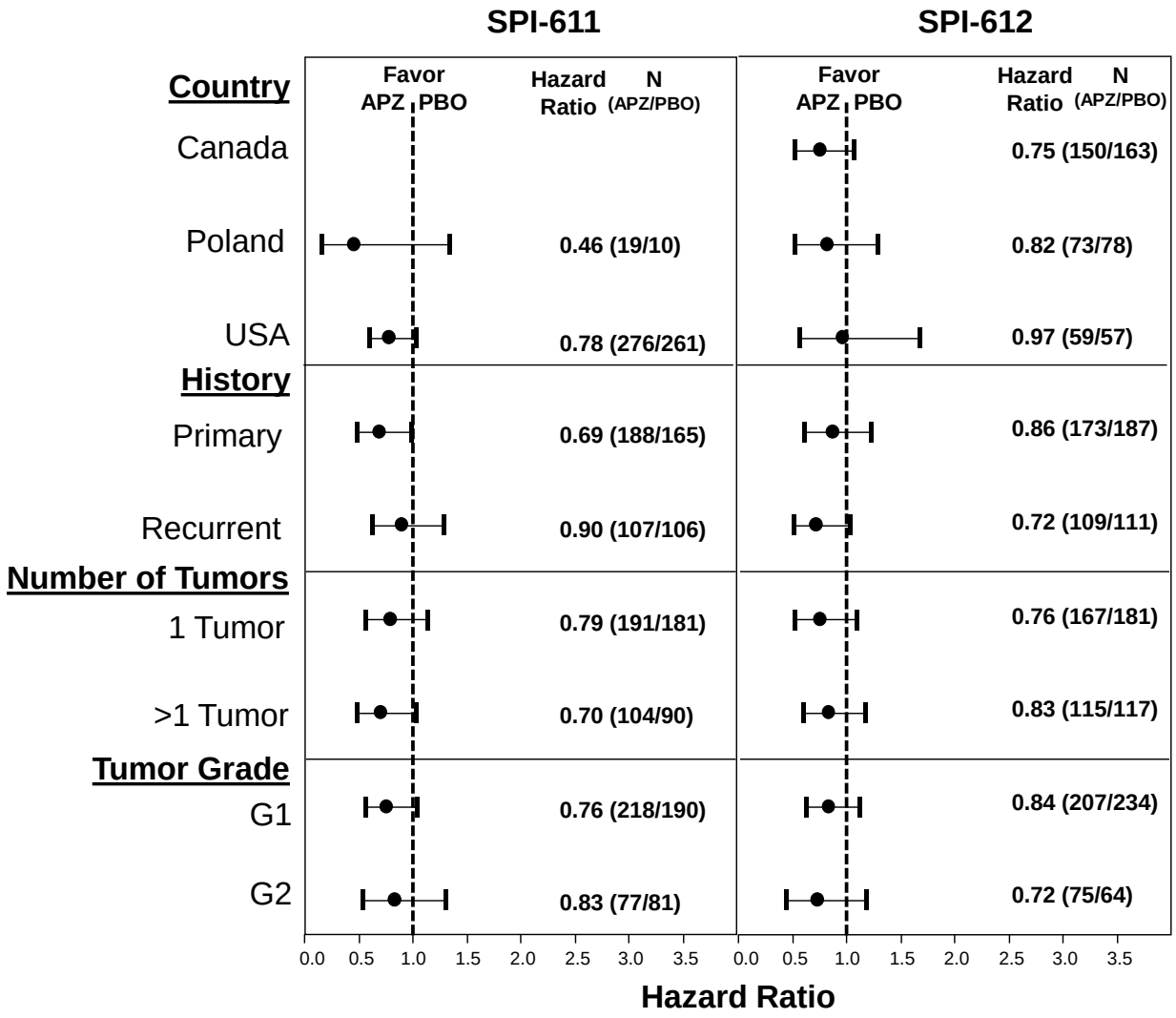


Figure 18 Hazard Ratios (95% CI) for Time to Recurrence by Study and Baseline Characteristics (Ta, G1-G2 Target Population)

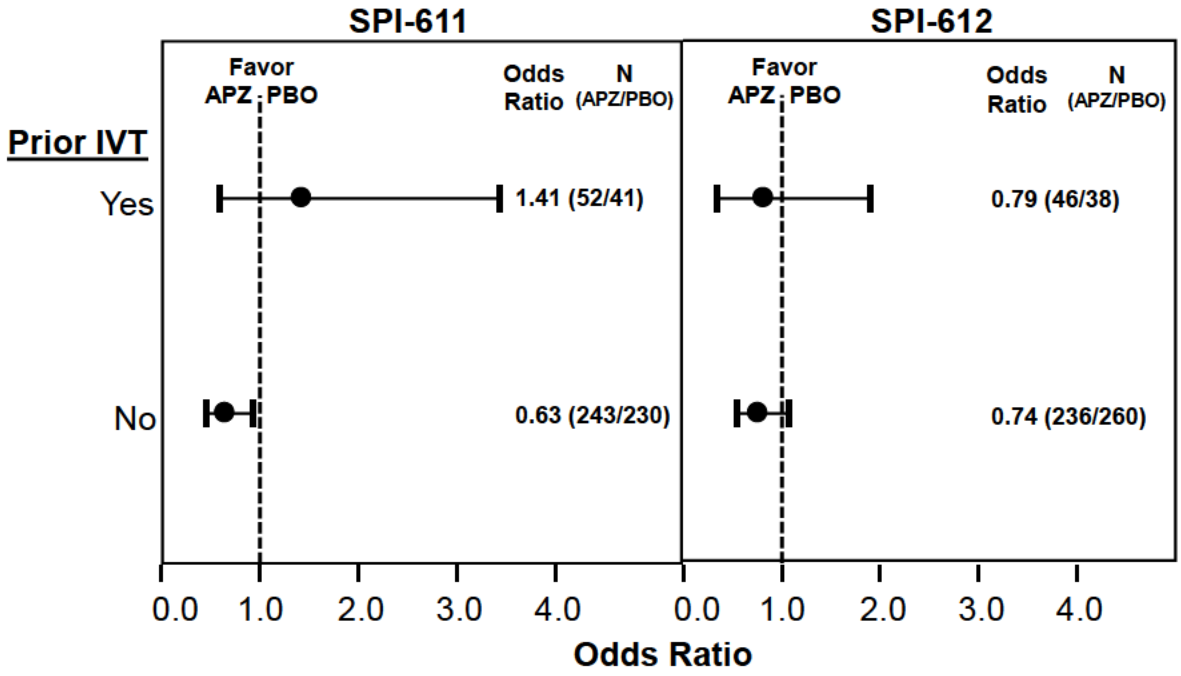


5.2.2.3.5.2 Prior Intravesical Therapy

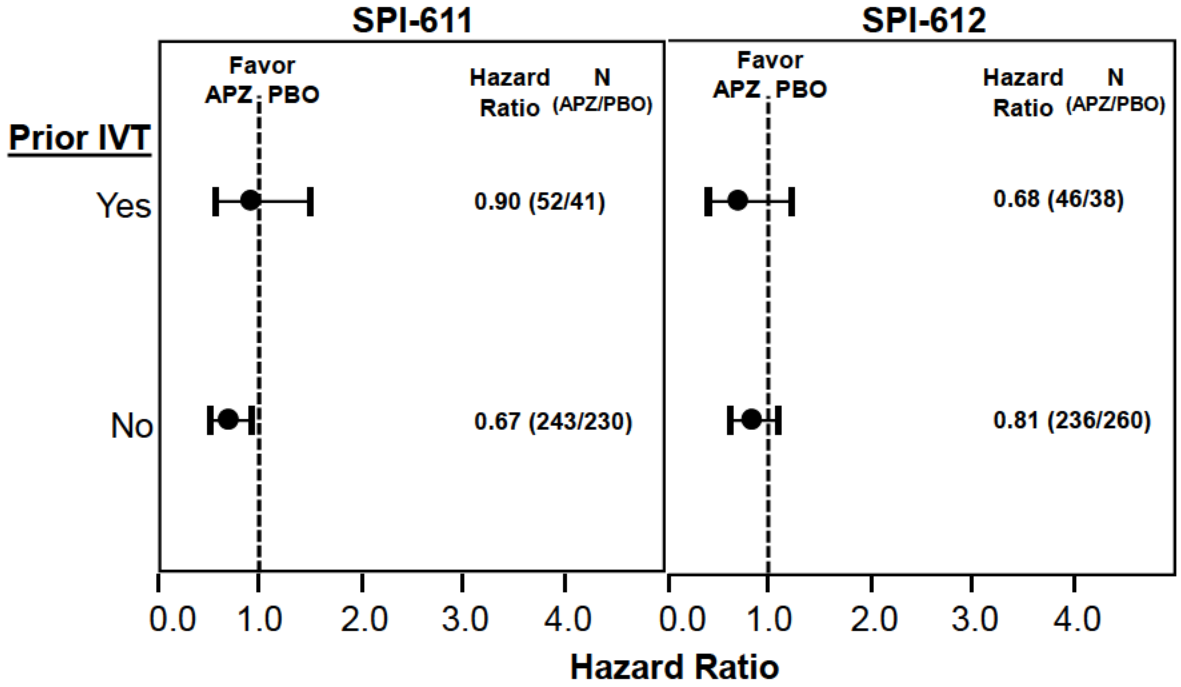
In **SPI-611**, apaziquone was numerically favored in patients who did not have previous intravesical treatments for both **2-Year Recurrence Rate** (nominal p=0.0181) and **Time to Recurrence** (nominal p=0.0105). In **SPI-612**, treatment with apaziquone was favored for both **2-Year Recurrence Rate** and **Time to Recurrence** in patients who did and did not have a prior intravesical treatment, though none of the differences were statistically significant **(Figure 19A** and **Figure 19B**).

Figure 19 Odds Ratios (95% CI) for 2-Year Recurrence Rate and Hazard Ratios (95% CI) for Time to Recurrence by Study and Prior Intravesical Treatment (Ta, G1-G2 Target Population)

A) 2-Year Recurrence Rate



B) Time to Recurrence



IVT=intravesical treatment

5.2.2.3.5.3 Time of Instillation

Since patients would be expected to have some degree of hematuria immediately upon completion of the TURBT procedure, the impact of time of instillation was investigated. A threshold of 30 minutes from end of TURBT was chosen as this is the typical time for hematuria to recede. The time of instillation of apaziquone post-TURBT (≤30 and >30 minutes) was found to be a factor in the efficacy of apaziquone in both studies, with improved efficacy when apaziquone was instilled >30 minutes post-TURBT. A potential explanation for the diminished efficacy when instilled ≤30 minutes post-TURBT is that apaziquone is being inactivated by red blood cells accumulating in the bladder immediately after TURBT (see **Section 2.3.2) [26]**. Since this finding could influence the use of apaziquone in the clinic setting, these analyses are presented in more detail below.

The proportion of patients treated >30 minutes post-TURBT was similar between the two studies and between treatment groups, with 161 patients in **SPI-611** and 183 patients in **SPI-612** having instillations of apaziquone >30 minutes post-TURBT (**Table 15**).

Table 15 Number (%) of Patients in the Time Stratified Populations of the Ta, G1-G2 Target Populations (SPI-611 and SPI-612)

Time post-TURBT (minutes)	SPI-611			SPI-612		
	APZ (N=295)	PBO (N=271)	Overall (n=566)	APZ (N=282)	PBO (N=298)	Overall (N=580)
≤30 minutes	134 (45.4)	145 (53.5)	279 (49.3)	99 (35.1)	78 (26.2)	177 (30.5)
>30 minutes	**161 (54.6)**	**126 (46.5)**	**287 (50.7)**	**183 (64.9)**	**220 (73.8)**	**403 (69.5)**

The efficacy of apaziquone was improved in the subgroup of patients who had instillations >30 minutes post-TURBT, with reduction in **2-Year Recurrence Rate** and increase in **Time to Recurrence** in the **Ta, G1-G2 Target Population** favoring apaziquone when given at this time in both studies **(Figure 20)** Thus for patients with instillations at >30 minutes post-TURBT:

- In **SPI-611**, there was a 10.2% absolute reduction in **2-Year Recurrence Rate** for patients treated with apaziquone compared to patients treated with placebo (31.1% vs 41.3%; nominal $p = 0.0733$; OR 0.64; 95% CI 0.39, 1.04), representing a 24.7% relative reduction compared to placebo
- In **SPI-612**, there was a 11.7% absolute reduction in **2-Year Recurrence Rate** for patients treated with apaziquone compared to patients treated with placebo (38.3% vs 50.0%; nominal $p = 0.0183$; OR 0.62; 95% CI 0.42, 0.92), representing a 23.5% relative reduction compared to placebo

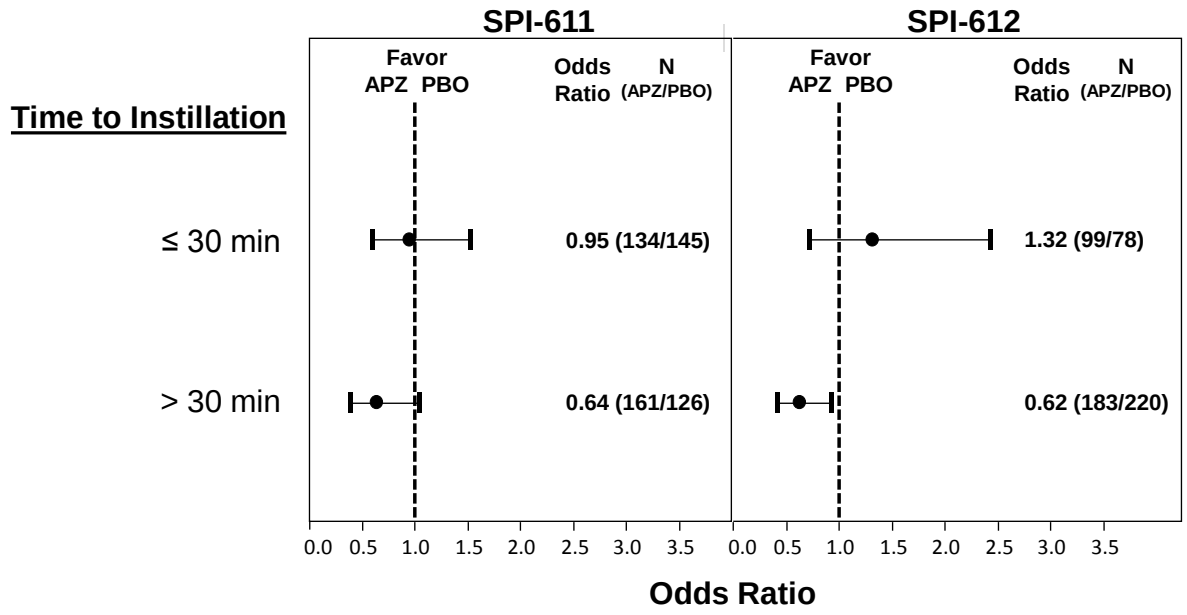
Kaplan-Meier estimates of **Time to Recurrence** by time of instillation showed apaziquone increase **Time to Recurrence** in both studies for patients with instillations at >30 minutes post-TURBT:

- In **SPI-611**, **Time to Recurrence** for patients treated with apaziquone compared to patients treated with placebo was 12.5 vs 8.3 months based on first quartile [25%] (nominal $p = 0.0328$; HR 0.66, 95% CI 0.45, 0.97) **(Figure 21A)**.

- In **SPI-612**, **Time to Recurrence** for patients treated with apaziquone compared to patients treated with placebo was 11.6 vs 6.3 months based on first quartile [25%]; (nominal p = 0.0189; HR 0.70, 95% CI 0.52, 0.95) (**Figure 21B**).

Figure 20 Two-Year Recurrence Rate Odds Ratios by Study and Time of Instillation (Target Ta, G1-G2 Population)

A) 2-Year Recurrence Rate



B) Time to Recurrence

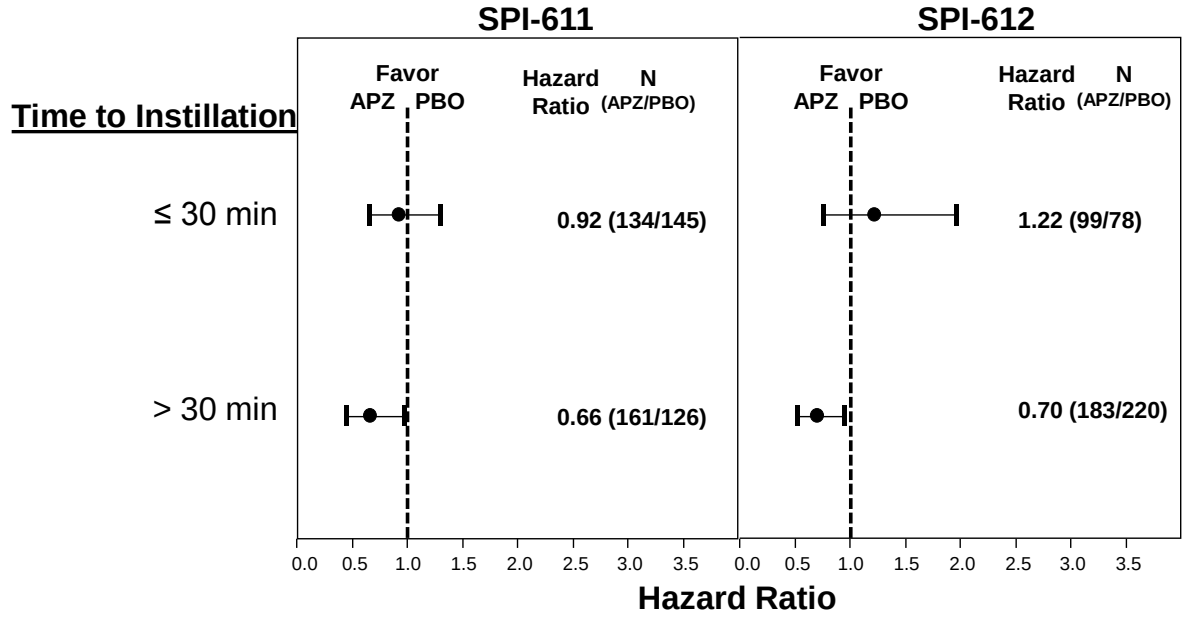
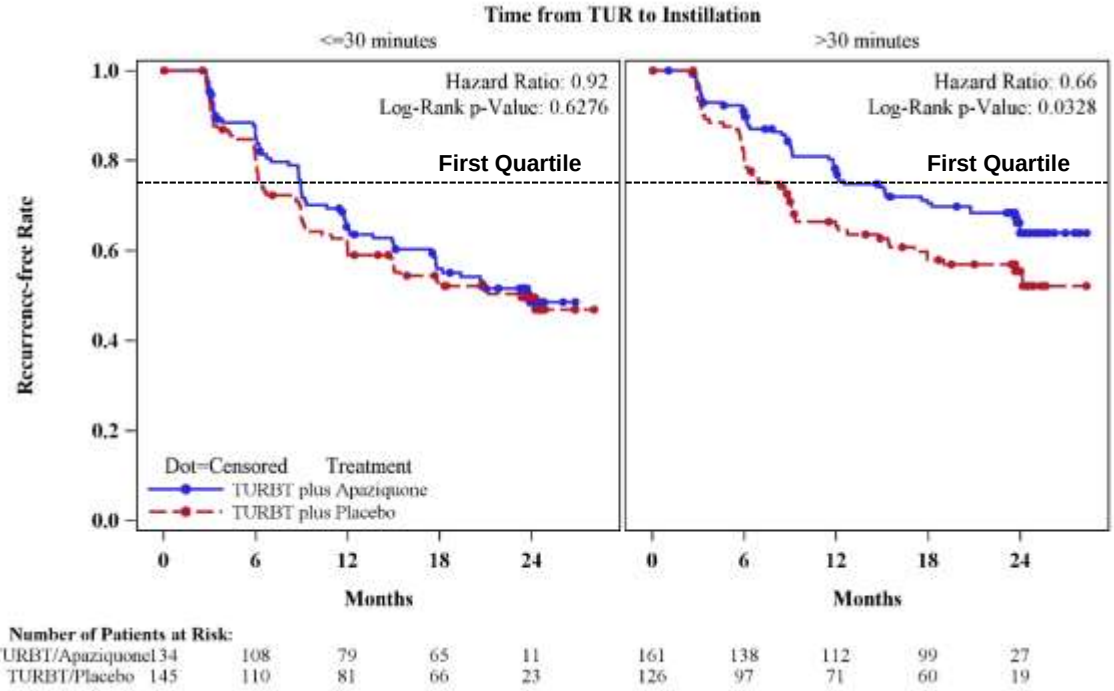
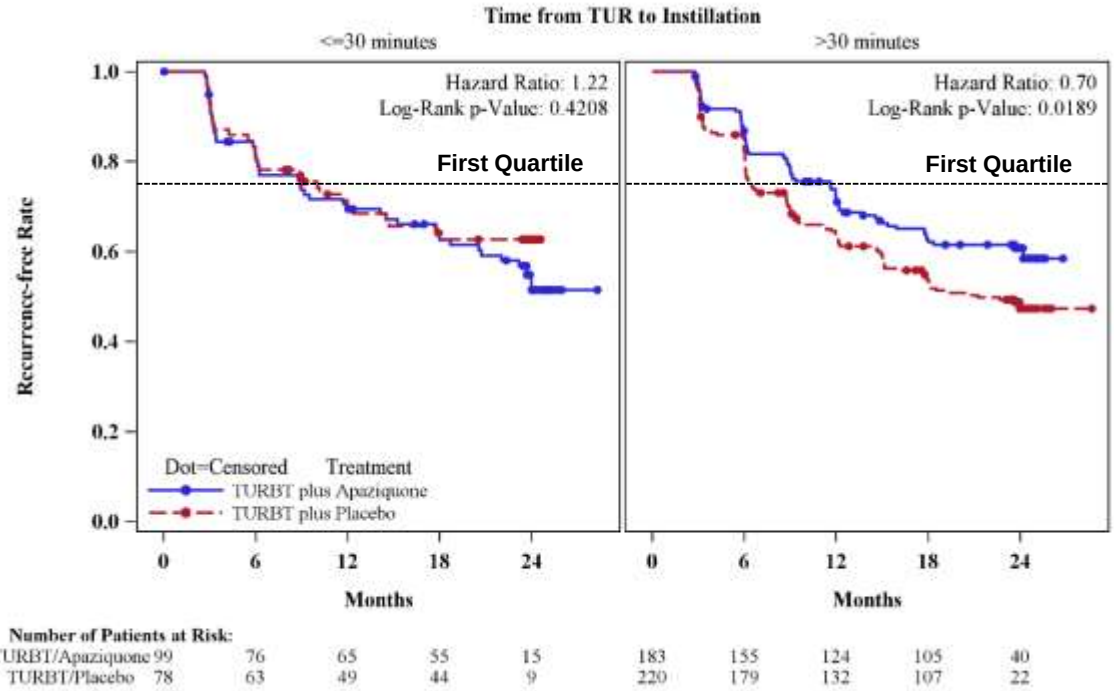


Figure 21 Kaplan-Meier Estimates of Time to Recurrence by Time of Instillation (Ta, G1-G2 Target Population)

A) SPI-611



B) SPI-612



The efficacy of apaziquone was further improved in subgroup of patients who had instillations between 31-90 minutes post-TURBT. In **SPI-611**, there was a 20.3% absolute reduction in **2-Year Recurrence Rate** for patients treated with apaziquone compared to patients treated with placebo (23.3% vs 43.6%; nominal p = 0.0346; odds ratio 0.39; 95% CI 0.16, 0.94), representing a 46.5% relative reduction compared to placebo. In **SPI-612**, there was a reproducible improvement with 20.8% absolute reduction in **2-Year Recurrence Rate** for patients treated with apaziquone compared to patients treated with placebo (33.3% vs 54.1%; nominal p = 0.0238; odds ratio 0.42; 95% CI 0.20, 0.89), representing a 38.4% relative reduction compared to placebo. The results for **Time to Recurrence** were consistent with the **2-Year Recurrence Rate** results in this subgroup of patients treated from 31-90 minutes. The results were also similar between **SPI-611** (Hazard Ratio 0.44, 95% CI 0.22, 0.90; nominal p = 0.0202, log-rank test) and **SPI-612** (Hazard Ratio 0.55, 95% CI 0.31, 0.97; nominal p = 0.0344, log-rank test). There were improvements in **2-Year Recurrence Rate** and **Time to Recurrence** in patients treated from 31-90 minutes post-TURBT in **SPI-611** and **SPI-612** that were clinically meaningful and were similar and reproducible between **SPI-611** and **SPI-612**.

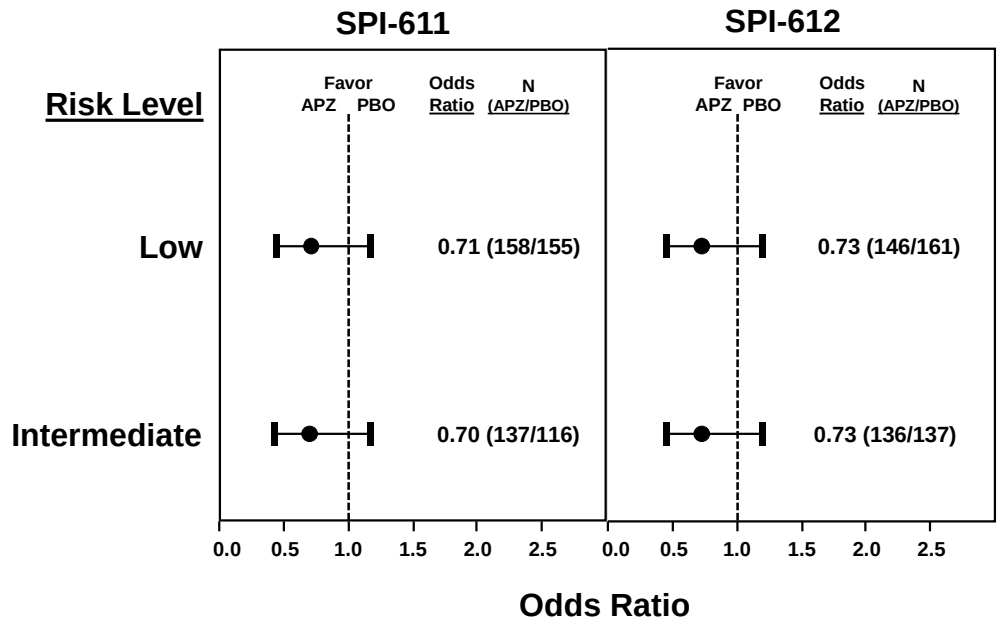
Given the impact of the timing of instillation of apaziquone post-TURBT observed in **SPI-611** and **SPI-612** studies, Spectrum proposes to recommend dosing with apaziquone after 30 minutes post-TURBT in the proposed labeling.

5.2.2.3.5.4 Risk Category

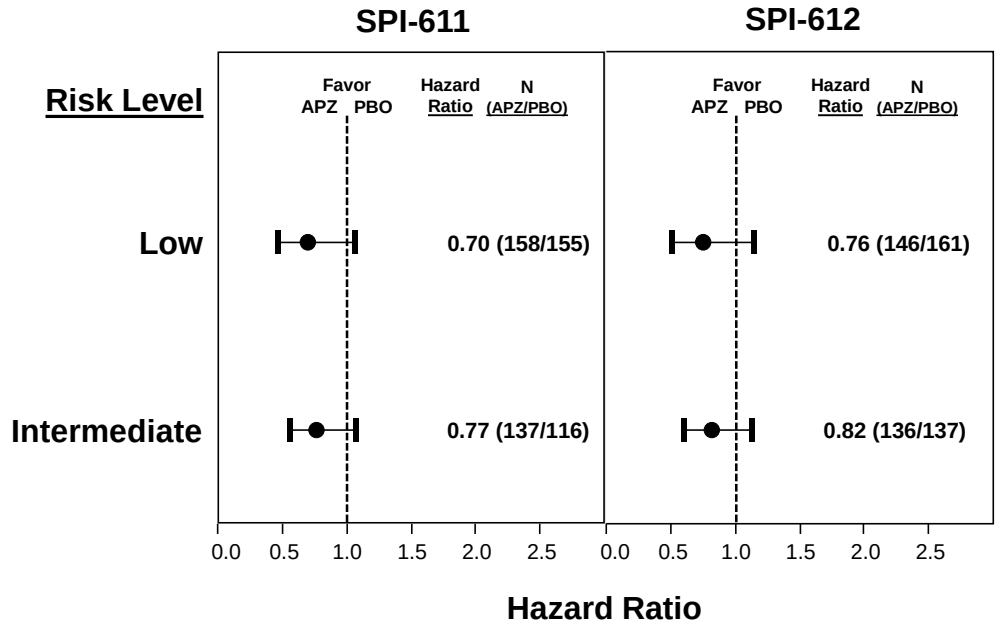
Based on 2016 AUA guideline **(Table 3)**, Spectrum further classified the **Ta, G1-G2 Target Population** in **SPI-611** and **SPI-612** into low- and intermediate-risk. Patients with tumor grade G2 were considered as low grade in order to be classified for AUA risk. In **SPI-611**, 313 patients were low-risk and 253 patients were intermediate-risk. In **SPI-612**, 307 patients were low-risk and 273 patients were intermediate-risk. As shown in **Figure 22**, the OR and HR were very similar between low- and intermediate-risk groups and all were in favor of apaziquone.

Figure 22 Two-Year Recurrence Rate and Time to Recurrence by Risk Level (Ta, G1-G2 Target Population)

A) 2-Year Recurrence Rate



B) Time to Recurrence



5.3 Efficacy Conclusions

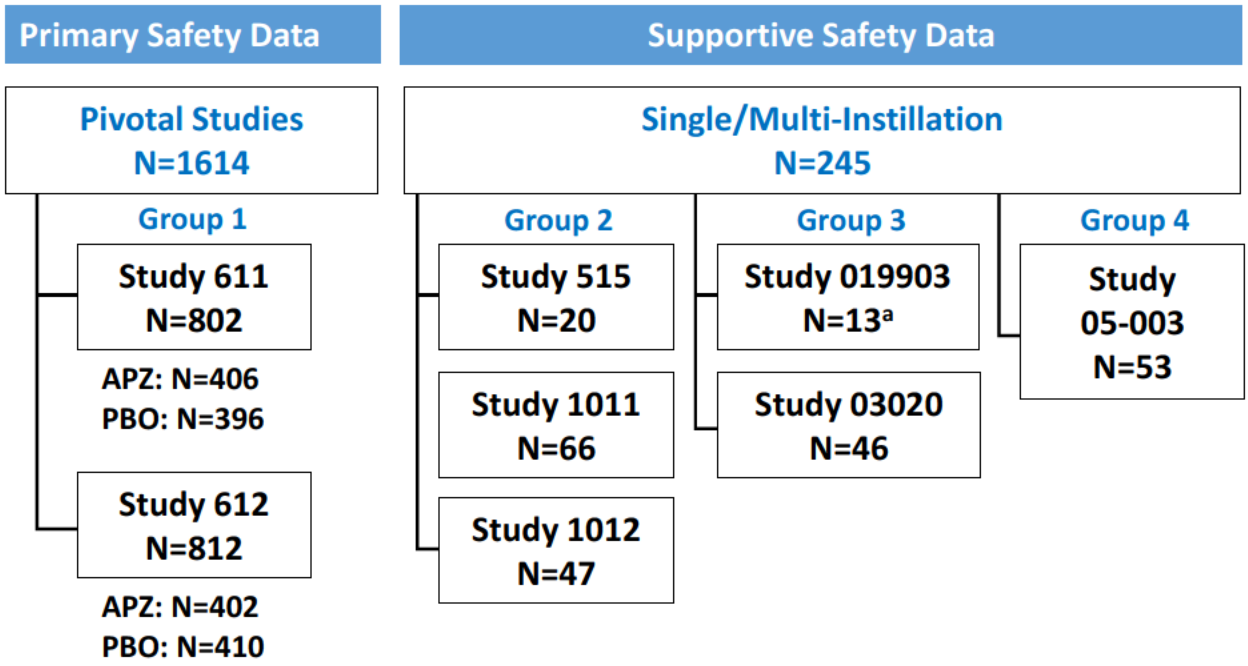
- Based on the results from a Phase 1 dose-escalation study (**ND-019903**), the dose of apaziquone selected for the Phase 3 clinical program was 4 mg in 40 mL diluent.
- Two Phase 2 marker lesion studies (**ND-019903** and **ND-03020**) both showed that 67% of patients had a complete response with no evidence of lesions 2 to 4 weeks after the last apaziquone instillation.
- Efficacy results were consistent between endpoints in two pivotal Phase 3 studies (**SPI-611** and **SPI-612**).
- Intravesical instillation of a single dose of apaziquone within 6 hours post-TURBT in patients with NMIBC in two independent Phase 3 studies (**SPI-611** and **SPI-612**) provided clinically meaningful improvements in the primary efficacy endpoint (**2-Year Recurrence Rate**) and the key secondary endpoint (**Time to Recurrence**), compared to placebo.
- In both **SPI-611** and **SPI-612**, the efficacy of apaziquone was greater when apaziquone was administered more than 30 minutes post-TURBT, suggesting that this is a better time for apaziquone instillation post-TURBT.
- The results of the secondary endpoint analyses generally supported the primary and key-secondary analyses for both **SPI-611** and **SPI-612**.
- The mean Number of Recurrences per patient at 2 Years was numerically lower in the apaziquone group in both studies (**SPI-611** and **SPI-612**) compared with placebo (0.6 vs 0.9 in both studies).
- Results from the subgroup analyses generally supported the primary analyses with each comparison favoring apaziquone.
- The totality of the efficacy data supports the efficacy of apaziquone as a single 4-mg dose, administered intravesically in a volume of 40 mL (0.1 mg/mL) of diluent, instilled into the bladder after 30 minutes post-TURBT and retained in the bladder for a period of 1 hour.

6 CLINICAL SAFETY RESULTS

6.1 Overview of Studies

The clinical safety of apaziquone was evaluated using data from 1859 patients (1053 patients treated with apaziquone) who participated in 8 Sponsor-conducted clinical studies (**Figure 23**). The majority of data came from the two pivotal studies, **SPI-611** and **SPI-612** comparing the safety of a single intravesical instillation of apaziquone (n=808) or placebo (n=806) in the post-TURBT setting. Supportive data were from the other six studies of apaziquone, which were pooled according to number of instillations (single/multiple); safety in high-risk patients was analyzed separately.

Figure 23 Eight Studies Assessed the Clinical Safety of Apaziquone



a) One patient received only part of the first instillation and is included in safety analyses but not efficacy analyses.

6.2 Primary Safety Data (SPI-611 and SPI-612)

6.2.1 Extent of Exposure

The extent of exposure to apaziquone or placebo, including study duration, duration of instillate retention, and volume of instillate, was similar in the two primary safety studies (**SPI-611** and **SPI-612**) (**Table 16**). In general, the median study duration was nearly 2 years (23.8 months). Post-TURBT, a single intravesical instillation of 40 mL was retained within the bladder for a median of 60 minutes. Although the median time from TURBT to instillation was slightly longer in **SPI-612** than in **SPI-611**, the distribution for each study was approximately the same.

Table 16 Extent of Overall Apaziquone Exposure (Primary Safety Studies)

Category	SPI-611		SPI-612		Overall	
	APZ (n=406)	PBO (n=396)	APZ (n=402)	PBO (n=410)	APZ (n=808)	PBO (n=806)
Study Duration (months)						
Median	23.8	23.8	23.7	23.8	23.8	23.8
Min, Max	0.2, 31.2	0.6, 29.5	1.9, 31.5	0.7, 30.6	0.2, 31.5	0.6, 30.6
Time from TURBT (hours)						
Median	0.8	0.5	1.3	1.6	1.0	1.1
Min, Max	-0.1, 5.9	-0.3, 5.5	-0.1, 5.8	-0.2, 5.9	-0.1, 5.9	-0.3, 5.9
Volume of Instillate (mL)						
Median	40.0	40.0	40.0	40.0	40.0	40.0
Min, Max	40.0, 40.0	37.0, 40.0	40.0, 40.0	20.0, 45.0	40.0, 40.0	20.0, 45.0
Duration of Retention (minutes)						
Median	60.0	60.0	60.0	60.0	60.0	60.0
Min, Max	13.0, 73.0	37.0, 75.0	7.0, 100.0	36.0, 99.0	7.0, 100.0	36.0, 99.0

APZ=apaziquone; Max=maximum; Min=minimum; PBO=placebo; TURBT=transurethral resection of bladder tumor.

6.2.2 Overview of Adverse Events

Approximately 80% of patients in the primary safety studies (**SPI-611** and **SPI-612**) experienced at least one treatment-emergent AE (TEAE), regardless of treatment group (**Table 17**). The majority of these TEAEs were Grade 1 or Grade 2 severity. The incidence of treatment-related TEAEs was low and did not exceed 13% in either group. A similar percentage of serious AEs occurred in apaziquone- and placebo-treated patients (23.4% vs 25.6%, respectively). Only two patients experienced SAEs that were reported as possibly treatment related, and no patients discontinued due to treatment-related TEAEs. Although 25 (3.1%) apaziquone-treated patients and 27 (3.3%) placebo-treated patients died during the course of the 2 pivotal studies, all of these occurred at least 30 days after the dose administration and none of the deaths were considered to be treatment related.

Table 17 Overall Summary of Adverse Events in Pivotal Clinical Studies (Primary Safety Studies)

Characteristic/ Category	SPI-611		SPI-612		Overall	
	APZ (n=406)	PBO (n=396)	APZ (n=402)	PBO (n=410)	APZ (n=808)	PBO (n=806)
Any TEAE, n (%)	**326 (80.3)**	**298 (75.3)**	**320 (79.6)**	**335 (81.7)**	**646 (80.0)**	**633 (78.5)**
All Grade 1-2	316 (77.8)	286 (72.2)	315 (78.4)	326 (79.5)	631 (78.1)	612 (75.9)
All Grade 3-4	76 (18.7)	85 (21.5)	67 (16.7)	80 (19.5)	143 (17.7)	165 (20.5)
All Grade 3	75 (18.5)	81 (20.5)	65 (16.2)	77 (18.8)	140 (17.3)	158 (19.6)
All Grade 4	3 (0.7)	8 (2.0)	5 (1.2)	5 (1.2)	8 (1.0)	13 (1.6)
All Grade 5	11 (2.7)	13 (3.3)	14 (3.5)	14 (3.4)	25 (3.1)	27 (3.3)
Any SAE, n (%)	**93 (22.9)**	**98 (24.7)**	**96 (23.9)**	**108 (26.3)**	**189 (23.4)**	**206 (25.6)**
All SAEs Other Than Death	92 (22.7)	96 (24.2)	93 (23.1)	101 (24.6)	185 (22.9)	197 (24.4)
All Treatment-Related SAEs	0	0	2 (0.5)	0	2 (0.2)	0
Any TEAE Leading to Discontinuation	**14 (3.4)**	**17 (4.3)**	**18 (4.5)**	**17 (4.1)**	**32 (4.0)**	**34 (4.2)**
All Treatment-Related TEAEs Leading to Discontinuation	0	0	0	0	0	0
Any Treatment-Related AE	**51 (12.6)**	**50 (12.6)**	**42 (10.4)**	**40 (9.8)**	**93 (11.5)**	**90 (11.2)**
All Grade 1-2 Treatment-Related AEs	50 (12.3)	50 (12.6)	38 (9.5)	40 (9.8)	88 (10.9)	90 (11.2)
All Grade 3-4 [a]	1 (0.2)	0	5 (1.2)	2 (0.5)	6 (0.7)	2 (0.2)
All Grade 5	0	0	0	0	0	0

AE=adverse event; APZ=apaziquone; PBO=placebo; SAE=serious adverse event; TEAE=treatment-emergent adverse event.
a) All AEs were Grade 3 in severity.

6.2.3 Common Treatment-Emergent Adverse Events

The most common (>5%) TEAEs and most common System Organ Classes (SOCs) with TEAEs (≥15%) in the primary safety studies are summarized in **Table 18** and **Table 19**, respectively. No clinically meaningful differences in the incidence of TEAEs were observed between apaziquone- and placebo-treated patients. Approximately 50% of patients in both treatment groups and in both studies experienced TEAEs in the **Renal and Urinary Disorders SOC**, with the most common TEAEs being dysuria, urinary tract infection, hematuria, and pollakiuria. The only other most common TEAEs not classified in this SOC were procedural pain and urinary tract infection—both of which are related to the urinary system. The incidence of these AEs was similar between patients administered apaziquone and patients administered placebo.

Table 18 Most Common Treatment-Emergent Adverse Events (>5%) of Any Causality by Preferred Term in Pivotal Clinical Studies (Primary Safety Studies)

Adverse Event Preferred Term	SPI-611		SPI-612		Overall	
	APZ (n=406)	PBO (n=396)	APZ (n=402)	PBO (n=410)	APZ (n=808)	PBO (n=806)
Any TEAE	**326 (80.3)**	**298 (75.3)**	**320 (79.6)**	**335 (81.7)**	**646 (80.0)**	**633 (78.5)**
Dysuria	74 (18.2)	67 (16.9)	86 (21.4)	62 (15.1)	160 (19.8)	129 (16.0)
Urinary Tract Infection	70 (17.2)	60 (15.2)	88 (21.9)	90 (22.0)	158 (19.6)	150 (18.6)
Hematuria	42 (10.3)	62 (15.7)	72 (17.9)	79 (19.3)	114 (14.1)	141 (17.5)
Pollakiuria	39 (9.6)	46 (11.6)	43 (10.7)	39 (9.5)	82 (10.1)	85 (10.5)
Micturition Urgency	31 (7.6)	37 (9.3)	31 (7.7)	37 (9.0)	62 (7.7)	74 (9.2)
Bladder Pain	22 (5.4)	18 (4.5)	30 (7.5)	25 (6.1)	52 (6.4)	43 (5.3)
Urinary Retention	18 (4.4)	31 (7.8)	30 (7.5)	30 (7.3)	48 (5.9)	61 (7.6)
Procedural Pain	31 (7.6)	27 (6.8)	14 (3.5)	22 (5.4)	45 (5.6)	49 (6.1)
Bladder Spasm	29 (7.1)	23 (5.8)	12 (3.0)	14 (3.4)	41 (5.1)	37 (4.6)

APZ=apaziquone; PBO=placebo; TEAE=treatment-emergent adverse event.

Table 19 Most Common System Organ Classes with Adverse Events in ≥15% of Patients in Pivotal Clinical Studies (Primary Safety Studies)

System Organ Class	SPI-611		SPI-612		Overall	
	APZ (n=406)	PBO (n=396)	APZ (n=402)	PBO (n=410)	APZ (n=808)	PBO (n=806)
Number of Patients Having at Least One TEAE	**326 (80.3)**	**298 (75.3)**	**320 (79.6)**	**335 (81.7)**	**646 (80.0)**	**633 (78.5)**
Renal and Urinary Disorders	196 (48.3)	210 (53.0)	222 (55.2)	213 (52.0)	418 (51.7)	423 (52.5)
Infections and Infestations	114 (28.1)	103 (26.0)	125 (31.1)	133 (32.4)	239 (29.6)	236 (29.3)
Gastrointestinal Disorders	66 (16.3)	66 (16.7)	69 (17.2)	75 (18.3)	135 (16.7)	141 (17.5)
Reproductive System and Breast Disorders	46 (11.3)	39 (9.8)	51 (12.7)	65 (15.9)	97 (12.0)	104 (12.9)

APZ=apaziquone; PBO=placebo; TEAE=treatment-emergent adverse event.

6.2.3.1 Treatment-Related Adverse Events

Few AEs (11.5% vs. 11.2% for apaziquone- and placebo-treated patients, respectively) were assessed by the Investigators as related to study treatment in either primary study (**SPI-611** and

SPI-612). Of the treatment-related TEAEs that were reported in at least 1% of patients in either group, all occurred within the urinary tract, and none of these AEs occurred in more than 5% of patients in either study (**Table 20**).

Table 20 Most Common (≥1%) Treatment-Related Adverse Events by Preferred Term in Pivotal Clinical Studies (Primary Safety Studies)

Characteristic/ Category	SPI-611		SPI-612		Overall	
	APZ (n=406)	PBO (n=396)	APZ (n=402)	PBO (n=410)	APZ (n=808)	PBO (n=806)
Any Treatment-Related TEAE	**51 (12.6)**	**50 (12.6)**	**42 (10.4)**	**40 (9.8)**	**93 (11.5)**	**90 (11.2)**
Dysuria	20 (4.9)	19 (4.8)	17 (4.2)	14 (3.4)	37 (4.6)	33 (4.1)
Bladder Spasm	8 (2.0)	5 (1.3)	3 (0.7)	4 (1.0)	11 (1.4)	9 (1.1)
Micturition Urgency	5 (1.2)	13 (3.3)	6 (1.5)	3 (0.7)	11 (1.4)	16 (2.0)
Bladder Pain	5 (1.2)	3 (0.8)	5 (1.2)	1 (0.2)	10 (1.2)	4 (0.5)
Hematuria	1 (0.2)	12 (3.0)	7 (1.7)	2 (0.5)	8 (1.0)	14 (1.7)
Urinary Tract Infection	4 (1.0)	1 (0.3)	4 (1.0)	0	8 (1.0)	1 (0.1)
Pollakiuria	4 (1.0)	10 (2.5)	2 (0.5)	5 (1.2)	6 (0.7)	15 (1.9)

APZ=apaziquone; PBO=placebo; TEAE=treatment-emergent adverse event.

6.2.3.2 Treatment-Related Severe/Life-Threatening Adverse Events

In **SPI-611**, 1 patient in the **Apaziquone Treatment Group** had a Grade 3 TEAE that was considered related to treatment. In **SPI-612** (1.2%) 5 patients in the **Apaziquone Treatment Group** and 2 patients (0.5%) in the **Placebo Treatment Group** had TEAEs of Grade 3 severity that were considered by the Investigators to be related to treatment. There were no treatment-related TEAEs of Grade 4 or Grade 5 severity in either treatment group in either study.

Table 21 Patient Listing of Treatment-Related Grade 3 Adverse Events in Pivotal Clinical Studies (Primary Safety Studies)

Investigator Term	MedDRA Preferred Term	Outcome	AE Start Day/ End Day
SPI-611			
Apaziquone			
Bladder pain	Bladder pain	Recovered/resolved	1/4
Placebo-None			
SPI-612			
Apaziquone			
Burning on urination	Dysuria	Recovered/resolved	1/2
Hematuria	Hematuria	Recovered/resolved	1/3
Bladder pain	Bladder pain	Recovered/resolved	1/2
Acute renal failure	Renal failure acute	Recovered/resolved	1/18
Macroscopic hematuria	Hematuria	Recovered/resolved	92/193
Placebo			
Pain with voiding	Dysuria	Recovered/resolved with sequelae	1/2
Urinary retention	Urinary retention	Recovered/resolved with sequelae	6/9

AE=adverse event.

6.2.3.3 Non-Fatal Serious Adverse Events

Approximately 25% of patients in **SPI-611** and in **SPI-612** reported SAEs. The incidence and types of SAEs were similar both between and within each study and between treatment groups **(Table 22)** and most of these SAEs occurred during the follow up. 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. Of these, all of the non-genitourinary SAEs are expected in an elderly population, which is the primary age group treated in these two studies. Only two patients, both in **SPI-612** and randomized to apaziquone experienced SAEs that were considered to be at least possibly treatment related **(Table 23)**. One patient had hematuria and the other acute renal failure, both Grade 3 severity. Both SAEs started on the day of study drug instillation, and both resolved. Narratives for these two patients are provided in **Appendix 4**.

Table 22 Most Common (≥1%) Serious Adverse Events by Preferred Term in Pivotal Clinical Studies (Primary Safety Studies)

Characteristic/ Category	SPI-611		SPI-612		Overall	
	APZ (n=406)	PBO (n=396)	APZ (n=402)	PBO (n=410)	APZ (n=808)	PBO (n=806)
Any Serious Adverse Event	**93 (22.9)**	**98 (24.7)**	**96 (23.9)**	**108 (26.3)**	**189 (23.4)**	**206 (25.6)**
Cardiac Failure Congestive	5 (1.2)	6 (1.5)	7 (1.7)	1 (0.2)	12 (1.5)	7 (0.9)
Hematuria	6 (1.5)	8 (2.0)	5 (1.2)	12 (2.9)	11 (1.4)	20 (2.5)
Urinary Retention	1 (0.2)	1 (0.3)	8 (2.0)	4 (1.0)	9 (1.1)	5 (0.6)
Atrial Fibrillation	6 (1.5)	0	2 (0.5)	0	8 (1.0)	0
Chronic Obstructive Pulmonary Disease	5 (1.2)	4 (1.0)	3 (0.7)	7 (1.7)	8 (1.0)	11 (1.4)
Pneumonia	5 (1.2)	7 (1.8)	3 (0.7)	3 (0.7)	8 (1.0)	10 (1.2)
Knee Arthroplasty	3 (0.7)	4 (1.0)	3 (0.7)	4 (1.0)	6 (0.7)	8 (1.0)
Coronary Artery Disease	3 (0.7)	6 (1.5)	2 (0.5)	2 (0.5)	5 (0.6)	8 (1.0)

APZ=apaziquone; PBO=placebo.

Table 23 Treatment-Related Serious Adverse Events in Pivotal Clinical Studies (Primary Safety Studies)

Patient No.	Investigator Term (Grade)	MedDRA Preferred Term	Outcome	AE Start Day/ End Day
Apaziquone-treated Patients				
612-091-2646	Hematuria (Grade 3)	Hematuria	Recovered/resolved	Day 1/Day 3
612-115-2250	Acute Renal Failure (Grade 3)	Renal Failure Acute	Recovered/resolved	Day 1/Day 18

AE=adverse event; MedDRA=Medical Dictionary for Regulatory Activities

6.2.3.4 Adverse Events Leading to Discontinuation from Study

Patients received one administration of study medication during the course of the study. There was little difference in the incidence of AEs leading to discontinuation from the study between apaziquone- and placebo-treated patients (**Table 17**), with approximately 4% of patients in each treatment group discontinuing from both studies. No individual AE leading to discontinuation was reported in more than 1% of patients, and none of the AEs leading to discontinuation were assessed as related to study treatment. All discontinuations occurred more than 30 days after treatment.

6.2.4 Deaths

In the pivotal studies, 25 (3.1%) apaziquone-treated and 27 (3.3%) placebo-treated patients had AEs that resulted in death. None of the AEs leading to death, in either treatment group, were assessed by the Investigators to be study drug or treatment-related. No patients died within 30 days of receiving study treatment. A listing of patients who died and the AE associated with each death is presented in **Appendix 3**.

6.2.5 Adverse Events of Special Interest

Genitourinary AEs are summarized in **Table 24**. Overall, genitourinary AEs were similar between studies and between treatment groups within each study.

Table 24 Most Common Genitourinary Adverse Events (>5%) of Any Causality by Preferred Term in Pivotal Clinical Studies (Primary Safety Studies)

Adverse Event Preferred Term	SPI-611		SPI-612		Overall	
	APZ (n=406)	PBO (n=396)	APZ (n=402)	PBO (n=410)	APZ (n=808)	PBO (n=806)
Dysuria	74 (18.2)	67 (16.9)	86 (21.4)	62 (15.1)	160 (19.8)	129 (16.0)
Urinary Tract Infection	70 (17.2)	60 (15.2)	88 (21.9)	90 (22.0)	158 (19.6)	150 (18.6)
Hematuria	42 (10.3)	62 (15.7)	72 (17.9)	79 (19.3)	114 (14.1)	141 (17.5)
Pollakiuria	39 (9.6)	46 (11.6)	43 (10.7)	39 (9.5)	82 (10.1)	85 (10.5)
Micturition Urgency	31 (7.6)	37 (9.3)	31 (7.7)	37 (9.0)	62 (7.7)	74 (9.2)
Bladder Pain	22 (5.4)	18 (4.5)	30 (7.5)	25 (6.1)	52 (6.4)	43 (5.3)
Urinary Retention	18 (4.4)	31 (7.8)	30 (7.5)	30 (7.3)	48 (5.9)	61 (7.6)
Bladder Spasm	29 (7.1)	23 (5.8)	12 (3.0)	14 (3.4)	41 (5.1)	37 (4.6)

APZ=apaziquone; PBO=placebo; TEAE=treatment-emergent adverse event

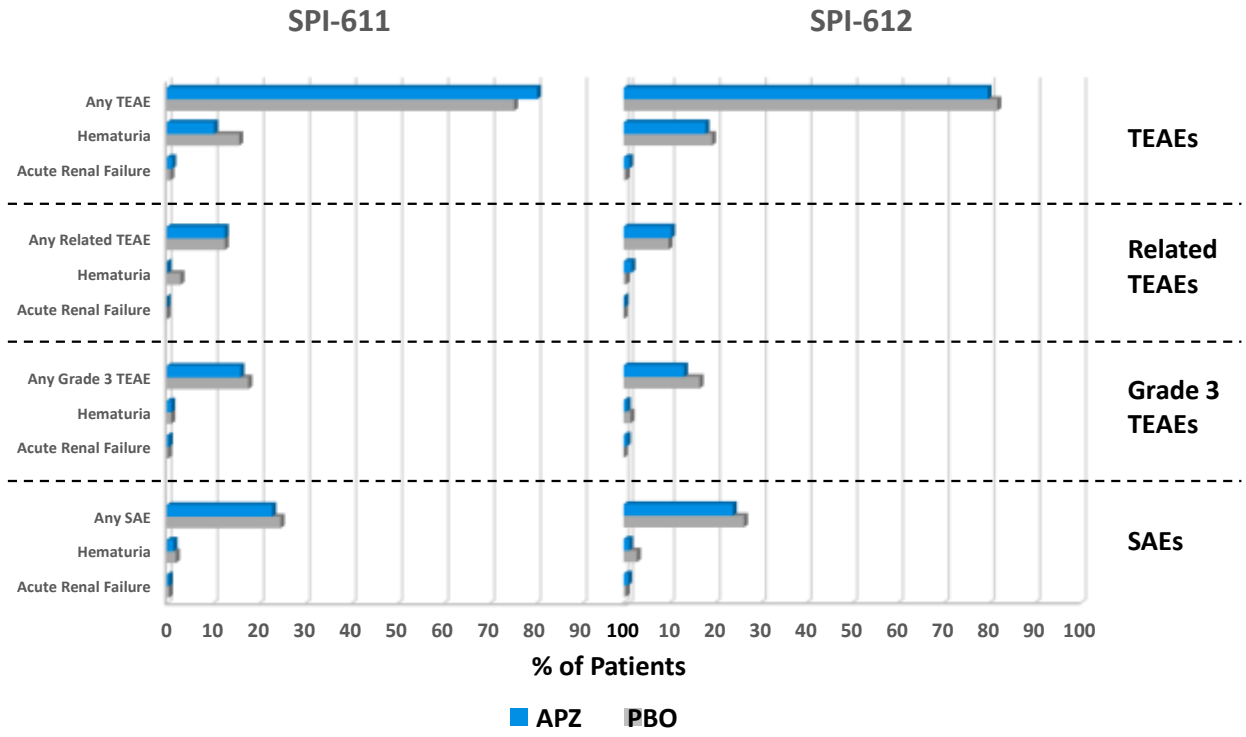
As noted in **Section 6.2.3.3**, one patient experienced a treatment-related SAE of Grade 3 hematuria and one a treatment-related SAE of Grade 3 acute renal failure, both starting on the day of instillation and resolving on Day 3 and Day 18, respectively. Another patient **(612-083-2389)** died due to acute renal failure 624 days after the last dose, and the event was not assessed to be treatment-related; a narrative for this patient is provided in **Appendix 4**. All three patients were enrolled in **SPI-612** and had been treated with apaziquone.

Acute renal failure was experienced by 15 patients, including 10 treated with apaziquone and 5 with placebo; of these, only 1 patient had acute renal failure that was attributed to study drug (apaziquone). Except for the patient who died due to acute renal failure (**Appendix 4**), the highest grade severity for each patient was Grade 3. The TURBT procedure for the patient who died from acute renal failure lasted 20 minutes. Renal insufficiency or failure is also a noted side effect of TURBT, and its incidence increases significantly with the duration of the procedure,

rising from 0.3% in procedures lasting less than 30 minutes to 1.2% in procedures lasting more than 90 minutes ($p = 0.002$) **[52]**.

The numbers of patients experiencing hematuria were similar between treatment groups, and in most patients, the investigator did not attribute hematuria to study drug. The maximum severity of hematuria was Grade 3. For comparison purposes, all other data related to hematuria and acute renal failure are presented in **Figure 24**.

Figure 24 Hematuria and Acute Renal (Primary Safety Studies)



6.2.6 Clinical Laboratory Data

There were no trends in changes from baseline in any hematologic, liver, kidney, or metabolic parameter in either of the pivotal safety studies. No clinically meaningful differences in hematology or chemistry parameters were observed between apaziquone and placebo treatment groups.

6.2.7 Vital Signs

Blood pressure, heart rate, and oral body temperature evaluations showed no consistent changes of clinical relevance, and remained within the range observed for healthy male and female subjects

6.2.8 Functional Bladder Capacity

In **SPI-611** a subset of patients was evaluated for functional bladder capacity. Frequency of urination, voided volume, and total bladder volume showed no statistically significant changes

from **Baseline** in either the **Apaziquone Treatment** or the **Placebo Treatment Group** (all p-values >0.05, paired t-test) (**Table 25**).

Table 25 Functional Bladder Capacity by Time in Pivotal Clinical Study SPI-611

	APZ (N=98)	PBO (N=93)
Baseline		
N	98	93
Mean (SD), mL	250.1 (187.95)	236.5 (183.88)
Median	199	185
Min, Max	30 - 1015	10 - 969
Visit 6: Month 12		
N	68	61
Mean (SD) Volume, mL	171.2 (169.61)	158.1 (103.20)
Median	120	120
Min, Max	0 - 985	30 - 431
Change from Baseline to Visit 6: Month 12		
Mean Change (SD), mL	-85.6 (180.75)	-65.9 (163.62)
Median Volume Change, mL	-58	-33
Min, Max	-613 - 495	-598 - 254
Mean % Change (SD)	-12.8 (78.05)	-0.8 (86.97)
Median % Change	-34	-25
p-value [a]	0.1808	0.9395
Visit 10: Month 24		
N	66	58
Mean (SD) Volume, mL	181.7 (169.20)	165.5 (137.65)
Median Volume, mL	133	120
Min, Max	0 - 830	0 - 601
Change from Baseline to Visit 10: Month 24		
Mean Volume Change (SD), mL	-52.4 (200.56)	-67.0 (166.73)
Median Volume Change, mL	-39	-43
Min, Max	-626 - 441	-614 - 201
Mean % Change (SD)	2.6 (109.28)	2.9 (130.23)
Median % Change	-28	-24
p-value [a]	0.8484	0.8660

a) p-values for % change from baseline are from one-sample T-test

6.3 Supportive Safety Studies

Supportive safety data came from the other 6 Sponsor-initiated studies, which included the two marker lesion studies (**ND-019903, ND-03020**), the Phase 2 pilot study (**SPI-515**), the discontinued Phase 3 studies (**SPI-1011** and **SPI-1012**), and an uncontrolled, open-label study that was conducted in patients with high-risk NMBIC (**SPI-05-003**) in these studies **(Figure 23)**. Among the 245 patients in these studies, 139 received multiple instillations of apaziquone. There were six studies that were divided into 3 groups:

- **Group 2:** Studies **SPI-515**, **SPI-1011**, and **SPI-1012**
- **Group 3:** Studies **ND-019903** and **ND-03020**
- **Group 4:** Study: **SPI-05-003**

The incidence of TEAEs was similar between these supportive studies and the primary studies. Approximately 61% of patients receiving single instillations of apaziquone and 63% to 92.5% receiving multiple instillations experienced at least one TEAE **(Table 26)**. The majority of these TEAEs were Grade 1 or Grade 2 severity. The incidence of Grade 3-4 TEAEs is relatively higher in patients receiving multiple instillations. The incidence of SAEs was 8.5% in patients receiving single instillations of apaziquone and ranged from 3.8% to 10.2% in the groups of patients receiving multiple instillations of apaziquone. No patients in the supportive safety studies discontinued due to AEs and there were no deaths reported.

Table 26 Overall Summary of Adverse Events (Groups 2 through 4; Supportive Safety Studies)

Characteristic/ Category	Group 2[a] Apaziquone		Group 3[a] Apaziquone Multiple Instillation (n=59)	Group 4[a] Apaziquone Multiple Instillation (n=53)
	Single Instillation (n=106)	Multiple Instillation (n=27)		
Any TEAE, n (%)	**65 (61.3)**	**17 (63.0)**	**49 (83.1)**	**49 (92.5)**
Grade 1-2	63 (59.4)	16 (59.3)	49 (83.1)	49 (92.5)
Grade 3-4	7 (6.6)	7 (25.9)	4 (6.8)	7 (13.2)
Grade 3	7 (6.6)	7 (25.9)	4 (6.8)	7 (13.2)
Grade 4	1 (0.9)	0	0	1 (1.9)
Grade 5	0	0	0	0
Any SAE, n (%)	**9 (8.5)**	**2 (7.4)**	**6 (10.2)**	**2 (3.8)**
SAE Other Than Death	9 (8.5)	2 (7.4)	6 (10.2)	2 (3.8)
Treatment-related SAE	3 (2.8)	0	4 (6.8)	0
Any AE Leading to Discontinuation	**0**	**0**	**0**	**0**
Treatment-related Leading to Discontinuation	0	0	0	0
Any Treatment-Related AE	**26 (24.5)**	**10 (37.0)**	**33 (55.9)**	**29 (54.7)**
Grade 1-2	25 (23.6)	9 (33.3)	33 (55.9)	29 (54.7)
Grade 3-4	2 (1.9)	5 (18.5)	3 (5.1)	3 (5.7)
Grade 3	2 (1.9)	5 (18.5)	3 (5.1)	3 (5.7)
Grade 4	0	0	0	0

a) See **Figure 23** for studies included in each group.

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 (approximately 15% to 46%) among patients receiving multiple instillations of apaziquone (**Table 27**).

Table 27 Most Common Treatment-emergent Adverse Events of Any Causality by Preferred Term (Groups 2 through 4; Supportive Safety Studies)

Characteristic/ Category	Group 2[a] Apaziquone		Group 3[a] Apaziquone Multiple Instillation (n=59)[d]	Group 4[a] Apaziquone Multiple Instillation (n=53)[e]
	Single Instillation (n=106)[b]	Multiple Instillation (n=27)[c]		
Number (%) of Patients Having at Least One TEAE	**65 (61.3)**	**17 (63.0)**	**49 (83.1)**	**49 (92.5)**
Dysuria	12 (11.3)	5 (18.5)	20 (33.9)	18 (34.0)
Urinary Tract Infection	7 (6.6)	3 (11.1)	8 (13.6)	7 (13.2)
Hematuria	16 (15.1)	4 (14.8)	27 (45.8)	15 (28.3)
Pollakiuria	7 (6.6)	5 (18.5)	11 (18.6)	11 (20.8)
Micturition Urgency	3 (2.8)	4 (14.8)	9 (15.3)	12 (22.6)
Bladder Pain	1 (0.9)	2 (7.4)	3 (5.1)	0
Urinary Retention	8 (7.5)	2 (7.4)	3 (5.1)	3 (5.7)
Procedural Pain	6 (5.7)	0	0	0
Constipation	5 (4.7)	2 (7.4)	0	1 (1.9)
Urge Incontinence	0	2 (7.4)	1 (1.7)	1 (1.9)
Nocturia	1 (0.9)	2 (7.4)	0	3 (5.7)

a) See **Figure 23** for studies included in each group.
b) Other TEAEs occurring in ≥5% of patients in this group included nausea (6.6%).
c) Other TEAEs occurring in ≥5% of patients in this group included urine analysis abnormal (11.1%) and hemorrhage urinary tract, hypercholesterolemia, and urinary tract pain (7.4% each)
d) Other TEAEs occurring in ≥5% of patients in this group included hemorrhage urinary tract (11.9%), pyrexia (8.5%), abdominal pain lower, fatigue, headache, and pruritus genital (all 6.8%), and hypertension (5.1%).
e) Other TEAEs occurring in ≥5% of patients in this group included cystitis bacterial and fatigue (both 11.3%), influenza (9.4%), pruritus, pruritus genital, and pyrexia (all 7.5%), and hemorrhage urinary tract and nausea (each 5.7%).

Treatment-related SAEs were reported for three patients who received single instillations of apaziquone (pelvic pain, postoperative urinary retention, and hematuria) and four patients receiving multiple instillations of apaziquone (dysuria, hematuria and hemorrhage urinary tract, chemical cystitis, pollakiuria); all patients recovered.

6.4 Safety Conclusions

In this large safety database of 1859 patients, including 1053 patients treated with apaziquone, from the pivotal safety studies and supportive safety studies, the totality of the data supports the safety of a single intravesical instillation of apaziquone in the post-TURBT setting. Apaziquone was well tolerated with minimal toxicity compared to placebo and there was a high degree of consistency between **SPI-611** and **SPI-612** in the reported events.

- Incidence of AEs and SAEs between apaziquone and placebo were similar in the primary safety studies **SPI-611** and **SPI-612**.
- Based on clinical laboratory assessments, there were no clinically meaningful changes in any hematologic, liver, kidney, or metabolic parameter for either the apaziquone or placebo group.
- No unexpected safety signals were identified and the AE profile of apaziquone instillation was reflective of what would be expected from the TURBT procedure itself, and most were not treatment-related.
- None of the reported deaths were related to study drug, and no patients died within 30 days of receiving study drug.
- Data from the six supportive safety studies support the safety results from the pivotal safety studies.

Apaziquone administered intravesically at 4 mg/40 mL post-TURBT was well tolerated and the safety profile was indistinguishable from placebo.

7 BENEFIT-RISK ASSESSMENT AND CONCLUSIONS

Noting the need for new, and better studied, therapies, the Bladder Cancer Task Force and the NCI recently acknowledged the lack of trials in NMIBC within the NCTN **[29]**. To help address the unmet need for the treatment of low-grade Ta/low-risk NMIBC, Spectrum has conducted a development program for apaziquone, a novel, fully synthetic, bioreductive alkylating indoloquinone, for immediate intravesical instillation post-TURBT. Spectrum submitted the NDA for apaziquone in November 2015 and if approved, apaziquone would meet a large area of therapeutic unmet need and be the first new drug approved for NMIBC in over 40 years. The totality of the data presented supports the safety and tolerability of apaziquone. The efficacy data from each pivotal study support a clinically meaningful benefit, and statistically significant when the data from the two pivotal studies is combined.

7.1 Nonclinical Studies Support the use of Intravesical Apaziquone in Patients with NMIBC

Apaziquone is a pro-drug that is enzymatically reduced by the enzyme DT-diaphorase to generate cytotoxic species. The basic mechanism of action is thought to be similar to that of other indolequinones, involving reduction by cellular enzymes that transfer one or two electrons, forming semiquinone and hydroquinone, respectively **[31]**. Apaziquone displays high potency against a broad spectrum of tumor lines, including human bladder cancer **[32-34]**. Importantly, the in vitro potency of apaziquone is 30- to 100-fold higher than that of MMC.

In-vitro studies show important features of apaziquone as a chemotherapeutic agent for bladder cancer. Apaziquone has a short half-life when administered intravenously. It is cleared from plasma rapidly, is quickly metabolized by red blood cells, and is converted to several inactive metabolites and an inactive degradation product seen only in urine. Even at a total dose seven times higher than the intended clinical dose of apaziquone in humans (4 mg) and 16 times higher than the intended clinical concentration (0.1 mg/mL), systemic exposure to apaziquone after intravesical instillation in dogs was minimal, and was most often below the LLOQ. Given that systemic absorption of apaziquone after intravesical administration is minimal, the likelihood of interaction with concomitant medications or the emergence of any systemic side effects is minimal. These are important considerations, given that bladder cancer occurs mainly in older people who often have medical comorbidities that may be treated with concurrent medications **[4]**.

Because apaziquone has demonstrated *in vitro* potency and is rapidly eliminated after systemic administration, it is ideally suited for local delivery to superficial tumors in the bladder by intravesical instillation. Thus, the intended indication for apaziquone is for intravesical instillation post-TURBT in patients with low-NMIBC. The goal of such therapy is to prevent or delay recurrence and prolong the time to repeat TURBT.

7.2 The Apaziquone Clinical Development Program Demonstrated the Safety and Efficacy of a Single Intravesical Instillation of Apaziquone

Data from the apaziquone clinical development program demonstrated the safety and efficacy of a single intravesical instillation of apaziquone (4 mg in 40 mL) post-TURBT for the treatment of patients with NMIBC. The primary basis for the safety and efficacy claims for intravesical apaziquone come from data from the two nearly identical pivotal Phase 3, randomized, double-blind, placebo-controlled, studies (**SPI-611**; **SPI-612**) that enrolled 1614 patients with clinically

apparent Stage Ta, Grade G1-G2 NMIBC. The primary efficacy endpoint of both studies was the **2-Year Recurrence Rate** of bladder cancer in randomized patients with low-grade (Ta, G1-G2) NMIBC who underwent TURBT followed by apaziquone instillation versus those who underwent TURBT followed by placebo instillation. An independent central pathology laboratory blinded to the treatment assignments performed definitive histologic assessment for eligibility for inclusion in the **Ta, G1-G2 Target Population** and outcome. **Time to Recurrence**, defined as time from randomization to date of first histologically confirmed recurrence of the patient's bladder tumor, was the key secondary endpoint in the studies. In addition to the data from these two pivotal studies, supportive efficacy data were provided by four additional clinical studies and supportive safety data from 6 additional clinical studies.

7.2.1 Efficacy

The intravesical instillation of a single dose of apaziquone within 6 hours post-TURBT in patients with NMIBC in two independent Phase 3 studies (**SPI-611** and **SPI-612**). While the primary endpoint was not met, apaziquone provided clinically meaningful improvements in the primary efficacy endpoint (**2-Year Recurrence Rate**) and the key secondary endpoint (**Time to Recurrence**), compared to placebo.

The absolute reduction in **2-Year Recurrence Rate** seen in **SPI-611** and **SPI-612** for the **Ta, G1-G2 Target Population** was consistent between studies (6.7% and 6.6% respectively; representing relative reductions of 15.0% and 14.2%). The integrated data from the two nearly identically designed clinical studies resulted in a 6.7% difference in **2-Year Recurrence Rate**s with a nominal p-value of p=0.0218 (OR 0.76; 95% CI 0.60, 0.96). Additionally, the recurrence rate improvements in the patients in the apaziquone groups compared to the placebo groups in the two pivotal, independent studies were consistent over the 2-year follow-up period at 6, 12, 18, and 24 months within and between each study.

Time to Recurrence was the key secondary endpoint in the studies. The distribution of **Time to Recurrence** by the Kaplan-Meier method showed a clear divergence between the apaziquone and placebo over the 2-year follow-up period in both studies (**SPI-611** and **SPI-612**), demonstrating an improvement in the **Time to Recurrence** for apaziquone-treated patients. A clinically meaningful increase in **Time to Recurrence** was demonstrated for apaziquone-treated patients in **SPI-611** (HR 0.77, 95% CI 0.59, 0.99; nominal *p*=0.0412), in **SPI-612** (HR 0.81, 95% CI 0.63, 1.04; nominal *p*=0.1038) and in the integrated data from the two studies (HR 0.79, 95% CI 0.66, 0.94; nominal p=0.0096).

Other secondary endpoint analyses for the **Ta, G1-G2 Target Population** in the pivotal efficacy studies (**SPI-611** and **SPI-612**) also generally supported the primary analysis that patients treated with apaziquone had a better outcome. In particular, fewer apaziquone-treated patients in both studies had progressed at 2 years (10.2% in **SPI-611** and 10.3% in **SPI-612**) compared with placebo (14.4% in **SPI-611** and 12.4% in **SPI-612**) and the mean Number of Recurrences per patient at 2 Years was numerically lower in the apaziquone group in both studies (**SPI-611** and **SPI-612**) compared with placebo (0.6 vs 0.9 in both studies).

Results from the subgroup analyses supported the primary analyses with each comparison favoring apaziquone.

When considering the totality of the efficacy data for the apaziquone clinical development program, it is important to consider several study design factors. First, at the time of protocol

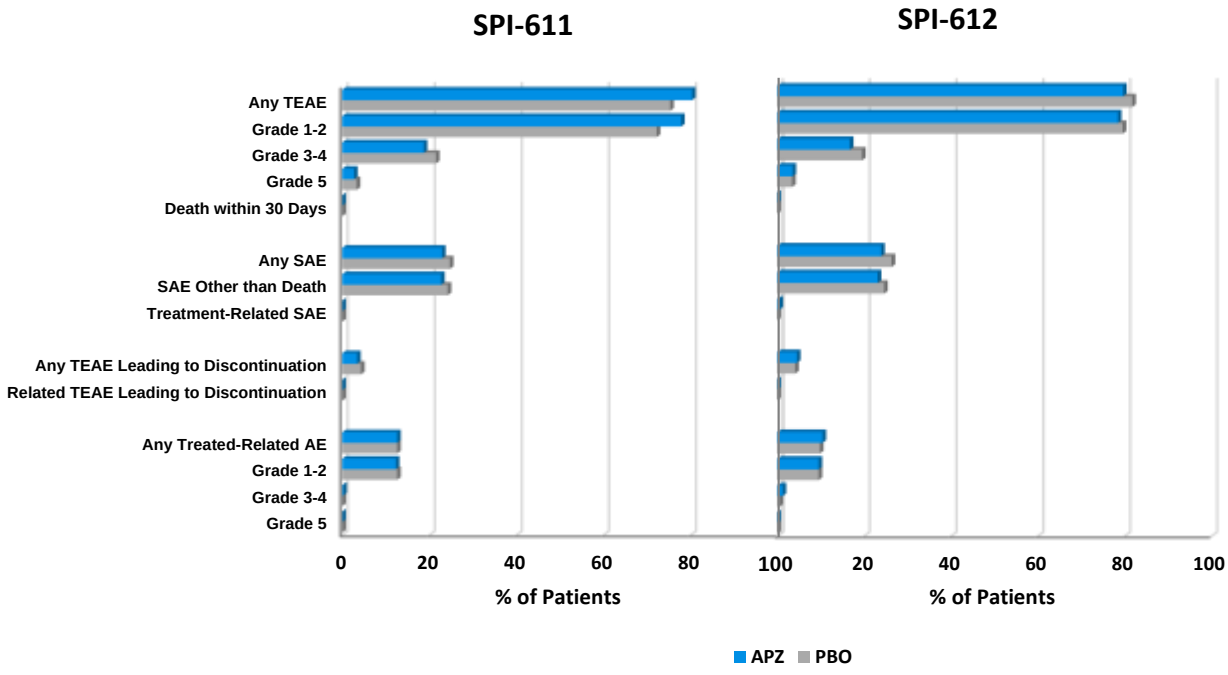
development for **SPI-611** and **SPI-612**, which enrolled their first patients in 2007, the studies were not adequately powered to show the 6-7% difference demonstrated in the primary analysis of each study but instead were powered for an absolute 12% difference. It is important to note that the majority of studies in the literature used TURBT alone as the control group and were not placebo-controlled studies. Additionally, in our clinical studies, the additional post-TURBT irrigation with placebo vehicle in **SPI-611** and **SPI-612** may have had a beneficial effect and resulted in lower recurrence rates in patients administered placebo compared to studies with TURBT alone that are described in the literature. In retrospect, the 12% difference may have been an unrealistic goal. Based on more recent data, the 2016 Clinical Trials Planning Meeting on Novel Therapeutics for NMIBC conducted under the auspices of the NCI and Bladder Cancer Task Force suggested that an absolute reduction of 6% in the percentage of patients with recurrence at 2 years would be a reasonable magnitude of effect to target for a clinical trial in patients with low-risk disease **[29]**.

In a subgroup analysis based on time of instillation, the efficacy of apaziquone was better demonstrated in a subgroup of patients who had instillations >30 minutes post-TURBT. In this subgroup there were clinically relevant reductions in the **2-Year Recurrence Rate** and increases in **Time to Recurrence** in the **Ta, G1-G2 Target Population** in both studies.

7.2.2 Safety

In this large safety database of 1859 patients, including 1053 patients treated with apaziquone, a single intravesical instillation of apaziquone in the post-TURBT setting was well tolerated, with a safety profile similar to placebo. **(Figure 25**).

Figure 25 Overall Similar AE Profile of Apaziquone in Pivotal Studies



Because of the minimal systemic absorption, no drug-drug interactions were expected and none were reported with apaziquone intravesical administration from the bladder post-TURBT. This is particularly important to bear in mind as the target population is older individuals with comorbid conditions who may be taking multiple concomitant medications.

Overall, no unexpected safety signals were identified. The AE profile of apaziquone was consistent with what would be expected from the TURBT procedure itself, and the majority of AEs were not treatment related. Of the 1053 patients treated with apaziquone, only nine patients were considered to have treatment-related SAEs, and of these, only one serious related and unexpected event was reported.

The safety profile of a single intravesical instillation of apaziquone was shown to be no different than that of placebo in controlled studies. The incidence of AEs between apaziquone and placebo were similar in the primary safety studies. The most common AEs were dysuria, urinary tract infection, hematuria, and pollakiuria, which are commonly seen after TURBT. Overall, in the two pivotal studies, genitourinary AEs, specifically hematuria and acute renal failure, were similar between studies and between treatment groups within each study. In addition, intravesical apaziquone did not affect functional bladder capacity and had no effect on frequency of urination, voided volume, or total bladder capacity.

Based on clinical laboratory assessments, there were no clinically meaningful changes in any hematologic, liver, kidney, or metabolic parameters for either the apaziquone or placebo group. Finally, none of the deaths that occurred in these trials were related to study drug, and no patients died within 30 days of receiving study drug.

Data from the six supportive safety studies support the safety results from the pivotal safety studies.

7.3 Overall Benefit-Risk Conclusions

Spectrum has worked closely with the FDA over the past 14 years in the development program for apaziquone, including two landmark placebo-controlled pivotal trials conducted in the largest number of patients ever treated in the intended patient population. While **SPI-611** and **SPI-612** did not meet their pre-specified primary endpoint, the individual study results and the combined results are clinically meaningful and given the absence of any significant safety issues or concerns fully support the contention that apaziquone is safe and effective for the treatment for low-risk NMIBC. These studies and data include:

- Two marker lesion studies demonstrating clear antitumor activity of apaziquone in NMIBC.
- A favorable outstanding safety profile and lack of toxicity for apaziquone in all studies, representing a clear advantage over other available therapy (MMC, epirubicin) given by single intravesical instillation.
- Efficacy data that were consistent between the landmark studies, **SPI-611** and **SPI-612**, showing a positive clinically meaningful benefit (6.7%).
- A significant increase in **Time to Recurrence** in one of the studies, delaying the need and frequency for repeat TURBT.

These data, taken together, support a positive benefit versus risk assessment for apaziquone given as a single 1-hour intravesical instillation at a dose of 4 mg in 40 mL of diluent post TURBT.

No drugs are currently approved in the US for the treatment of low-risk NMIBC. As such, chemotherapeutic agents such as MMC and epirubicin, which are recommended by various national and international organizations for immediate intravesical therapy in the treatment of low-risk NMIBC are being used "off-label" and are not specifically formulated for intravesical use. BCG, which is approved for the treatment of CIS and high-grade papillary NMIBC, has no role in the immediate postoperative setting for low-risk NMIBC because of the risk of systemic adverse effects.

Spectrum believes that the approval of apaziquone by the FDA, coupled with efforts by Spectrum to educate practitioners about the benefits of this treatment, could significantly improve the adherence to recommended treatment guidelines that support instillation of a chemotherapeutic agent post-TURBT. Greater use of intravesical chemotherapy in the US has the potential to substantially reduce the economic and humanistic burdens of NMIBC—one study estimated that over a 2-year period, about 8,000 recurrences could be avoided if all eligible patients received intravesical chemotherapy, resulting in an aggregate cost savings of $30 million **[30]**.

Following prior discussion with FDA, Spectrum has already begun another large multicenter placebo-controlled Phase 3 study designed to further assess the safety and efficacy of apaziquone in low-risk NMIBC. The study is currently enrolling but not expected to be complete until at least 2021. In the meantime, adoption of this treatment strategy—giving tens of thousands of patients each year timely access to an effective and well-tolerated therapy—would prevent tumor recurrence in thousands of patients a year, bringing significant benefit to the patient and substantial cost savings to the management of this disease.

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9 APPENDICES

Appendix 1 SPI-611 Synopsis

Title of Study: A Multicenter, Randomized, Placebo-Controlled, Double-Blind, Phase 3 Trial of Single-Dose Intravesical Apaziquone (EOquin®) as a Surgical Adjuvant Instilled in the Early Postoperative Period in Patients Undergoing Transurethral Resection for Noninvasive Bladder Cancer (Protocol **SPI-611**)	
Investigator(s): 83 Investigators	
Study Center(s): 76 sites in the US and 7 sites in Poland	
Publication(s): Not applicable	
Studied Period: 25 Apr 2007 to 19 Jan 2012	**Clinical Phase:** 3

Objectives:

Primary: To evaluate the **2-Year Recurrence Rate** of bladder cancer in randomized patients with tumor histology Ta, G1-G2 who received TURBT plus apaziquone versus those who received TURBT plus placebo.

Secondary:

- Evaluate **Time to First Recurrence** in patients with Ta, G1-G2 bladder cancer who received TURBT plus apaziquone versus those who received TURBT plus placebo.
- Evaluate Progression to higher stage or grade, Number of Recurrences per patient, Disease-Free Interval, Disease-Free Survival and Overall Survival.
- Assess the safety of apaziquone instilled into the bladder in the early postoperative period.
- Assess functional bladder capacity in a 150-patient subset of randomized patients.

Methodology: This was a Phase 3, multicenter, randomized, double-blind, placebo-controlled study. Within 14 days of **Screening**, eligible patients underwent a TURBT during **Visit 1** (**Day 0**) following which they were immediately randomized in a 1:1 ratio to receive either placebo or 4 mg apaziquone, instilled in a volume of 40 mL into the bladder within 6 hours from the end of the TURBT procedure. After a 60-minute retention period, study drug was drained from the bladder.

A postoperative follow-up examination and review of the local pathology report was performed at **Visit 2**, which occurred 21 days (±10 days) after the TURBT (**Week 3**).

- If the histology of the patient's tumor was confirmed as Ta, G1-G2 (ie, low grade according to World Health Organization [WHO]/International Society of Urologic Pathology [ISUP] classification]), no further treatment was given and the patient was observed cystoscopically every 3 months through **Year 2** for tumor recurrence (**Visit 3** through **Visit 10**).
- If the histology of the patient's tumor was other than Ta, G1 or G2 (low grade [WHO/ISUP classification]), further treatment was given in accordance with current treatment guidelines, and the patient was followed up cystoscopically every 3 months through **Year 2** for tumor recurrence (**Visit 3** through **Visit 10**).

All patients were to be followed for 2 years.

Number of Subjects: 802 patients were enrolled and randomized. All 802 (406 apaziquone, 396 placebo) patients were included in the **Intent-to-treat (ITT) Population** and **Safety Population**; 566 (295 apaziquone, 271 placebo) were included in the **Ta, G1-G2 Target Population**. The **Safety Population** and **ITT Population** were the same in this study and are referred to as the **ITT/Safety Population**.

Diagnosis and Criteria for Inclusion:

Inclusion Criteria

A patient was eligible for participation in the study based on affirmative responses to the Inclusion Criteria listed below:

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

Exclusion Criteria

A patient was excluded from participation in the study based on negative responses to the Exclusion Criteria below:

1. Does the patient have more than 4 bladder tumors?
2. Does any single bladder tumor exceed 3.5 cm in diameter?
3. Does the patient have a single, primary (no previous diagnosis of transitional cell carcinoma) bladder tumor < 0.5 cm?
4. Has the patient ever received apaziquone?
5. Does the patient have, or has the patient ever had, any bladder tumor known to be other than stage Ta or Grade G1 or G2 (low grade [WHO/ISUP classification])?
6. Does the patient have, or has the patient ever had any bladder tumor with histology other than transitional cell carcinoma?
7. Does the patient have, or has the patient ever had, CIS?
8. Does the patient have an active urinary tract infection?
9. Does the patient have a bleeding disorder or a screening platelet count < 100×10^9/L?
10. Does the patient have any unstable medical condition that would make it unsafe for him/her to undergo TURBT under general or spinal anesthesia?
11. Does the patient have a screening hemoglobin < 10 mg/dL, a screening absolute neutrophil count < 1.5 × 109/L or a screening creatinine > 2 mg/dL?
12. Does the patient have a known immunodeficiency disorder?
13. Has the patient received any investigational treatment within the past 30 days?
14. Is the patient breast feeding?
15. Does the patient have a history of interstitial cystitis?
16. Does the patient have a history of allergy to red color food dye?
17. Has the patient had transitional cell carcinoma of the bladder within the past 4 months?

Test Product, Dose, Mode of Administration, Batch No(s): A single dose of apaziquone (4 mg in 40 mL) was instilled into the bladder via an indwelling Foley catheter.

Apaziquone (EOquin) Lot Number: 7J002

Duration of Treatment: Single 60-minute intravesical exposure to study drug with a 2-year follow-up.

Reference Therapy, Dose, Mode of Administration, Batch No(s): Matching placebo (40 mL) for apaziquone was instilled into the bladder via an indwelling Foley catheter.

Placebo Lot Number: 324-04-001

Criteria for Evaluation: Efficacy was assessed by cystoscopy, performed every 3 months from the date of the TURBT through **Year 2**. Number, size and location of the recurrent tumors, if any, were reported. Suspicious lesions were biopsied or resected, with all histology specimens being read by a blinded, central laboratory that specialized in urologic pathology. Tumor stage and grade were assessed by the WHO 1973 criteria. The date of the biopsy or resection at which the bladder tumor was confirmed histologically was used as the date of recurrence.

Safety was evaluated from study therapy exposure and included reported adverse events (AEs), changes in laboratory values, vital signs, physical examination findings, and functional bladder capacity.

Statistical Methods: All analyses and tabulations were performed using SAS® Version 9.3. The primary population used in the analyses of efficacy was the **Ta, G1-G2 Target Population**, which included patients who had 4 or fewer tumors that were ≤ 3.5 cm each at the time of randomization and who had subsequent histological confirmation from the central pathology lab that the tumors resected at the time of randomization were Ta, Grade 1 or 2. The **ITT/Safety Population** included all randomized patients who received an instillation of apaziquone or placebo, regardless of duration of retention. Summary statistics included descriptive statistics (mean, SD, median, minimum, and maximum) for continuous variables and counts and percentages of patients in corresponding categories for categorical variables.

Analyses of efficacy endpoints employed a hierarchical closed testing procedure, where endpoints were tested in sequence. The **2-Year Recurrence Rate** was the proportion of patients with a documented recurrence on or before **Year 2**. Treatment effect was compared using the chi-squared test. Log rank test was used to compare time-to-event data for treatment groups. Kaplan-Meier estimates of survival curves and hazard ratios were presented. Study populations, demographics and **Baseline** characteristics were summarized by treatment group. Safety analyses were performed on the **ITT/Safety Population**. Treatment-emergent AEs (TEAEs) were recorded through **Month 6** of the study; after 6 months on study, only genitourinary AEs and serious AEs (SAEs) were recorded. Laboratory parameters were summarized over time. Summary statistics were reported for all measures of bladder capacity by treatment group. Vital signs were summarized by treatment group and time points.

Subgroup analyses based on time of instillation post-TURBT (≤30 minutes, 31 to 90 minutes, >90 minutes were also performed. This analysis was undertaken because of the potential for apaziquone to be inactivated by whole blood in the early period following TURBT.

SUMMARY-CONCLUSIONS:

RESULTS:

A total of 802 patients were enrolled and randomized at 72 sites in the US and 7 sites in Poland. There were 4 sites in the US that did not enroll any patients. All 802 patients (406 patients in the **Apaziquone Treatment Group** and 396 patients in the **Placebo Treatment Group**) underwent TURBT and were included in the **ITT/Safety Population**. A total of 566 patients (70.6%) were confirmed as the **Ta, G1-G2 Target Population**; 279 patients received the study drug within 30 minutes, 99 patients received between 31-90 minutes and the remaining 188 patients received the study drug after 90 minutes from TURBT**.**

Efficacy:

There was an absolute 6.7% reduction in the **2-Year Recurrence Rate** for the **Ta, G1-G2 Target Population**, the primary study endpoint, for the **Apaziquone Treatment Group** compared to the **Placebo Treatment Group**. While this difference did not reach statistical significance (38.0% vs 44.6%, chi-square p-value=0.1068), it represented a 15.0% relative reduction in the **2-Year Recurrence Rate** with apaziquone compared to placebo. **Time to Recurrence** was statistically significant in favor of apaziquone for the **Ta, G1-G2 Target Population** (p=0.0412, log-rank test; hazard ratio 0.77, 95% confidence interval [CI] 0.59, 0.99).

In the subgroup of patients in the **Ta, G1-G2 Target Population** treated 31 to 90 minutes post-TURBT (**Ta, G1-G2 Target Population$_{31\ to\ 90\ minutes}$**), the **Apaziquone Treatment Group** had a clinically and statistically significant absolute 20.3% reduction in **2-Year Recurrence Rate** compared to the **Placebo Treatment Group** (23.3% vs 43.6%; p=0.0346), with the odds ratio (0.39; 95% CI 0.16, 0.94) in favor of apaziquone; this represented a 46.5% relative reduction in the **2-Year Recurrence Rate** with apaziquone compared to placebo. **Time to**

Recurrence was also statistically significant in favor of apaziquone (HR=0.44; p=0.0202) in this subgroup of patients. In the subgroups of patients who received study drug at ≤30 minutes or >90 minutes post-TURBT, there were no significant differences between treatments in **2-Year Recurrence Rate** or **Time to Recurrence**.

A similar statistically significant improvement was demonstrated for **2-Year Recurrence Rate** and **Time to Recurrence** in the **ITT Population$_{31 \text{ to } 90 \text{ minutes}}$**. Analyses of other secondary efficacy variables in subgroups treated at 31 to 90 minutes post-TURBT, including **Time to Progression**, **Progression Rate at 2 Years**, **Overall Survival**, **Disease-Free Interval**, **Disease-Free Survival**, and **Number of Recurrences Within 2 Years** supported the primary analyses.

Safety:

All 406 patients in the **Apaziquone Treatment Group** received 40-mL apaziquone and only 3 of the 396 patients in the **Placebo Treatment Group** received less than 40-mL of placebo; all other patients in the **Placebo Treatment Group** received 40 mL of placebo. The mean **Time of Instillation post-TURBT** was 1.2 hours in both treatment groups and the mean **Duration of Treatment Exposure** (ie, retention time of study drug in the bladder) was similar in both treatment groups, 59.9 vs 60.1 minutes, respectively).

The most frequently reported drug-related TEAE after treatment with apaziquone was dysuria, which occurred with similar incidence in the patients treated with placebo (4.9% vs 4.8%). The next-most common drug-related TEAE was bladder spasm, which again occurred with a similar incidence in the two treatment groups (2.0% vs 1.3%). Most AEs were of mild or moderate severity. There were no trends in the incidence of AEs based on relationship to apaziquone or placebo. Over the 2-year study, genitourinary TEAEs were experienced by 64.3% patients in the **Apaziquone Treatment Group** compared with a comparable proportion (61.6%) patients in the **Placebo Treatment Group**. There were slightly lower incidences of hematuria and urinary retention in the **Apaziquone Treatment Group** (10.3% and 4.4%, respectively) compared to the **Placebo Treatment Group** (15.7% and 7.8%, respectively)**.** Most genitourinary TEAEs were mild or moderate; no patients in either treatment group had genitourinary TEAEs of Grade 4 severity, and there were no patients treated in the 31-90 minute window who experienced a Grade 3 to Grade 5 treatment-related AE.

There were no notable differences in the incidence or type of TEAEs or treatment-related AEs between the two treatment groups in the **ITT/Safety Population**. In the patients treated in the 31-90 minute window subgroup, SAEs were experienced by 24.4% vs 30.5% of patients in the **Apaziquone** and **Placebo Treatment Groups**, respectively, with 13.4% vs 23.7% having Grade 3-4 SAEs. The only SAEs to occur in more than one patient in this subgroup were hip arthroscopy in two patients in the **Apaziquone Treatment Group**, and syncope and pulmonary embolism, each in two patients in the **Placebo Treatment Group.**

No patients died within 30 days of study drug instillation. A total of 11 patients treated with apaziquone (2.7%) and 13 treated with placebo (3.3%) died during the study. Serious AEs (SAEs other than death) were experienced by similar percentages of apaziquone- and placebo-treated patients (22.7% vs 24.2%),, as were SAEs that led to withdrawal from the study (3.2% vs 4.0%, including patients who died). None of the deaths, SAEs, or AEs leading to discontinuation in this study were related to study treatment.

Laboratory evaluations also showed that apaziquone was not associated with any laboratory abnormalities that were not also observed in placebo-treated patients. Vital signs, physical examination, and functional bladder capacity also showed no differences except for one patient in the **Apaziquone Treatment Group** treated in the 31-90 minute post-TURBT window with Grade 3 increased creatinine.

CONCLUSIONS:

The following conclusions can be drawn from this study:

- Apaziquone treatment resulted in a clinically meaningful 6.7% absolute reduction in the **2-Year Recurrence Rate** for the **Ta, G1 G2 Target Population**, the primary study endpoint, compared to the **Placebo Treatment Group**, which did not reach statistical significance (38.0% vs 44.6%, chi-square p-value=0.1068); this represented a 15.0% relative reduction in the **2-Year Recurrence Rate** with apaziquone compared to placebo.
- There was a 20.3% absolute reduction in the **2-Year Recurrence Rate** in the group of patients in the **Ta, G1 G2 Target Population$_{\text{31-90 minutes}}$** (apaziquone, 23.3%; placebo, 43.6%) that was statistically significant (p=0.0346), with the odds ratio (0.39; 95% CI 0.16, 0.94) in favor of apaziquone; this represented a 46.5% relative reduction in the **2-Year Recurrence Rate** with apaziquone compared to placebo. A similar significant reduction in the **2-Year Recurrence Rate** was observed in the **ITT/Safety Population$_{\text{31-90 minutes}}$**.
- **Time to Recurrence** was statistically significant in favor of apaziquone for both the overall **Ta, G1-G2 Target Population** (p=0.0412, log-rank test; hazard ratio 0.77, 95% CI 0.59, 0.99), and the **Ta, G1-G2 Target Population$_{\text{31-90 minutes}}$** (p=0.0202). Similar improvements were observed in the corresponding subgroups of the **ITT/Safety Population**.
- Analyses of other secondary efficacy variables, including Time to Progression, Progression Rate at 2 Years, Overall Survival, Disease-Free Interval, Disease-Free Survival, and Number of Recurrences Within 2 Years also supported the results of the primary analyses.
- Subgroup analysis showed the clinical benefit of apaziquone to be higher in those patients who had multifocal tumors, higher grade tumors, and who had not been previously treated.
- Apaziquone was well tolerated when instilled immediately after TURBT in patients with NMIBC.
- The type and incidence of AEs were similar between the **Apaziquone** and **Placebo Treatment Groups**.
- The most common treatment-related TEAEs in apaziquone-treated patients were dysuria (4.9%) and bladder spasm (2.0%).
- There were no patients treated in the 31-90 minute window who experienced a Grade 3 to Grade 5 treatment-related AE
- None of the deaths, SAEs, or AEs leading to discontinuation observed in this study were considered by the Investigators to be related to study treatment.
- Laboratory abnormalities in apaziquone treated patients were similar to those observed in placebo-treated patients.
- Vital signs and functional bladder capacity showed no significant change from **Baseline** in either group except for a significant decrease in total bladder volume in the **Placebo Treatment Group** at 12 months in the **Ta, G1-G2 Target Population$_{\text{31-90 minutes}}$**.

Overall, **SPI-611** demonstrated that intravesical apaziquone was well tolerated with manageable toxicities, and a clinically meaningful reduction in the **2-Year Recurrence Rate** in patients with NMIBC, particularly in the subgroup of patients treated 31-90 minutes post-TURBT.

Date of the Report: 09 Oct 2015

Appendix 2 SPI-612 Synopsis

Title of Study: A Multicenter, Randomized, Placebo-Controlled, Double-Blind, Phase 3 Trial of Single-Dose Intravesical Apaziquone (EOquin®) as a Surgical Adjuvant Instilled in the Early Postoperative Period in Patients Undergoing Transurethral Resection for Noninvasive Bladder Cancer (Protocol **SPI-612**)	
Investigators: 73 Investigators experienced in the therapeutic area of bladder cancer	
Study Centers: 23 sites in the US, 30 sites in Canada, and 20 sites in Poland	
Publication(s): Not applicable	
Studied Period: 28 Aug 2007 to 25 Jan 2012	Clinical Phase:3

Objective(s):

Primary: To evaluate the **2-Year Recurrence Rate** of bladder cancer in randomized patients with tumor histology Ta, G1-G2 who received TURBT plus apaziquone versus those who received TURBT plus placebo.

Secondary:

- Evaluate **Time to First Recurrence** in patients with Ta, G1-G2 bladder cancer who received TURBT plus apaziquone versus those who received TURBT plus placebo.
- Evaluate Progression to higher stage or grade, Number of Recurrences per patient, Disease-Free Interval, Disease-Free Survival and Overall Survival.
- Assess the safety of apaziquone instilled into the bladder in the early postoperative period.

Methodology: This was a Phase 3, multicenter, randomized, double-blind, placebo-controlled study. Within 14 days of **Screening**, eligible patients underwent a TURBT during Visit 1 (**Day 0**) following which they were immediately randomized in a 1:1 ratio to receive either placebo or 4 mg apaziquone, instilled in a volume of 40 mL into the bladder within 6 hours from the end of the TURBT procedure. After a 60-minute retention period, study drug was drained from the bladder.

A postoperative follow-up examination and review of the local pathology report were performed at **Visit 2**, which occurred 21 days (±10 days) after the TURBT (**Week 3**).

- If the histology of the patient's tumor was confirmed as Ta, G1-G2 (ie, low grade according to World Health Organization [WHO]/International Society of Urologic Pathology [ISUP] classification), no further treatment was given and the patient was observed cystoscopically every 3 months through **Year 2** for tumor recurrence (**Visit 3** through **Visit 10**).
- If the histology of the patient's tumor was other than Ta, G1 or G2 (low grade [WHO/ISUP classification]), further treatment was given in accordance with current treatment guidelines, and the patient was followed up cystoscopically every 3 months through **Year 2** for tumor recurrence (**Visit 3** through **Visit 10**).

All patients were to be followed for 2 years.

Number of Subjects: A final enrollment of 800 patients was planned; 812 patients were enrolled and randomized. All 812 (402 apaziquone, 410 placebo) were included in the **Intent-to-Treat** (**ITT**) **Population** and the **Safety Population**, and 580 (282 apaziquone, 298 placebo) were included in the **Ta, G1-G2 Target population**. Since the **ITT Population** and **Safety Population** were the same in this study, they are subsequently referred to as the **ITT/Safety Population**.

Diagnosis and Criteria for Inclusion:

Inclusion Criteria

A subject was eligible for participation in the study based on affirmative responses to all of the Inclusion Criteria listed below:

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

Exclusion Criteria

A subject was excluded from participation in the study based on negative responses to any of the Exclusion Criteria below:

1. Does the patient have more than 5 bladder tumors?
2. Does any single bladder tumor exceed 3.5 cm in diameter?
3. Does the patient have a single, primary bladder tumor <0.5 cm in diameter and no previous diagnosis of bladder cancer?
4. Has the patient ever received apaziquone?
5. Does the patient have, or has the patient ever had, any bladder tumor known to be other than stage Ta or Grade G1 or G2 (low grade [WHO/ISUP classification])?
6. Does the patient have, or has the patient ever had, any bladder tumor with histology other than transitional cell carcinoma?
7. Does the patient have, or has the patient ever had, CIS?
8. Does the patient have an active urinary tract infection?
9. Does the patient have a bleeding disorder or a screening platelet count $<100 \times 10^9$/L?
10. Does the patient have any unstable medical condition that would make it unsafe for him/her to undergo TURBT under general or spinal anesthesia?
11. Does the patient have a screening hemoglobin <10 mg/dL, a screening absolute neutrophil count $<1.5 \times 10^9$/L?
12. Does the patient have a known immunodeficiency disorder?
13. Has the patient received any investigational treatment within the past 30 days?
14. Is the patient breast feeding?
15. Does the patient have a history of interstitial cystitis?
16. Does the patient have a history of allergy to red color food dye?
17. Has the patient had transitional cell carcinoma of the bladder within the past 4 months?

Test Product, Dose, Mode of Administration, Batch No(s): A single dose of apaziquone (4 mg in 40 mL) was instilled into the bladder via an indwelling Foley catheter.

Apaziquone (EOquin) Lot Number: 7J002

Duration of Treatment: Single 60-minute intravesical exposure to study drug with a 2-year follow-up.

Reference Therapy, Dose, Mode of Administration, Batch No(s): Matching placebo (40 mL) for apaziquone was instilled into the bladder via an indwelling Foley catheter.

Placebo Lot Number: 324-04-001

Criteria for Evaluation: Efficacy was assessed by cystoscopy, performed every 3 months from the date of the TURBT through **Year 2**. Number, size, and location of the recurrent tumors, if any, were reported. Suspicious lesions were biopsied or resected, with all histology specimens being read by a blinded, central laboratory that specialized in urologic pathology. Tumor stage and grade were assessed by the WHO criteria. The date of the biopsy or resection at which the bladder tumor was confirmed histologically was used as the date of recurrence.

Safety was evaluated from study therapy exposure and included reported adverse events (AEs), changes in laboratory values, vital signs, and physical examination findings.

Statistical Methods: All analyses and tabulations were performed using SAS® Version 9.3. The primary population used in the analyses of efficacy was the **Ta, G1-G2 Target Population**, which included patients who had 4 or fewer tumors that were ≤ 3.5 cm each at the time of randomization and who had subsequent histological confirmation from the central pathology lab that the tumors resected at the time of randomization were Ta Grade 1 or 2. The **ITT/Safety Population** included all randomized patients who received an instillation of apaziquone or placebo, regardless of duration of retention. Summary statistics included descriptive statistics (mean, SD, median, minimum, and maximum) for continuous variables and counts and percentages of patients in corresponding categories for categorical variables.

Analyses of efficacy endpoints employed a hierarchical closed testing procedure, where endpoints were tested in sequence. The **2-Year Recurrence Rate** was the proportion of patients with a documented recurrence on or before **Year 2**. Treatment effect was compared using the chi-squared test. Log rank test was used to compare time-to-event data for treatment groups. Kaplan-Meier estimates of survival curves and hazard ratios were presented. Study populations, demographics and **Baseline** characteristics were summarized by treatment group. Safety analyses were performed on the **ITT/Safety Population**. Treatment-emergent AEs (TEAEs) were recorded through **Month 6** of the study; after 6 months on study, only genitourinary AEs and serious AEs (SAEs) were recorded. Laboratory parameters were summarized over time. Summary statistics were reported for all measures of bladder capacity by treatment group. Vital signs were summarized by treatment group and time points.

Subgroup analyses based on **Time of Instillation** post-TURBT (≤30 minutes, 31 to 90 minutes, >90 minutes were also performed. This analysis was undertaken because of the potential for apaziquone to be inactivated by whole blood that may be present in the bladder in the early period following TURBT.

SUMMARY-CONCLUSIONS:

RESULTS:

A total of 812 patients were enrolled and randomized at 23 sites in the US, 30 sites in Canada, and 20 sites in Poland. All 812 patients (402 patients in the **Apaziquone Treatment Group** and 410 patients in the **Placebo Treatment Group**) underwent TURBT and were included in both the **ITT Population** and the **Safety Population** (**ITT/Safety Population**); 402 received apaziquone and 410 received placebo. A total of 580 patients (71.4%) were confirmed as the **Ta, G1-G2 Target Population**; 177 patients received study drug within 30 minutes, 118 patients received between 31 to 90 minutes (**Ta, G1-G2 Target Population$_{31\ to\ 90\ minutes}$**), and 285 patients received the study drug after 90 minutes from TURBT.

Efficacy:

There was an absolute 6.6% reduction in the **2-Year Recurrence Rate** for the **Ta, G1-G2 Target Population**, the primary study endpoint, for the **Apaziquone Treatment Group** compared to the **Placebo Treatment Group**. While this difference did not reach statistical significance (39.7% vs 46.3%, chi-square p-value=0.1094), it represented a 14.2% relative reduction in the **2-Year Recurrence Rate** with apaziquone compared to placebo. **Time to Recurrence** was not statistically significantly different between treatment groups in the **Ta, G1-G2 Target Population** (p=0.1038, log-rank test; hazard ratio 0.81, 95% CI 0.63, 1.04).

In the subgroup of patients in the **Ta, G1-G2 Target Population** treated 31 to 90 minutes post-TURBT (**Ta, G1-G2 Target Population**$_{\text{31 to 90 minutes}}$), the **Apaziquone Treatment Group** had a clinically and statistically significant absolute 20.8% reduction in **2-Year Recurrence Rate** compared to the **Placebo Treatment Group** (33.3% vs 54.1%; p=0.0238), with the odds ratio (0.42; 95% CI 0.20, 0.89) in favor of apaziquone; this represented a 38.4% relative reduction in the **2-Year Recurrence Rate** with apaziquone compared to placebo. **Time to Recurrence** was also statistically significant in favor of apaziquone (HR=0.55; p=0.0344) in this subgroup of patients. In the subgroups of patients who received study drug at ≤30 minutes or >90 minutes post-TURBT, there were no significant differences between treatments in **2-Year Recurrence Rate** or **Time to Recurrence**.

A similar statistically significant improvement was demonstrated for **2-Year Recurrence Rate** and **Time to Recurrence** in the **ITT/Safety Population** subgroups of patients treated in the 31 to 90 minute window, post-TURBT. Analyses of other secondary efficacy variables in subgroups treated at 31 to 90 minutes post-TURBT, including **Time to Progression, Progression Rate at 2 Years, Overall Survival, Disease-Free Interval, Disease-Free Survival,** and **Number of Recurrences Within 2 Years** supported the primary analyses.

Safety:

All 402 patients in the **Apaziquone Treatment Group** received 40-mL apaziquone. No patients in the **Apaziquone Treatment Group** received more or less than 40 mL of instillate; two patients in the **Placebo Treatment Group** received less than 40 mL of instillate, two received more than 40 mL. The mean **Time of Instillation** post-TURBT was similar in both treatment groups (1.7 vs. 1.8 hours), as was the mean **Duration of Treatment Exposure** (ie, retention of study drug in the bladder) (60.3 vs 60.4 minutes). The mean **Study Duration** was also similar in the **Apaziquone and Placebo Treatment Groups** (22.2 vs 22.4 months) and the majority of patients in each treatment group completed >21 to 24 months of treatment (53.2% vs 57.3%) or >24 months of treatment (31.8% vs 28.8%).

The most frequently reported drug-related TEAEs after treatment with apaziquone were dysuria (4.2%) and micturition urgency (1.5%), which occurred with similar incidence in the patients treated with placebo. Most AEs were of mild or moderate severity. There were no obvious trends in the incidence of AEs based on relationship to apaziquone or placebo. In the **ITT/Safety Population**, most genitourinary TEAEs were mild or moderate, with 24 (6.0%) patients in the **Apaziquone Treatment Group** and 38 (9.3%) patients in the **Placebo Treatment Group** having genitourinary TEAEs of Grade 3 severity. No patients in the **Apaziquone Treatment Group** had Grade 4 or 5 genitourinary TEAEs. One patient in the **Placebo Treatment Group** had a genitourinary TEAE of Grade 4 severity (metastatic carcinoma of the bladder), and one had a genitourinary TEAE that was of Grade 5 severity (renal failure acute).

There were no notable differences in the incidence or type of TEAEs or treatment-related AEs between the two treatment groups in the **ITT/Safety Population**. Among the patients treated in the 31 to 90 minute window, SAEs were experienced by 31.6% vs 23.7% of patients in the **Apaziquone** and **Placebo Treatment Groups**, with 17.1% vs 13.2% having Grade 3-4 SAEs. The only SAEs to occur in more than a single patient within this subgroup were cardiac arrest, hematuria, hydronephrosis, and urinary retention (each in two patients in the **Apaziquone Treatment Group**), knee arthroscopy (two patients in the **Apaziquone Treatment Group** and two in the **Placebo Treatment Group**), and cerebrovascular accident and cystocele repair (each in two patients in the **Placebo Treatment Group**).

No patients died within 30 days of study drug instillation. A total of 14 patients treated with apaziquone (3.5%) and 14 treated with placebo (3.4%) died during the study. Serious AEs (SAEs other than death) were experienced by similar percentages of apaziquone- and placebo-treated patients (23.1% vs 24.6%), as were SAEs that led to

withdrawal from the study (4.0% vs 3.4%, including patients who died). None of the deaths, SAEs, or AEs leading to discontinuation in this study were related to study treatment.

Laboratory evaluations also showed that apaziquone was not associated with any laboratory abnormalities that were not also observed in placebo-treated patients. There were no differences in vital signs or physical examinations between treatment groups.

CONCLUSIONS:

- Apaziquone treatment resulted in a clinically meaningful 6.6% absolute reduction in the **2-Year Recurrence Rate** for the **Ta, G1-G2 Target Population**, which did not reach statistical significance (39.7% vs 46.3%, chi-square p-value=0.1094); importantly, this represented a 14.2% relative reduction in the **2-Year Recurrence Rate** with apaziquone compared to placebo.
- There was a 20.8% absolute reduction in the **2-Year Recurrence Rate** in the group of patients in the **Ta, G1-G2 Target Population$_{31\ to\ 90\ minutes}$** (apaziquone, 33.3%; placebo, 54.1%) that was statistically significant (p=0.0238), with the odds ratio (0.42; 95% CI 0.20, 0.89) in favor of apaziquone. Importantly, this represented a 40.3% relative reduction in the **2-Year Recurrence Rate** with apaziquone compared to placebo. A similar significant reduction in **2-Year Recurrence Rate** was observed in the **ITT Population$_{31\ to\ 90\ minutes}$.**
- **Time to Recurrence** was not statistically significantly different between treatment groups in the **Ta, G1-G2 Target Population** (p=0.1038, log-rank test; hazard ratio 0.81, 95% CI 0.63, 1.04), but was statistically significant in favor of apaziquone in the **Ta, G1-G2 Target Population$_{31\ to\ 90\ minutes}$** (p=0.0344, log-rank test; hazard ratio 0.55, 95% CI 0.31, 0.97). Similar improvements were observed in the corresponding subgroup of the **ITT/Safety Population** and the **ITT/Safety Population$_{31\ to\ 90\ minutes}$.**
- Analyses of other secondary efficacy variables, including Time to Progression, Progression Rate at 2 Years, Overall Survival, Disease-Free Interval, Disease-Free Survival, and Number of Recurrences within 2 Years also supported the primary analyses.
- The multiple logistic regression analysis showed that, in the **Apaziquone Treatment Group,** patients who had tumors ≤1cm in size (p=0.0006, odds ratio 0.32, 95% CI 0.17, 0.62), and who had a single tumor site (p=0.0168, odds ratio 0.36, 95% CI 0.16, 0.83) had significantly lower odds for recurrence.
- Apaziquone was shown to be well tolerated when instilled immediately post-TURBT in patients with NMIBC.
- The type and incidence of AEs were similar between the **Apaziquone** and **Placebo Treatment Groups**.
- The most common treatment-related TEAEs in apaziquone-treated patients were dysuria (4.2%), hematuria (1.7%), and micturition urgency (1.5%).
- The number of deaths in the two treatment groups was comparable.
- Serious AEs were reported at similar frequencies in apaziquone- and placebo-treated patients.
- None of the deaths, SAEs, or AEs leading to discontinuation were considered by the Investigators to be related to study treatment.
- Laboratory abnormalities in apaziquone-treated patients were similar to those observed in placebo-treated patients.
- Vital signs showed no differences between treatment groups.

Overall, **SPI-612** demonstrated that intravesical apaziquone was well tolerated with manageable toxicities, and a clinically meaningful reduction in the **2-Year Recurrence Rate** in patients with NMIBC.

Date of the Report: 19 Oct 2015

Appendix 3 Group 1 Patient Listing of Adverse Events Resulting in Death (SPI-611 + SPI-612)

Patient Number	Patients Sex/Race/ Age (years)	Investigator Term	MedDRA Preferred Term	Day of Death Relative to Last Dose
Apaziquone Treatment Group				
611-048-1164	Male/White/79	Suicide	Completed suicide	32
612-092-2224	Male/White/73	Metastatic lung cancer - non small cell carcinoma	Non-small cell lung cancer metastatic	78
611-048-1319	Female/White/80	Myocardial infarction	Myocardial infarction	87
612-107-2445	Male/White/68	Severe respiratory distress	Respiratory distress	91
612-103-2218	Female/White/86	Cholangio cancer	Cholangiocarcinoma	125
611-131-1905	Male/White/76	Cardiac arrest	Cardiac arrest	141
612-162-2588	Male/White/83	Cerebrovascular accident	Cerebrovascular accident	155
611-006-1026	Male/White/70	Ventricular fibrillation	Ventricular fibrillation	202
611-031-1143	Female/White/78	Respiratory failure	Respiratory failure	224
611-031-1144	Male/Black or African American/77	Respiratory failure	Respiratory failure	236
612-210-4186	Male/White/56	Cardiopulmonary arrest	Cardio-respiratory arrest	284
612-208-4033	Female/White/77	Metastatic carcinoma of the liver	Hepatic cancer metastatic	289
612-104-2383	Male/White/85	Cardiac arrest	Cardiac arrest	327
612-148-2606	Male/White/80	Death	Death NOS	331
611-013-1152	Male/White/75	Death of unknown cause	Death	348
611-015-1122	Male/White/76	Heart attack	Myocardial infarction	363
611-034-1476	Male/White/88	Death	Death NOS	378
611-044-1715	Male/White/73	Respiratory failure	Respiratory failure	392
612-082-2276	Male/White/75	Metastases to liver	Metastases to liver	436
612-168-2834	Male/White/76	Decompensated heart failure	Cardiac failure	464
612-084-2853	Male/White/70	Multi-organ failure	Multi-organ failure	517
612-162-2809	Male/White/80	Pneumonia	Pneumonia	572
611-048-1459	Male/White/77	Worsening of CHF	Cardiac failure congestive	628
612-213-4152	Male/White/83	Cardiogenic shock	Cardiogenic shock	722
612-116-2234	Male/White/67	Cardiopulmonary arrest	Cardio-respiratory arrest	738

Patient Number	Patients Sex/Race/ Age (years)	Investigator Term	MedDRA Preferred Term	Day of Death Relative to Last Dose
Placebo Treatment Group				
611-021-1111	Male/White/79	Respiratory failure	Respiratory failure	377
612-206-4071	Male/White/77	Death	Death	~669[a]
611-071-1574	Male/White/70	Metastases to lung	Metastases to lung	68
611-067-1179	Female/White/84	Spinal Metastatic Disease	Metastases to spine	124
612-142-2473	Male/White/59	Cardiac arrest	Cardiac arrest	164
612-077-2209	Male/White/76	Cerebral neoplasm	Brain neoplasm	240
612-083-2866	Male/White/55	Automobile accident	Road traffic accident	248
611-118-1851	Male/White/79	Respiratory failure	Respiratory failure	273
612-086-2769	Male/White/55	Bilateral carcinoma of the lungs	Lung neoplasm malignant	275
612-086-2611	Male/White/70	Cardiogenic shock	Cardiogenic shock	276
612-088-2643	Male/White/87	Possible CVA	Cerebrovascular accident	267
612-206-4126	Male/White/78	Acute circulatory failure	Circulatory collapse	280
612-204-4029	Male/White/75	Cardiac arrest	Cardiac arrest	325
611-250-4502	Male/White/60	Cardiopulmonary failure	Cardiopulmonary Failure	423
611-002-1395	Male/White/91	Congestive heart failure decompensation	Cardiac failure congestive	425
611-067-1180	Male/White/78	CVA	Cerebrovascular accident	474
611-069-1230	Male/White/68	Respiratory failure	Respiratory failure	496
612-109-2757	Male/White/76	Advanced neuroendocrine carcinoma	Neuroendocrine carcinoma	511
612-211-4011	Female/White/67	Circulatory failure	Circulatory collapse/	554
611-006-1080	Male/White/73	Myocardial infarction	Myocardial infarction	558
611-250-4552	Female/White/72	Pulmonary embolism	Pulmonary embolism	593
612-130-2663	Male/White/79	Acute myocardial infarction	Acute myocardial infarction	601
612-083-2389	Male/White/78	Acute renal failure	Renal failure acute	624
612-206-4073	Male/White/70	Cardiac failure	Cardiac failure	625
611-044-1029	Male/White/83	Progression metastatic prostate cancer	Prostate Cancer	656

Patient Number	Patients Sex/Race/ Age (years)	Investigator Term	MedDRA Preferred Term	Day of Death Relative to Last Dose
611-031-1141	Female/White/82	Sepsis	Sepsis	687
611-064-1584	Male/White/46	Prescription drug toxicity	Toxicity to various agents	733

CHF=congestive heart failure; CVA=cerebrovascular accident; MedDRA=Medical Dictionary for Regulatory Activities; NOS=not otherwise specified.

(a) Days relative to death not listed for **Patient 612-206-4071**. Per **SPI-612**, date of study drug was (b) (6) and date of death was (b) (6)

Note: Adverse events are listed in order first by the number of days relative to the last dose, then by patient number.

Appendix 4 Narratives of Patients

Patient SPI-612/091-2646

SAE: Hematuria [Hematuria]

Patient 091-2646, a 48-year-old Caucasian male, was diagnosed with primary bladder cancer at Screening on (b) (6). The patient's past medical history was significant for mild left ventricular dilation, gastroesophageal reflux disease, low back and neck pain, head injury due to motor vehicle accident, numbness and tingling in the extremities, and hematuria. The patient's concomitant medications included ibuprofen (Advil), ciprofloxacin (Ciprol XL), docusate sodium (Colace), oxycocet (Percocet), and panadeine co (Tylenol 3).

The patient was randomized to the **Apaziquone Treatment Group** on (b) (6) (**Day 1** of the study), underwent transurethral resection of bladder tumor (TURBT), and received intravesical instillation of 40 mL of study drug (apaziquone, 4 mg). Study drug instillation was completed within 6 hours of the end of the TURBT procedure, and the patient was able to retain the study drug instillation within the bladder for 60 minutes.

Although the patient tolerated the procedure well as a standard of care for this site, the patient was admitted to the hospital for observation for 24 hours following the procedure. This hospitalization was prolonged as patient developed hematuria. The patient was initially treated with intermittent bladder irrigations followed by cauterization of the bleeding area under local anesthesia in the cystoscopic suite. The hematuria resolved, and the patient was discharged to home on (b) (6) (**Day 2** post-apaziquone instillation).

The event of Hematuria resolved without sequelae and was classified by the Investigator as serious (hospitalization) and unrelated to apaziquone treatment.

Patient SPI-612/115-2250

SAE: Acute Renal Failure [Renal Failure Acute]

SAE: Cerebral Vascular Accident [Cerebrovascular Accident]

SAE: Vertigo [Vertigo]

Patient 115-2250, a 62-year-old Caucasian female, was diagnosed with primary bladder cancer at Screening on (b) (6). The patient's past medical history was significant for history of chronic obstructive pulmonary disease, hypertension, cholecystectomy, appendectomy, nausea and vomiting, osteoarthritis, and carpal tunnel right hand (released).The patient's concomitant medications included levonorgestrel (Mirena), hydrochlorothiazide, metoprolol, pethidine hydrochloride (Demerol), tolterodine l-tartrate (Detrol LA), dimenhydrinate (Gravol), oxycocet (Percocet), calcium carbonate (Apo-Cal), docusate sodium, magnesium oxide, rabeprazole, felodipine, norfloxacin (Noroxin), acetylsalicylic acid, rosuvastatin (Crestor), glyceryl trinitrate (Nitrolingual Pump Spray), ramipril, lorazepam (Ativan), and fluconazole (Diflucan).

The patient was randomized to the **Apaziquone Treatment Group** on (b) (6) (**Day 1** of the study), underwent transurethral resection of bladder tumor (TURBT), and received intravesical instillation of 40 mL of study drug (apaziquone, 4 mg). Study drug instillation was completed within 6 hours of the end of the TURBT procedure, and the patient was able to retain the study drug instillation within the bladder for 60 minutes.

After surgery and prior to study drug administration the patient complained of nausea, vomiting, and lower abdominal pain. The study drug was instilled 5 hours after TURBT in the office over approximately 5 minutes via a syringe. Approximately 25 minutes into retention, the patient was medicated with meperidine (Demerol, 50 mg) and dimenhydrinate (Gravol, 50 mg) for nausea, urgency, and abdominal pain. She retained the study drug for 1 hour. Upon unclamping, the Foley catheter did not drain well, and the patient's bladder was irrigated with 500 mL of normal saline. The patient felt better after irrigation and was discharged to home with a Foley catheter. The patient returned to the emergency room later that evening ((b) (6)) (**Day 1** of the study) with persistent nausea, vomiting, and feeling unwell and was admitted to the hospital with a diagnosis of acute renal failure.

At the patient's **Screening Visit**, on (b) (6) (**Day 6** pre-apaziquone instillation), laboratory test results included a blood urea nitrogen value of 9 mg/dL and creatinine value was 0.7 mg/dL. On (b) (6) (**Day 2** pre-apaziquone instillation) (pre randomization), the patient's and blood urea nitrogen value was 8 mg/dL and creatinine value was 0.8 mg/dL. On admission, the patient's serum creatinine value was 1.76 mg/dL and on (b) (6) (**Day 1** post-apaziquone instillation), serum creatinine had increased to 4.99 mg/dL. The patient was diagnosed with acute renal failure and hemodialysis was started after the patient failed to respond to conservative management, which included hydration and supportive care. It is unclear from the medical summary report whether a Foley catheter was indwelling all this time. It was noted that the patient had been discharged on (b) (6) (**Day 7** post-apaziquone instillation) to continue with hemodialysis every other day from home. On (b) (6) (**Day 8** post-apaziquone instillation), the patient's serum creatinine was 5.03 mg/dL and blood urea nitrogen values ranged from 18 mg/dL to 72 mg/dL. Serum amylase and lipase were normal. The results of a renal ultrasound revealed a bilateral mild prominence of the collecting system that was suggestive of mild hydronephrosis. The results of an abdominal computed tomography scan showed fluid around the pancreas and mild inflammation, mild diverticulitis, and some left pelvic gas associated with dissection of the tumor. The patient was seen in the office on (b) (6) (**Day 9** post-apaziquone instillation), and a repeat kidney ultrasound showed mild bilateral hydronephrosis. The course of patient's recovery from acute renal failure was felt to support the cause of acute renal failure secondary to vomiting, dehydration and hypovolemia.

On (b) (6) (**Day 11** post-apaziquone instillation), the patient was admitted to the hospital with slurred speech and a tentative diagnosis of urosepsis. Her white blood cell count was 27,400/L, and urinalysis showed 20-50 white blood cells and 8-30 red blood cells and was positive for bacteria. The urine culture was negative for bacterial growth (preliminary report noted "no growth less than 24 hours"). The patient had been administered norfloxacin (Noroxin) since her admission to the hospital. The patient started producing urine spontaneously and has not required hemodialysis since (b) (6) (**Day 13** post-apaziquone instillation). On (b) (6) (**Day 13** post-apaziquone instillation), her blood urea nitrogen (9.1 mmol/L) and creatinine (2.01 mg/dL) values had stabilized. The patient's pre-discharge serum creatinine value was 1.04 mg/dL and BUN value was 8.4 mg/dL. The urine microscopic exam showed elevated cellular count, predominantly neutrophils and red blood cells. The patient refused a recommended kidney biopsy, and the nephrologist continued to follow the patient on an outpatient basis. The admitting diagnosis of urosepsis was not confirmed, as the patient's urine and blood cultures were reported to be normal. The patient's last hemodialysis was on (b) (6); therefore, the stop date for acute renal failure was amended to (b) (6)

(**Day 17** post-apaziquone instillation). The patient was discharged from the hospital on (b) (6) (**Day 17** post-apaziquone instillation).

The patient was evaluated for the slurred speech with a computed tomography (CT) scan of the head on (b) (6) (**Day 11** post-apaziquone instillation) and on (b) (6) (**Day 17** post-apaziquone instillation). The CT scan of the head performed on (b) (6) (**Day 11** post-apaziquone instillation) revealed a subtle hypodensity in the left occipital region, but no acute intracranial pathology. The CT scan of the head on (b) (6) (**Day 17** post-apaziquone instillation) showed interval progression of the subtle density to findings consistent with an acute infarct. The patient was diagnosed with cerebrovascular accident. The patient continued to have some residual speech and gait deficit and received physical, occupational and speech therapy as an outpatient.

Additionally, compared with a prior electrocardiogram performed on 29 Mar 2006, the patient's electrocardiogram was read as abnormal, citing evidence of a normal sinus rhythm, left anterior fascicular block, possible inferior infarct (age undetermined), anterior infarct (age undetermined), T-wave abnormality, and considerable lateral ischemia. A transthoracic echocardiogram performed on (b) (6) (**Day 15** post-apaziquone instillation) showed abnormal left ventricular diastolic filling consistent with impaired left ventricle relaxation and a trace of aortic, mitral, tricuspid and pulmonic regurgitation.

On (b) (6) (**Day 32** post-apaziquone instillation), the patient was readmitted in the hospital with complaints of spinning sensation not accompanied with nausea and vomitting. She was diagnosed with vertigo. The patient was treated for vertigo. At the time of discharge on (b) (6) (**Day 37** post-apaziquone instillation), the patient was still experiencing vertigo several times a day but was slowly improving.

The event of Acute Renal Failure resolved without sequelae was classified by the Investigator as serious (hospitalization) and possibly related to apaziquone treatment. The event of Cerebrovascular Accident resolved with sequelae and was classified by the Investigator as serious (life-threatening) and unrelated to apaziquone administration. The event of Vertigo resolved without sequelae and was classified by the Investigator as serious (hospitalization) and unrelated to apaziquone treatment.

Patient SPI-612/083-2389

SAE: Aspiration Pneumonia [Pneumonia Aspiration]

SAE: Acute Renal Failure [Renal Failure Acute]

Patient 083-2389, a 78-year-old Caucasian male with a diagnosis of recurrent bladder cancer (first diagnosed: (b) (6); date of last recurrence: (b) (6)), had received prior intravesical therapy with mitomycin C. The patient's past medical history was significant for glaucoma, chronic obstructive pulmonary disease, atrial fibrillation, edema, coronary artery disease with coronary artery bypass graft, hypertension, hypercholesterolemia, vascular peripheral disease, some ongoing ecchymosis, chronic hypokalemia, type 2 diabetes mellitus, dementia, neuralgia, bladder pain, urinary incontinence, and dysuria. The patient's concomitant medications included cilostazol, warfarin sodium (Coumadin), diltiazem, furosemide, gabapentin, hypromellose (Genteal Ophth Gtts), glimepiride, hydrocodone/acetaminophen (Vicodin), ibuprofen, isosorbide, potassium chloride, metolazone, memantine hydrochloride (Namenda), clopidogrel (Plavix), primidone, simvastatin, paracetamol, latanoprost, ezetimibe

(Zetia), imipramine hydrochloride (Imipram), utira (Utira-C), augmentin, sulfamethoxazole/trimethoprim (Bactrim DS), and ciprofloxacin (Cipro).

The patient was randomized to the **Placebo Treatment Group** on (b) (6) (**Day 1** of the study), underwent transurethral resection of bladder tumor (TURBT), and received intravesical instillation of 40 mL of study drug (placebo). Study drug instillation was completed within 6 hours of the end of the TURBT procedure, and the patient was able to retain the study drug instillation within the bladder for 60 minutes.

On (b) (6) (**Day 606** post-placebo instillation), the patient was admitted to the hospital complaining of shortness of breath and cough and phlegm production with an inability to expectorate for the previous 10 days. The patient was also unable to swallow and eat and showed increased weakness and irritability with some progressive mental status changes. The results of a physical examination showed a temperature of 96ºF, pulse of 99 bpm, respiratory rate of 20 breaths/min, and a blood pressure of 112/59 mmHg. Rales were present in the right base of the lungs with some rhonchi. Results of a neurological examination showed altered mental status. Laboratory test results showed a blood urea nitrogen value of 30 mg/dL, creatinine value of 1.4 mg/dL, sodium value of 135 mmol/L, ammonia level of 38 µmol/L, serum glutamate oxaloacetic transaminase (SGOT) value of 110 U/L, serum glutamate pyruvic transaminase (SGPT) value of 118 U/L, international normalized ratio of 1.3, white blood cell count of $12x10^9$/L, hemoglobin value of 12 g/dL. Sputum showed Gram-positive cocci clusters. Chest x-rays showed evolving right lung consolidation compatible with pneumonia pattern. A computed tomography scan of the head was negative for active bleeding. The patient was diagnosed with aspiration pneumonia and was treated with bronchodilators (not specified), levofloxacin (Levaquin), piperacillin/tazobactam (Zosyn), and esomeprazole magnesium (Nexium). On (b) (6) (**Day 608** post-placebo instillation), the patient's mental state deteriorated displaying hallucinations, picking at things, grabbing things in the air, increased confusion, disorientation, and agitation. The patient's vital signs showed a blood pressure of 140/70 mmHg, irregular heart rate of 80 bpm, and respiratory rate of 16 breaths/min. An electrocardiogram showed atrial fibrillation, non-specific ST changes and poor R-wave progression, and a probable old anterior wall myocardial infarction. The patient was placed on low dose of beta-blockers (not specified). A barium swallow study dated (b) (6) (**Day 613** post-placebo instillation) was positive for oropharyngeal dysphagia. The patient had a percutaneous endoscopic gastrostomy (PEG) tube placed on (b) (6) (**Day 614** post-placebo instillation). On (b) (6) (**Day 620** post-placebo instillation), the patient developed persistent diarrhea, cough with sputum production, and lethargy, and displayed decreased breath sounds on lung examination. Laboratory test results showed a white blood cell count of $21x10^9$/L, neutrophil count of $54x10^9$/L, creatinine value of 1.5 mg/dL, blood urea nitrogen value of 50 mg/dL, glucose value of 445 mg/dL, and an ammonia level of 52 µmol/L. The patient's blood and urine cultures were negative. A computed tomography (CT) scan of the abdomen was normal. The patient's treatment was changed to vancomycin, piperacillin/tazobactam (Zosyn), and metronidazole (Flagyl). On (b) (6) (**Day 622** post-placebo instillation), the patient became hypotensive and severely septic. A CT scan of the brain and abdomen revealed nonspecific findings. Repeat chest and abdominal x-rays revealed nonspecific changes. The patient developed acute respiratory failure with septic shock and was transferred to the intensive care unit. An electrocardiogram revealed nonsustained wide complex tachycardia and chronic atrial fibrillation. The patient's glucose became severely uncontrollable, sodium value was 147 mmol/L, potassium value was 3.9 mmol/L, chloride value was 116 mmol/L, carbon dioxide

was 20 mIU/L, blood urea nitrogen was 101 mg/dL, creatinine was 3.1 mg/dL, estimated glomerular filtration rate was 20.8 mL/min/1.73m^3, SGOT value was 742 U/L, SGPT value was 361 U/L, amylase value was 214 U/L, and lipase value was 436. The patient developed acute renal failure and was severely dehydrated with respiratory alkalosis. The patient was treated with intravenous fluids, famotidine (Pepcid), acetazolamide (Diamox), lactulose, lorazepam (Ativan), insulin drip, haloperidol (Haldol), olanzapine (Zyprexa), cefepime, vancomycin, and insulin glargine (Lantus). His blood pressure medication and PEG tube feedings were held. The source of the septic shock was unclear. The patient was pronounced dead on (b) (6) (**Day 623** post-placebo instillation).

The event of Pneumonia Aspiration resolved with sequelae and was classified by the Investigator as serious (hospitalization) and unrelated to placebo treatment. The event of Renal Failure Acute was classified by the Investigator as fatal and unrelated to placebo treatment.