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

Study: **SPI-EOQ-13-305**

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

Sponsor: Spectrum Pharmaceuticals, Inc.

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Date : 06 Aug 2015

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1 INTRODUCTION

This statistical analysis plan (SAP) includes information on statistical design of this clinical study, definitions of efficacy and safety endpoints, and plans for the analysis of primary and secondary endpoints of the study. The statistical methods and analyses described here are based on those presented in the clinical study protocol, and supersede definitions and procedures described in any other past and/or present documents regarding the statistical analyses of the efficacy and safety endpoints of study **SPI-EOQ-13-305**.

2 STUDY OBJECTIVES

2.1 Primary Objective(s)

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

2.2 Secondary Objectives

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

3 INVESTIGATIONAL PLAN

3.1 Study Population

Patients with primary or recurrent ≤4 non-muscle noninvasive bladder tumors, who satisfy all protocol-defined enrollment criteria, are eligible to enroll in this randomized study.

3.2 Study Design

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

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

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

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

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

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

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

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

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

The full investigational plan is detailed in the clinical protocol.

3.3 Visit Definitions

Data will be summarized by visit. A patient may or may not have come to the clinic at the scheduled visit time per protocol. Therefore, non-overlapping intervals are defined for visits.

Table 1 List of Scheduled Visits and Visit Windows

Scheduled Visits	Visit Window for Analysis
Day 1	Day of TUR and Apaziquone Instillation (Baseline)
Day 15	**Day 10** to **Day 20;** Apaziquone Instillation for two-dose treatment arm
Month 3	**Day 80** to **Day 100**
Month 6	**Day 170** to **Day 190**
Month 9	**Day 260** to **Day 280**
Month 12	**Day 355** to **Day 375**
Month 15	**Day 445** to **Day 465**
Month 18	**Day 535** to **Day 555**
Month 21	**Day 625** to **Day 645**
Month 24	**Day 720** to **Day 765**

The visit windows should not contain multiple observations for a patient that fall into the same time window. However, if the visit windows do contain multiple observations the following rules will be used. For most analyses, the observation that is closest to the target day will be used. For laboratory data, the "worst case" observation will be used, where "worst case" is defined as the highest toxicity grade or the most abnormal value.

3.4 Study Endpoints

3.4.1 Primary Efficacy Endpoint

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

3.4.2 Secondary Efficacy Endpoints

The secondary efficacy endpoints, ranked according to clinical relevance, are:

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

3.4.3 Safety Endpoints

- All AEs
- All related adverse events
- Serious Adverse Events (SAEs)
- AEs leading to drug discontinuation
- Vital signs (blood pressure and pulse) and routine laboratory parameters (hematology, chemistry)
- Deaths

4 DEFINITIONS AND ALGORITHMS

4.1 Derived Variables

Baseline: Day of Transurethral Resection of Bladder Tumor (TURBT) performed on **Day 1**.

Study Duration: Date of the last patient visit minus date of randomization.

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 will be used for **Recurrence Rate**.

Date of Recurrence: The date of the first cystoscopically confirmed recurrence. The confirmation of the recurrence will be made using an independent pathology report. The detailed algorithm of determination of recurrence and **Time to Recurrence** is provided in **Section 7.3.1**.

Time to Recurrence: Time from randomization to date of first histologically confirmed recurrence of the patients' bladder tumor. Patients without recurrence by **Month 24** cystoscopy assessment visit will be considered to be censored at the last available visit/contact. Patients who died due to any cause before confirmed recurrence by **Month 24** cystoscopy assessment visit will be considered to be censored on the date of death. If the date of death is after **Month 24** cystoscopy assessment visit without a recurrence, the patient will be censored at 24 months. If a patient had a suspected lesion and died before histological confirmation, the date of suspected recurrence will be used as the date of recurrence. The detailed algorithm for the determination of recurrence and **Time to Recurrence** is provided in **Section 7.3.1**.

Time to Progression: Time from randomization to date of first histologically confirmed progression to higher stage of the patients' bladder tumor. Patients without recurrence will be considered to be censored at the last available visit/contact. Patients who died due to any cause before confirmed recurrence will be considered to be censored on the date of death.

5 STATISTICAL CONSIDERATIONS

5.1 General Analysis Considerations

The statistical analyses will be reported using summary tables, figures, and data listings. All analyses and tabulations will be performed using SAS® Version 9.3 or higher. All tables, listings, and figures will be validated and reviewed before being finalized. Independent programming will be conducted to verify tables and listings as appropriate for efficacy endpoint analysis. Tables will be reviewed for accuracy, consistency with this plan, consistency within tables, and consistency with corresponding output.

For the continuous variables, number of non-missing values and mean, standard deviation, median, minimum, and maximum will be tabulated by treatment arm. For the categorical variables, the counts and percent for each possible value will be tabulated by treatment arm. Treatment arms will be compared using chi-square (with continuity correction) or Cochran-Mantel-Haenszel test and two-sided 95% confidence intervals will be provided for proportions and difference in proportions. For time to event data, the log rank test will be used. The distribution of time will be displayed using Kaplan-Meier curves. Hazard ratio and its 95% confidence interval will be provided.

5.2 Sample Size

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

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

The primary analyses of tests of pairwise comparisons of one dose vs. placebo and two doses vs. placebo arms will be performed using 2-sided log-rank test each at 5% level of significance. The primary analysis will be conducted using a hierarchical procedure of hypothesis testing. Hochberg procedure [1] will be used to control the overall Type I error rate due to multiple comparisons for the primary endpoint. If the larger p-value of the two comparisons (one dose vs placebo, two doses vs placebo) is ≤ 0.05, then both comparisons will be considered statistically significant. If the larger p-value of the two comparisons is >0.05 but the smaller p-value is ≤ 0.025, the comparison associated with the smaller p-value will be considered statistically significant. If the larger p-value of the two comparisons is >0.05 and the smaller p-value is >0.025, then neither comparison will be considered statistically significant.

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

1. If both comparisons of primary endpoints (one dose vs. placebo, two doses vs. placebo) are significant ($p \leq 0.05$), the Type I error will be reused for the pairwise comparisons of each secondary endpoint until a test p-value >0.05 in a pairwise comparison (one dose vs. placebo or two dose vs. placebo). No comparison will be made after this point.
2. If one of the comparisons of primary endpoints (either one dose vs. placebo or two doses vs. placebo) is not significant, no reuse of Type I error will be attempted for any of the secondary endpoints.

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

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

Approximately 1869 patients will be enrolled and treated in this study. Accrual time is estimated as 3 years and follow-up time as 24 months. Assuming 54% of patients are recurrence-free for placebo and 60.5% of patients are recurrence-free for the apaziquone treatment arm (assumed to be the same for each arm) at the end of 24-month follow-up, sample sizes of 519 per treatment arm will achieve 80% power to detect superiority in each comparison using log-rank test at 5%

level of significance. The above sample size accounts for 5% of patients lost to follow-up. At the end of the 2-year follow up, this total is assumed to provide 336 recurrence events in the **Placebo Treatment Arm** and 295 recurrence events in each **Apaziquone Treatment Arm** (Hintze, J. [2013]. PASS 12, NCSS, LLC, Kaysville, Utah, USA). The final analysis of the primary endpoint will be conducted once all 336 recurrence events in the **Placebo Treatment Arm** are accrued.

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

5.3 Randomization

The randomization plan will use a permuted block design and will not be stratified. Study drug kits will contain either 1 vial of apaziquone plus 1 vial of placebo, 2 vials of apaziquone, or two vials of placebo and will be patient specific. Patients will be randomized within a center. Patient numbers will be assigned sequentially at each site. Patients will be randomized within a center with a block size of 9. Patient numbers will be assigned sequentially at each site. The study drug will be shipped to study sites in blocks of two to ensure balance at each site. The study drug will be labeled with the randomization numbers, which will consist of four digits that start from 1001 and increase sequentially.

Patients who meet all eligibility criteria may be considered for randomization. Eligibility of all patients will be reviewed and approved for randomization by the Sponsor's Medical Monitor, or designee. Patients approved for randomization will be randomized 1:1:1 to receive either one instillation of 4 mg apaziquone (**Day 1**) plus one dose of placebo (**Day 15** [±5 days]) or two instillations of apaziquone, or two doses of placebo. Following a futility analysis, if a non-efficacious **Apaziquone Treatment Arm** is dropped, the study will be re-randomized to include the remaining **Apaziquone Treatment Arm** and **Placebo Treatment Arm** in a 1:1 ratio as described in **Section 5.6** below.

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

5.4 Baseline Measurements

Baseline measurement of any variable for each patient will be the last available value of the variable on or before the date of **Visit 1**, **Day 1**, which is the day on which the patient undergoes TURBT and first study drug instillation.

5.5 Handling of Missing Data

Except for partial dates, missing data will not be imputed. That is, the analyses will be performed considering all observed data. The effect of missing data on the primary endpoint of **Time to Recurrence** will be evaluated through a series of pre-specified sensitivity analyses (**Section 7.4.2**).

For the date of historical events prior to the study, if the month and day are missing, the date will be imputed as July 1. If the day is missing, it would be imputed as the 15th of the month.

For start date of adverse events and concomitant medications, if the month is missing and the year is the same as the year of randomization, it is assumed that the event is treatment-emergent, and that the medication is taken during the study, unless the stop date occurs prior to the first dose date. In such cases, the start date is imputed as the date of first dose of study drug.

If the year is missing, no imputation will be done for the year, and the entire date variable will be set to missing, and the AE is assumed to be treatment emergent, and concomitant medication is assumed to be started during the study.

The imputed date value will only be used for the calculation of derived variables. The originally collected date value will be presented in the data listings.

For the dates of events which occurred during the study, a missing day is set to the 15th of the month. No imputation will be performed if month and/or year are missing, however missing values will be queried.

5.6 Interim Analysis

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

5.7 Final Analysis

The final analysis of the primary endpoint will be conducted once all 336 recurrence events in the **Placebo Treatment Arm** are accrued. The above required number of events needed to decide on the timing of the final analysis will be tracked by independent, unblinded data monitoring personnel.

Statistical tests of significance will not be stratified. All statistical tests will be conducted at the two-sided 5% level of significance for treatment effects. Statistical tests for primary endpoint analysis are conducted using the method described in **Section 5.2**.

In the event that the primary analysis is performed before all patients complete their **24-Month Follow-up Visit**, a final analysis will be conducted on full data after all patients have the opportunity to complete the 24 month duration of study. The final analysis in this case will be considered to be a sensitivity analysis.

6 STUDY PATIENTS

6.1 Disposition of Patients

Patients will be enrolled after granting informed consent. The following will be summarized on all randomly assigned patients by treatment arms:

- Accrual by country and the Principal Investigator (site)
- Accrual by version of the protocol (if applicable)
- Patients with the target tumor histology (Ta, G1-G2)
- Patients completing the **24-Month Follow-up Visit**
- Patients withdrawn before the **24-Month Follow-up Visit** and reasons for discontinuation

6.2 Protocol Deviations

Deviations will be determined by an internal review of clinical data. These results will be entered into the clinical database and locked prior to breaking the study blind. All important deviations related to study inclusion or exclusion criteria, conduct of the trial, patient management or patient assessment will be recorded, such as:

- Those who entered the study even though they did not satisfy the entry criteria
- Those who developed withdrawal criteria during the study but were not withdrawn.
- Those who received the wrong treatment or with dose compliance outside 80% to 120% of the target dose.
- Those who received an excluded concomitant treatment.

All remaining deviations that are minor will be listed.

7 EFFICACY EVALUATION

7.1 Datasets Analyzed

Four datasets will be analyzed:

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

- **Safety (SAF) Population**: all randomized patients classified according to the actual treatment received, regardless of random assignment.

7.2 Pretreatment Characteristics

Demographics and other **Baseline** characteristics will be summarized for all randomized patients by treatment arms. This includes, among others, age, gender, race, as well as tumor stage and grade based on pathology review.

7.3 Evaluation Criteria

After two instillations of study treatment, patients will be closely followed for the recurrence and/or progression of bladder tumors with assessments and examinations including cystoscopy, urine cytology, and biopsy (if indicated) at 90 day (±10 days) intervals calculated from the date of TURBT throughout the 24-month study participation.

All biopsies/slides will be read by the local pathology laboratory and the results will be used in the analyses of efficacy endpoints. Failure events in this study will be defined as:

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

7.3.1 Algorithm for the Derivation of Recurrence Rate, Time to Recurrence, Progression and Time to Progression

The study efficacy dataset for the study will have the following variables:

1. Time of Instillation relative to TURBT
   a. Date/time of TURBT at **Day 1** – This should be the randomization time point or **Baseline**
   b. Date/time of instillation at **Day 1**
   This Date/Time will be used to calculate the time of instillation relative to TURBT.
2. **Recurrence Rate** and **Time to Recurrence** – following variables will be used.
   a. Date and time of randomization/TURBT
   b. Date of TUR may be available at any post-**Day 1** visits – This will be the time of resection if patient undergoes subsequent resection.
   c. Date of Cystoscopy – to be performed every 3 months. If tumor seen, biopsy will be performed and samples sent to the local pathology laboratory.
   d. Date of Urine Cytology - to be performed every 3 months.
   e. Pathology report date for all visits – when cystoscopy is performed, if tumor is seen by cystoscopy, a biopsy will be performed and the samples will be sent to the local pathology laboratory. This will be the report date. The report date may be much lagged in time due to review and report creation at the pathology lab.
   f. Pathology collection date – available for all time points when samples collected from biopsy and sent to the local pathology laboratory. It is the collection date at the pathology laboratory.

g. Tumor seen (Y/N) at every visit – this is the Site Investigator's observation of whether tumor is seen at the cystoscopy.
h. Histologic grade and stage at every visit – based on the pathology confirmation upon review.

The algorithm should be the following

1. **Recurrence**
   a. Any re-occurrence of either histologic grade or stage or both at any post baseline visit should be considered as recurrence. This can include stage (Ta, T1, T2, Cis) or grade (G1, G2, G3, low grade or high grade).
   b. The baseline is the Date of TURBDT at **Day 1**.
   c. Use the date of recurrence in the following sequence
   d. Date of cystoscopy of a visit when the tumor is histologically confirmed by pathology.
   e. If the date of cystoscopy is not available but histologic stage or grade is positive, use the date of pathology collection for that patient.
   f. If the date of pathology collection is not available but histologic stage or grade is positive and TUR is performed, use the TUR date for that patient. The report date is very late and this scenario should be very rare.
   g. If a patient does not have a recurrence in 2 years ie when 24 month cystoscopy follow up is completed (should be the case for ~50% of patients), the patient should be censored with recurrence is 'No' and the date of the last measurement should be as follows
   h. Date of last cystoscopy performed in that patient by 24 months.
   i. If date of cystoscopy is not available, use the date of pathology collection date.
   j. *If above two are not available, ie, if a patient does not have any follow up cystoscopy, the patient should be censored at baseline.*
   k. If a patient died without any recurrence or prior to recurrence, the patient would be censored using date of death.
   l. If a patient died after 24 month follow up without any recurrence, the date of 24 month follow up will be considered as the date with patient being censored.
2. **Progression**
   a. Disease progression should be considered by reviewing only one histologic Stage only.
   b. Sequence of progression for stage is Cis -> Ta -> T1 -> T2.
   c. Patient is considered progressed if stage progression is observed.
   d. The date of progression uses the same date algorithm as the Item (1) above for recurrence.
   e. If a patient died without any recurrence or prior to recurrence, the patient would be considered progressed with date of death as the date.
   f. If a patient died after 24 month follow up without any recurrence, the date of 24 month follow up will be considered as the date with patient being censored.

The efficacy analysis will be performed using data from the local pathology laboratory.

7.4 Efficacy Results

7.4.1 Efficacy Variables

The primary efficacy variable of the study is **Time to Recurrence**, documented by a local pathology review. The final analysis of **Time to Recurrence** will be conducted once all 336 recurrence events in the **Placebo Treatment Arm** are accrued. Secondary efficacy variables in this study are **Recurrence Rates** at 12 and 24 months, and **Time to Progression**, all documented by local pathology review.

Data from cystoscopy and pathology review will be analyzed for the duration of time between visits, and the number and percent of patients with missing or not evaluable visits. A "missing visit" is a missed scheduled cystoscopy. A "not evaluable visit" is a visit with a "lost" or "inadequate" biopsy specimen.

The following analyses are intended to ensure that missed evaluations are uniform on both arms in a pairwise comparisons and explore whether differences in assessment time intervals exist, and if so, whether or not these differences may account (or partially account) for any observed improvement in **Time to Recurrence**. Data will be summarized by treatment arms:

- Patients with one, two, three, … missing or "not evaluable" follow-up visits
- Product limit estimates of time from randomization to the date of first, second, third, … evaluable visit

For these last set of sensitivity analyses, which evaluate the impact of assessment schedules on **Time to Recurrence**, distribution of time to the *n*th evaluable visit will be estimated using the Kaplan-Meier method. Patients with no *n*th evaluable visit will be excluded.

7.4.2 Time to Recurrence

Time to Recurrence is the time from date of randomization to the date of first documentation of recurrent disease. The detailed algorithm of **Time to Recurrence** is provided in **Section 7.3.1**. **Time to Recurrence** of patients with no documented recurrence while on study will be censored at the date of last evaluable visit (cystoscopy or TURBT) on-study. **Time to Recurrence** of patients with no evaluable visit on-study will be censored at randomization. An evaluable visit is a visit at which the results of pathology review are available.

The primary endpoint of **Time to Recurrence** will be analyzed using the **Target (Ta, G1-G2) Population** as defined above. In addition, the following additional sensitivity analyses will be provided:

- Analysis of **Time to Recurrence** in **Target (Ta, G1-G2) Population** who received only one dose of apaziquone
- Analysis of **Time to Recurrence** in **Target (Ta, G1-G2) Population** who received both doses of apaziquone
- Analysis of **Time to Recurrence** in the **Per-protocol Population** in **Target (Ta, G1-G2) Population** receiving one dose of apaziquone and those receiving both doses of apaziquone
- If a patient undergoes a change in treatment during the follow up without a recurrence, patient is considered to have an event

- If a patient drops out prior to completion of follow up or recurrence, patient is considered to have an event.

The following patient data will be considered as protocol deviations and will be addressed in the analysis of **Time to Recurrence** using the **Per-Protocol Population**.

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

For the above analysis, following data handling rules will be used.

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

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

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

7.4.3 Recurrence Rates

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

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

7.4.4 Time to Progression

Time to Progression (or progression-free interval, PFI) is the time from randomization to the first documentation of progression as confirmed by pathology review in the **Target (Ta, G1-G2) Population**. **Time to Progression** of patients with no documented progression on-study will be

censored at the time of last evaluable visit on-study. **Time to Progression** of patients with no evaluable visit on-study will be censored at randomization.

Distribution of **Time to Progression** will be estimated using the Kaplan-Meier method. The median times to progression with two-sided 95% confidence intervals will be estimated, together with the estimates at 6, 12, 18 and 24 months. A log-rank test will be used as the primary analysis for treatment comparison. A Cox proportional hazards model will be used to estimate the hazard ratio, and its 95% confidence interval.

7.4.5 Subgroup Analyses

Time to Recurrence and the **1-Year** and **2-Year Recurrence Rates** will also be analyzed by the stratification factors and other relevant pretreatment characteristics including age, gender, primary or recurrent disease, tumor stage and grade at entry, and other important factors like white light TURBT and blue light TURBT, and the resulting hazard or odds ratios, with corresponding 95% confidence intervals, will be summarized by treatment arms.

8 SAFETY EVALUATION

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

8.1 Extent of Exposure

Number of instillations per patient, instillation interruptions and delays, withdrawals, and reasons for exposure modifications will be summarized by treatment arms.

8.2 Concomitant Medications

Concomitant medications will be classified by WHO Drug Dictionary, and summarized by the WHO preferred name and Anatomical Therapeutic Chemical (ATC) classification and by treatment arms.

8.3 Adverse Events

All treatment emergent adverse events will be graded according to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 4.03, and grouped by the MedDRA preferred term, and summarized by worst grade severity per patient by treatment arms. Similar summaries will be generated for treatment-related adverse events, which are adverse events deemed to be possibly, probably, or definitely related to study treatment.

Treatment emergent adverse events are those adverse events that occur or worsen on or after the initial post-TURBT instillation of apaziquone, through 35 days after the last instillation of apaziquone, and/or treatment-related adverse events, regardless of the onset date. After 35 days and through 24 months, only SAEs and AEs ≥Grade 3 will be recorded.

8.4 Deaths, Other Serious Adverse Events, Other Significant Adverse Events

Serious adverse events are those events that result in death, are life-threatening, require or prolong inpatient hospitalization, result in persistent or significant disability/incapacity, or cause congenital anomaly/birth defect.

8.4.1 Deaths

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

8.4.2 Other Serious Adverse Events

Other serious adverse events will be tabulated and summarized by MedDRA preferred term and treatment arm. Similar summaries will be generated for treatment-related serious adverse events.

8.4.3 Other Significant Adverse Events

All other events leading to discontinuation of study therapy or any other premature interruption will be tabulated and summarized by treatment arm.

8.5 Clinical Laboratory Evaluations

Clinical laboratory samples are collected pretreatment and throughout study. Blood samples are to be analyzed at central laboratories. Clinically significant laboratory abnormalities are to be reported as adverse events.

Where applicable, all laboratory results will be classified according to the NCI CTCAE version 4.03. Results will be summarized by worst grade per patient and treatment arms. Shifts in laboratory CTCAE grades from baseline grade to the worst grade toxicity on-study will be summarized.

8.6 Vital Signs

Data on Vital signs at each time point and change from baseline will be summarized by treatment arm.

9 REFERENCES

1. Hochberg Y. A Sharper Bonferroni Procedure for Multiple Tests of Significance. Biometrika. 1988;75(4):800-2.