Clinical Study Report Synopsis for Public Disclosure

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The study listed may include approved and non-approved uses, formulations, or regimens. It is not intended to promote any product or indication and is not intended to replace the advice of a health care professional. The results reported in any single study may not reflect the overall profile of a product. Patients should always seek medical advice before making any decisions on their treatment. Before prescribing any product mentioned in this report, healthcare professionals should consult local prescribing information for the product approved in their country or region.

2. SYNOPSIS

Name of Sponsor/Company: Spectrum Pharmaceuticals, Inc	Individual Study Table Referring to Part of the Dossier	(For National Authority Use Only)
Name of Finished Product: EOquin™	Volume	
Name of Active Ingredient: Apaziquone	Page	

Title of study:	Pilot study of the intravesical administration of EOquin® immediately following transurethral resection in patients with superficial bladder cancer
Protocol no:	SPI-515
Primary Principal Investigator:	Professor [redacted], M.D., and [redacted], M.D.
Study center(s):	9 centers (8 in USA and 1 in The Netherlands)
Publication(s)	Not applicable

Studied period (years): 1 First subject enrolled: 25 July 2006 Last subject completed: 13 March 2007	**Phase of development:** 2

Objectives:

Primary objective: To investigate the safety and tolerability of a single immediate post-transurethral resection (TUR) intravesical instillation of 4 mg/40 mL EOquin®.

Secondary objective: To evaluate the pharmacokinetics of EOquin® following immediate post-TUR intravesical instillation.

Methodology: This study was designed as an open-label pilot trial to evaluate the safety, tolerability, and pharmacokinetics of a single immediate post-TUR intravesical instillation of 4 mg/40 mL EOquin® in patients with superficial bladder cancer (SBC).

All patients were screened for study eligibility up to two weeks before the scheduled TUR. Eligible patients were scheduled for instillation of EOquin® 4 mg/40 mL on day 1 (within six hours from TUR) and evaluated on days 8 and 15. The first 10 patients with histologically confirmed Stage Ta or T1, Grade 1-2 tumors were evaluated at month 3 with cystoscopy. At each visit patients had a physical examination with vital sign measurements, clinical laboratory samples obtained, and the recording of adverse events and concomitant medications. In addition, selected sites obtained blood samples for pharmacokinetic (PK) parameters on day 1.

Number of subjects (planned and analyzed): Planned: 20; Enrolled: 23;
Evaluable (received treatment): 20

Diagnosis and main criteria for inclusion:

Patients were 18 years of age and older with Stage Ta or T1, Grade 1-2 superficial bladder cancer (SBC) and with ≤ 4 lesions, largest diameter being < 3.5 cm. Patients had to have an ECOG performance status ≤ 2, ANC ≥ 1.5×10^9/L, platelets ≥ 100×10^9/L, serum creatinine and bilirubin ≤ 1.5 × upper local normal (ULN), and transaminases ≤ 3 × ULN. Patients were excluded if they had likelihood of a muscle-invasive (T2) or higher stage disease, a recurrence within 3 months from the last previous manifestation of SBC, or prior intravesical treatment with either 3 or more single dose instillations or one 6-week course of chemotherapy or any prior intravesical BCG.

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Test product, dose and mode of administration, batch number:

EOquin®, 4 mg in 40 mL, administered by intravesical instillation within six hours from TUR. Retention of instillate was one hour. Lot number of EOquin® was: 101005JH2. The diluent (sodium bicarbonate and disodium edetate in a 60:40 mixture of propylene glycol and water) lot number was 051020E1.

Duration of treatment:

The treatment was single dose (EOquin 4mg/40mL) intravesical instillation within 6 hours of TUR. The instillate was retained in the bladder for 1 hour. All subjects were followed for 15 days and 10 of these subjects were also followed at 3 months (day 85) with cystoscopy.

Reference therapy, dose and mode of administration, batch number: Not applicable

Criteria for evaluation:

Efficacy: Not applicable

Safety: Safety was monitored by physical examinations, vital signs, clinical laboratory parameters (hematology, chemistry, and urinalysis), adverse events, and performance status scores. The first 10 patients with histologically confirmed Stage Ta or T1, Grade 1-2 tumors were monitored 3 months after TUR by clinical laboratory tests, urinalysis, and cystoscopy.

Statistical methods:

The statistical analysis incorporates all study visits. This was an open label pilot study and therefore no comparisons between groups were made.

Cystoscopic (activity) The cystoscopic analyses was performed on the cystoscopic population, defined as the first ten patients who had Ta or T1 and G1 or G2 grade histology and who had undergone the cystoscopic evaluation scheduled for month 3.

Safety: All patients who received one dose of EOquin® and who had at least one post-treatment safety assessment were included in the safety analyses. Exposure to treatment and dosing data were summarized using descriptive statistics and frequency counts. Adverse events (AEs) coded to MedDRA terminology (version 9.0) were summarized in tables showing both incidence and total reports. AEs were summarized by maximum severity and closest relationship to treatment. Serious adverse events were summarized separately.

Laboratory data were graphically summarized for each treatment visit and summarized by patient. Vital signs were also summarized by each visit and cystoscopic examination was reported using frequency counts and percents for patients who met the criteria. Urine cytology and physical examinations were listed separately for each patient.

Pharmacokinetic: The PK population is comprised of patients who received EOquin®, gave informed consent to blood samples, and have at least one PK blood sample drawn. Descriptive statistics and frequency counts were used to summarize the detectability of serum apaziquone and the metabolite E05A.

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Summary and conclusions:

Disposition: A total of 23 patients were enrolled in the study and 20 received treatment. Three patients did not receive treatment for the following reasons: bladder perforation at TUR, no tumor seen at TUR, and one patient was hospitalized prior to TUR for an unrelated medical problem. Of the 20 patients treated, one patient (5%) did not complete day 15 as [redacted] was hospitalized for post procedural haemorrhage and cystitis. The ten patients meeting histologic criteria (Ta or T1, G1-2) completed 85 days on study. The mean age of the study population was 72.5 years and ranged from 54 to 86 years. Eighteen patients (90%) were White and 15 patients (75%) were male. The mean number of lesions was 1.3 with a mean lesion size of 1.6 cm.

Pharmacokinetic: Six patients had blood sampling for PK parameters. Apaziquone and its metabolite (E05) were not detectable at any time point.

Safety Results: All patients who received EOquin®, received 40 mL of instillate and all patients tolerated the EOquin®, retention for one hour.

Thirteen patients (65%) reported 35 treatment-emergent AEs. AEs most often occurred in the Renal and Urinary or Gastrointestinal Disorders systems with the most frequently reported adverse events occurring in more than one patient being dysuria (7 patients, 35%), abdominal pain lower (5 patients, 25%), haematuria (3 patients, 15%), and urinary retention, and urinary tract infection (2 patients each, 10%).

Eight patients (40%) reported at least one adverse event that was considered related to treatment. Adverse events considered related to treatment include dysuria, haematuria, bladder spasm, abdominal pain, asthenia, and urinary retention post operatively. All related AEs except bladder spasm were classified as possibly related to treatment; bladder spasm was classified as definitely related to treatment.

The majority of adverse events were mild to moderate in intensity. Two patients (10%) reported four grade 3 or 4 AEs. The AEs were flank pain, urinary retention, cystitis, and post procedural haemorrhage and all were considered by the Investigator to be unrelated to treatment.

There were four SAEs experienced by three patients. Two - SAEs were classified as possibly related to treatment; urinary retention post operatively (Patient [redacted]) and haematuria (Patient [redacted]). Patient [redacted] did not complete the day 15 visit as [redacted] was hospitalized at the time of that visit for cystitis and post procedural haemorrhage, which were considered by the Investigator to be unrelated to treatment. No patient died during the study.

No clinically meaningful changes were observed in clinical laboratory test results, physical examinations, vital sign measurements, performance status scores, urine cytology, and cystoscopic examination results.

Conclusions: These study results in 20 patients demonstrate that instillation of EOquin® within 6 hours following TUR for superficial bladder cancer was well tolerated with a relatively benign safety profile. The most common AEs observed in this study are also known complications of TUR. EOquin® was not absorbed in any detectable amounts through the bladder.

Date of the report: 17 August 2007