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

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STATISTICAL ANALYSIS PLAN

Study: **SPI-QAP-306**

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

Sponsor: Spectrum Pharmaceuticals, Inc.

Version: 1.0

Date: 30 May 2019

Author: [redacted] 8/27/2020

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Approval: [redacted] 8/27/2020

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[redacted]

Summary of Changes from protocol

The SAP is to accommodate the early termination of the study due to business reason. Important changes are summarized below.

1. All efficacy objectives are removed.
2. All efficacy endpoints are removed, including all corresponding analysis.
3. The following Analysis Populations are removed.
    - Target Population
    - Non-Target Population
    - Per-Protocol (PP) Population
4. Interim Analysis is removed.
5. Sensitivity analysis and subgroup analysis are removed.

TABLE OF CONTENTS

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-13-306**.

2 STUDY OBJECTIVES

2.1 Primary Objective

- To evaluate the safety in patients with low- to intermediate-risk NMIBC who receive either 8 mg Qapzola or placebo post- TransUrEthral Resection of Bladder Tumors (TURBT).

3 INVESTIGATIONAL PLAN

3.1 Study Population

Patients with low- to intermediate-risk non-muscle invasive bladder cancer, who satisfy all protocol-defined enrollment criteria, are eligible to enroll in this randomized study.

3.2 Study Design

This is a randomized, multicenter, two-arm, double-blind, placebo-controlled study of Qapzola in patients with low- to intermediate-risk NMIBC.

At Screening, patients will undergo an assessment of urothelial carcinoma of the bladder via cystoscopy for clinically apparent tumor of Ta histology, including PUNLMP.

On **Day 1**, eligible patients will be randomized to one of the two treatment arms in a 2:1 ratio:

- **Arm 1- One Dose of 8 mg Qapzola**
- **Arm 2- One Dose of Placebo**

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

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

3.3 Study Duration

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

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

The study was terminated early due to business reason and no patient was followed more than 24 months.

3.4 Study Endpoints

3.4.1 Efficacy Endpoints

The study was terminated early due to business reason and analysis for efficacy endpoints will not be performed.

3.4.2 Safety Endpoints

- All TEAEs
- Treatment related adverse events
- Serious Adverse Events (SAEs)
- TEAEs leading to drug discontinuation
- Routine laboratory test parameters (hematology, chemistry)
- Deaths

4 STATISTICAL CONSIDERATIONS

4.1 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 9.4 or higher. All tables, listings, and figures will be validated and reviewed before being finalized. 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.

4.2 Sample Size

The sample size calculation assumes a hazard ratio (HR) of 0.65 based on the results from previous Phase 3 studies (**SPI-611 and SPI-612**) of Qapzola and placebo comparisons overall and in the drug instillation time window 31-90 minutes post-TURBT. The enrolled patients will be randomized in a 2:1 ratio to either Qapzola or placebo.

Approximately 500 patients will be enrolled and treated in this study. Accrual time is estimated as 24 months and follow-up time as approximately 24 months. For the sample size calculation, a hazard ratio (HR) of 0.65 is assumed for the improvement in **Time to Recurrence** in favor of Qapzola as compared to the placebo with a hazard rate of 0.3 in placebo arm. In a 2:1 randomization of Qapzola and placebo, sample sizes of 284 in APZ and 141 in PBO Target disease patients (total of 425) will provide 85% power. This sample size is estimated to provide a total of 208 recurrence events during the follow-up duration of at least 24 months.

The study was terminated early due to business reason and patient recruitment was incomplete.

4.3 Randomization

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

Patients who meet all eligibility criteria may be considered for randomization. Eligibility of all patients will be reviewed and approved for randomization by the Sponsor's Medical Monitor, or designee. Patients approved for randomization will be randomized 2:1 to receive either one instillation of 8 mg Qapzola (**Day 1**) or one dose of placebo.

4.4 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.

4.5 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.

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 or year is missing, however missing values will be queried.

4.6 Analysis Population

- **Safety Population**: including all patients who have had a TURBT and have received treatment of study drug. The patients in safety population will be classified according to the actual treatment received, regardless of random assignment.

4.7 Final Analysis

The study was terminated early due to business reason and the final analysis will be performed for safety endpoints only.

5 STUDY PATIENTS

5.1 Disposition of Patients

Patients in defined populations as shown in **Section** 4.6 and reasons for discontinuation will be summarized by randomized treatment arms.

5.2 Pretreatment Characteristics

Demographics, including gender, age, race, and smoking status will be summarized by actual treatment arms for patients in **Safety Population**.

6 EFFICACY EVALUATION

The study was terminated early due to business reason and analysis for efficacy endpoints will not be performed.

7 SAFETY EVALUATION

Safety endpoints will be evaluated for **Safety Population** and patients will be classified according to actual treatment received.

7.1 Extent of Exposure

Summary table and listing will be provided for instillation time from TURBT, volume of instillation, and duration of retention.

7.2 Concomitant Medications

Concomitant medications will be classified by WHO Drug Dictionary and be reported in listing.

7.3 Adverse Events

An overall summary table of treatment emergent adverse events (TEAE) will be provided. The summary will include any TEAE, TEAE by severity, SAE, TEAE and SAE leading to study drug discontinuation, any treatment-related AE, treatment-related AE by severity, treatment-related SAE, and treatment-related AE leading to study drug discontinuation.

7.3.1 Treatment Emergent Adverse Events

A TEAE is any AE that occurs from the first dose of study treatment until 35 days after the last dose of study drug administration. TEAEs 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.

The incidences of treatment emergent AEs will be presented by MedDRA SOC and PT with any grade and with Grade 3 or 4. Patients who experience more than one type of AE will be counted under each of the corresponding PT. Patients who experience different episodes of the same AE will be counted only once under the corresponding PT. Similarly, for determination of MedDRA SOC incidences, patients who experience multiple AEs under the same SOC will be counted only once for that SOC. Listing of all TEAEs will also be provided.

7.3.2 Treatment-Related Adverse Events

Assessment of relatedness to study drug for all AEs will be classified by investigators and reported. "Definitely related", "probably related" and "possibly related" AEs will be considered as treatment related. An AE will be assigned as treatment-related if the relationship to study drug is missing.

The incidences of treatment-related AEs will be presented by MedDRA SOC and PT with any grade and with Grade 3 or 4.

7.3.3 Serious 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.

All SAEs will be provided in listing and the incidence will be summarized in the overall summary of TEAE table.

7.3.4 Other Important Adverse Events

TEAEs leading to death and study drug discontinuation will be presented in separate listings and the incidence will be summarized in the overall summary of TEAE table.

7.4 Clinical Laboratory Evaluations

Clinical laboratory samples are collected pretreatment and throughout study. Where applicable, all laboratory results will be classified according to the NCI CTCAE version 4.03. Results will be provided in listing.

8 REFERENCES

None.