ClinicalTrials.gov Protocol Registration and Results System (PRS) Receipt
Release Date: September 7, 2017

ClinicalTrials.gov ID: NCT00461591

Study Identification

Unique Protocol ID:	SPI-611
Brief Title:	Single Dose Intravesical Apaziquone Postoperative in Patients Undergoing TURBT for Noninvasive Bladder Cancer (SPI-611)
Official Title:	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)
Secondary IDs:	

Study Status

Record Verification:	July 2017
Overall Status:	Completed
Study Start:	April 2007 [Actual]
Primary Completion:	January 2012 [Actual]
Study Completion:	January 2012 [Actual]

Sponsor/Collaborators

Sponsor:	Spectrum Pharmaceuticals, Inc
Responsible Party:	Sponsor
Collaborators:	

Oversight

U.S. FDA-regulated Drug:	

U.S. FDA-regulated Device:	
Unapproved/Uncleared Device:	No
U.S. FDA IND/IDE:	Yes
IND/IDE Information:	FDA Center: CDER IND/IDE Number: 73572 Serial Number: 0018 Has Expanded Access: No
Human Subjects Review:	Board Status: Approved Board Name: New England IRB Board Affiliation: NEIRB Phone: (800)232-9570 Email: kerri.yuszkus@neirb.thomson.com Address: 40 Washington Street Wellesley, MA 02481
Data Monitoring:	No
FDA Regulated Intervention:	Yes
Section 801 Clinical Trial:	Yes

Study Description

Brief Summary:	The purpose of this study was to evaluate the 2-Year Recurrence Rate of bladder cancer in randomized patients with tumor histology Ta, G1-G2 who received TransUrethral Resection of Bladder Tumor (TURBT) plus apaziquone versus those who received TURBT plus placebo.
Detailed Description:	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.

Conditions

Conditions: Bladder Cancer

Keywords: Noninvasive Bladder Cancer

Study Design

Study Type: Interventional

Primary Purpose: Treatment

Study Phase: Phase 3

Interventional Study Model: Parallel Assignment

Number of Arms: 2

Masking: Quadruple (Participant, Care Provider, Investigator, Outcomes Assessor)

Allocation: Randomized

Enrollment: 802 [Actual]

Arms and Interventions

Arms	Assigned Interventions
Experimental: Apaziquone TURBT + a single intravesical dose of Apaziquone 4mg in 40ml instilled into the bladder post-TURBT	Drug: Apaziquone A single intravesical dose of Apaziquone 4mg in 40ml instilled into the bladder post-TURBT Other Names: • EOquin®, Qapzola Procedure/Surgery: TURBT TransUrethral Resection of the Bladder Tumor
Placebo Comparator: Placebo TURBT + a single intravesical dose of placebo instilled into the bladder post-TURBT	Drug: Placebo A single intravesical dose of placebo instilled into the bladder post-TURBT Procedure/Surgery: TURBT TransUrethral Resection of the Bladder Tumor

Outcome Measures

[See Results Section.]

Eligibility

Minimum Age: 18 Years

Maximum Age:

Sex: All

Gender Based:

Accepts Healthy Volunteers: No

Criteria: Inclusion Criteria: (All questions must be answered YES)

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

Exclusion Criteria: (All questions must be answered NO)

- Does the patient have more than 4 bladder tumors?
- Does any single bladder tumor exceed 3.5 cm in diameter?
- Does the patient have a single, primary (no previous diagnosis of TCC) bladder tumor <0.5 cm?
- Has the patient ever received Apaziquone?
- 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])?
- Does the patient have, or has the patient ever had any bladder tumor with histology other than transitional cell carcinoma?
- Does the patient have, or has the patient ever had, carcinoma in situ (CIS)?
- Does the patient have an active urinary tract infection?
- Does the patient have a bleeding disorder or a screening platelet count < 100 x 10^9/L?
- Does the patient have any unstable medical condition that would make it unsafe for him/her to undergo TURBT under general or spinal anesthesia?
- Does the patient have a screening hemoglobin < 10 mg/dL, a screening absolute neutrophil count < 1.5 x 10^9/L or a screening creatinine > 2 mg/dL?
- Does the patient have a known immunodeficiency disorder?
- Has the patient received any investigational treatment within the past 30 days?
- Is the patient breast feeding?
- Does the patient have a history of interstitial cystitis?
- Does the patient have a history of allergy to red color food dye?
- Has the patient had transitional cell carcinoma of the bladder within the past 4 months?

Contacts/Locations

Central Contact Person: William Le

Telephone: 972-207-4209
Email: william.le@sppirx.com

Central Contact Backup:

Study Officials: Shanta Chawla, MD
Study Director
Spectrum Pharmaceuticals, Inc

Locations: **United States, Alaska**
Alaska Clinical Research Center, LLC
Anchorage, Alaska, United States, 99508
Contact: Mary Anderson 907-276-1455
Principal Investigator: William Clark, MD

United States, Arizona
BCG Oncology
Phoenix, Arizona, United States, 85032
Contact: Mary Heeley 602-493-6626
Principal Investigator: Don Lamm, MD

United States, California
Urology Associates Medical Group
Burbank, California, United States, 91505
Contact: Alicia Buenrostro 818-843-1700
Principal Investigator: Phillip Weintraub, MD

Urology Associates of Central CA
Fresno, California, United States, 93720
Contact: Marj Henry 559-321-2841
Principal Investigator: William Schiff, MD

Citrus Valley Medical Research
Glendora, California, United States, 91741
Contact: Lisa Regan 626-914-3295
Principal Investigator: Edward L. Davis, MD

South Orange County Medical Research Center
Laguna Woods, California, United States, 92653
Contact: Erika Pirtle, RN 949-215-9515 Ext. 1
Principal Investigator: Richard Greengold, MD

Kaiser Permanente Los Angeles Medical Center
Los Angeles, California, United States, 90027
Contact: Sandra T. Baker, RN 323-783-5532
Principal Investigator: Stephen G. Williams, MD

Cancer Research Dept/St. Joseph Hospital
Orange, California, United States, 92868
Contact: Carol Dickey 714-734-6220
Contact: Ron Bati 714-734-6220
Principal Investigator: William Pearce, MD

San Bernardino Urologic Association
San Bernardino, California, United States, 92404
Contact: Charity Hernandez 909-881-0555
Principal Investigator: Daniel Lama, MD

VA San Diego Healthcare System
San Diego, California, United States, 92161
Contact: Kimberly Christensen 858-552-8585 Ext. 2711
Principal Investigator: Tracy M. Downs, MD

VA Medical Center
San Francisco, California, United States, 94121
Contact: Evelyn Badua 415-221-0481 Ext. 4455
Principal Investigator: Kristen Greene, M.D.

United States, Colorado
The Urology Center of Colorado
Denver, Colorado, United States, 80211
Contact: Valerie Conaway 303-421-5783
Principal Investigator: Lawrence Karsh, MD

United States, Connecticut
Connecticut Clinical Research Center
Middlebury, Connecticut, United States, 06762
Contact: Brendaliz Konopka 203-757-3588 Ext. 368
Principal Investigator: Robert Feldman, MD

United States, District of Columbia
Urologic Surgeons of Washington
Washington, District of Columbia, United States, 20006
Contact: Ruby Marcias 202-223-1024 Ext. 225
Principal Investigator: Jason D. Engel, MD

United States, Florida
Lakeland Regional Cancer Center
Lakeland, Florida, United States, 33805
Contact: Robin Stewart, RN, PhD 893-904-1877
Principal Investigator: Byron G. Hodge, MD

Urology Consultants

Longwood, Florida, United States, 32750
Contact: Stacey Kinsey 407-332-0777
Principal Investigator: Steven Brooks, MD

University of Miami
Miami, Florida, United States, 33136
Contact: Angelique Brown 305-243-7207
Principal Investigator: Mark Soloway, MD

Advanced Research Institute
New Port Richey, Florida, United States, 34652
Contact: Gabrielle Handerson 727-835-3261
Principal Investigator: Juan Otheguy, MD

Advanced Research Institute
New Port Richey, Florida, United States, 34655
Contact: Gabrielle Henderson 727-835-3262
Principal Investigator: Ramon Perez-Marrero, MD

Florida Foundation for Healthcare Research
Ocala, Florida, United States, 34474
Contact: Joanne Grover 352-237-3949
Principal Investigator: Ira Klimberg, MD

Florida Urology Specialists
Sarasota, Florida, United States, 34237
Contact: Janice Spector 941-309-7000 Ext. 7117
Principal Investigator: Thomas Williams, MD

Southeastern Research Group, Inc.
Tallahassee, Florida, United States, 32308
Contact: Laurel Manfre 850-201-0411
Principal Investigator: J. Daniell Rackley, MD

Tampa Bay Urology Research
Tampa, Florida, United States, 33607
Contact: Linda Seibert 813-872-7881
Principal Investigator: Tod Fusia, MD

United States, Georgia
Gainesville Urology, PC
Gainesville, Georgia, United States, 30501
Contact: Suzanne McNeal 770-532-8438
Principal Investigator: David Woo, M.D.

Urological Professional Association

Macon, Georgia, United States, 31217
Contact: Ginger Stafford 478-742-0932 Ext. 305
Principal Investigator: Lance Patterson, MD

United States, Idaho
North Idaho Urology
Coeur d'Alene, Idaho, United States, 83814
Contact: Patti Patterson, RN 208-667-0621 Ext. 225
Principal Investigator: Randil L. Clark, MD, PhD

Idaho Urologic Institute, P.A.
Meridian, Idaho, United States, 83642
Contact: Shana Vail 208-639-4938
Principal Investigator: Stephen Miller, MD

United States, Illinois
University of Chicago
Chicago, Illinois, United States, 60637
Contact: Josephine Silvestre 773-702-0792
Principal Investigator: Gary Steinberg, MD

Urology Associates, SC
Mattoon, Illinois, United States, 61938
Contact: Keith Ballinger 217-348-4186
Principal Investigator: David Di Domenico, MD, DO

Speciality Care Research
Peoria, Illinois, United States, 61614
Contact: Diane Koch 309-683-1125
Principal Investigator: Giovanni Colombo, MD

United States, Indiana
Northeast Indiana Research, LLC
Fort Wayne, Indiana, United States, 46825
Contact: Linda Keller, RN 260-434-1939
Principal Investigator: Christopher Steidle, MD

Metropolitan Urology
Jeffersonville, Indiana, United States, 47130
Contact: Debbie Johnson 812-288-2611
Principal Investigator: James Bailen, MD

United States, Kansas
Kansas City Urology Care, P.A.
Overland Park, Kansas, United States, 66211
Contact: John Beuscher 913-647-4173

Principal Investigator: Steven Nash, MD

United States, Louisiana
Regional Urology, LLC
Shreveport, Louisiana, United States, 71106
Contact: Tracey Robinson 318-683-0411 Ext. 173
Principal Investigator: Ralph J. Henderson, MD

United States, Maryland
Anne Arundel Urology
Annapolis, Maryland, United States, 21401
Contact: Elizabeth D'Antonio 410-266-8049 Ext. 143
Principal Investigator: Kent Krejci, MD

Myron Murdock, MD, LLC
Greenbelt, Maryland, United States, 20770
Contact: Lisa Drezer, MD 301-474-1111
Principal Investigator: Myron Murdock, MD

United States, Michigan
MMPC Urology
Grand Rapids, Michigan, United States, 49546
Contact: Maureen S. Gebben, RN 616-974-4604
Principal Investigator: Richard J. Kahnoski, MD

Lakeside Urology, PC
Saint Joseph, Michigan, United States, 49085
Contact: Barbara Krantz, LPN 269-982-7076 Ext. 21
Principal Investigator: Benjamin Stockton, M.D.

Michigan Institute of Urology, PC
Troy, Michigan, United States, 48084
Contact: Danielle Osterhout 248-786-0467
Principal Investigator: Juan Rene Frontera-Castillo, MD

United States, Montana
Five Valleys Urology
Missoula, Montana, United States, 59802
Contact: Jennifer Hays 406-329-2864
Principal Investigator: Karl Westenfelder, MD

United States, Nebraska
Urology Health Center
Fremont, Nebraska, United States, 68025
Contact: Tonya Hemmer 402-727-5000
Contact: Deb Womeldorf 402-727-5000

Principal Investigator: A. U. Khan, MD

United States, New Jersey

Coastal Urological Associates, PA
Brick, New Jersey, United States, 08724
Contact: Carol A. McGee, RN 732-840-4300
Principal Investigator: Daniel T. Burzon, MD

AdvanceMed Research
Lawrenceville, New Jersey, United States, 08648
Contact: Deb Kenner 609-482-2237
Principal Investigator: Gary Karlin, MD

Delaware Valley Urology, LLC-Marlton
Marlton, New Jersey, United States, 08053
Contact: Diane Horner 856-985-4286
Principal Investigator: Charles Orth, Jr., MD

Deleware Valley Urology, LLC-Washington Township
Sewell, New Jersey, United States, 08080
Contact: Barbara Schaffhauser 856-218-3025
Principal Investigator: Robert Barsky, DO

Delaware Valley Urology, LLC - Voorhees
Voorhees, New Jersey, United States, 08043
Contact: Jael Johnson 856-751-5288
Principal Investigator: Louis Keeler, MD

Delaware Valley Urology, LLC-Westampton
Westampton, New Jersey, United States, 08060
Contact: Renee Haney 609-914-0021 Ext. 125
Principal Investigator: Robert Goldlust, MD

United States, New Mexico

Urology Group of New Mexico
Albuquerque, New Mexico, United States, 87109
Contact: Mary Lou Jones 505-872-4090 Ext. 118
Principal Investigator: Frederick Snoy, MD

United States, New York

The Urological Institute of NE NY
Albany, New York, United States, 12208
Contact: Donna Julian 518-262-8579
Contact: Brenda Romeo 518-262-8579
Principal Investigator: Badar Mian, MD

Capital Region Urological Surgeons
Albany, New York, United States, 12208
Contact: Linda Abriel, ANP 518-438-1019 Ext. 256
Principal Investigator: Michael Perrotti, MD

Adult and Pediatric Urology
Carmel, New York, United States, 10512
Contact: Shanna McEnaney 845-279-1100 Ext. 104
Principal Investigator: Jay S. Motola, MD, FACS

Urological Surgeons of Long Island, P.C.
Garden City, New York, United States, 11530
Contact: Vincent Gandolfo 516-742-3200
Principal Investigator: Robert Edelman, MD

Accumed Research Associates
Garden City, New York, United States, 11530
Contact: Kerri Weingard 516-746-2190
Principal Investigator: Mitchell Efros, MD

Hudson Valley Urology, PC
Kingston, New York, United States, 12401
Contact: Jeanie Hefele 845-339-4900 Ext. 110
Principal Investigator: Jose Sotolongo, MD

University Urology Associates
New York, New York, United States, 10016
Contact: Betsy Ortiz-Moclair 212-686-9015 Ext. 9
Principal Investigator: Jed Kaminetsky, MD

CNY Urology, PC
Oneida, New York, United States, 13421
Contact: Melissa Clark 315-363-8862
Principal Investigator: Bashar Omarbasha, MD

Hudson Valley Urology
Poughkeepsie, New York, United States, 12601
Contact: Alexa H Markiewicz 845-458-8730 Ext. 1051
Principal Investigator: Evan Goldfischer, MD

Urology Associates of Rochester, LLC
Rochester, New York, United States, 14618
Contact: Paul Scheib 585-232-2980
Principal Investigator: David Dever, MD

Center for Urologic Research of WNY, LLC

Williamsville, New York, United States, 14221
Contact: Debbie A. D'Orazio, RN 716-631-9654
Principal Investigator: Philip J. Aliotta, MD

United States, North Carolina
Wake Urological Associates
Raleigh, North Carolina, United States, 27607
Contact: Jan Vickerson 919-782-1255
Principal Investigator: Richard D. Kane, MD

United States, Ohio
TriState Urologic Services PSC, Inc.
Cincinnati, Ohio, United States, 45212
Contact: Pamela Ervin 513-366-3412
Principal Investigator: Bernard L Hertzman, MD

University Urologists of Cleveland, Inc.
Cleveland, Ohio, United States, 44106
Contact: Claudia Lillibridge 216-844-8205
Principal Investigator: Edward Cherullo, MD

Columbus Urology Research, LLC
Columbus, Ohio, United States, 43220
Contact: Pam Detillio, LPN 614-457-6028
Principal Investigator: Jeffrey D. Harbrecht, MD

United States, Oregon
Oregon Urology Institute
Springfield, Oregon, United States, 97477
Contact: Janice Bebee 541-284-5508
Principal Investigator: Dawn Bodell, DO

United States, Pennsylvania
Urologic Consultants of South Eastern Pennsylvania
Bala-Cynwyd, Pennsylvania, United States, 19026
Contact: Cheryl Zinar 610-667-0458
Principal Investigator: Lawrence Belkoff, DO

Urological Associates of Lancaster
Lancaster, Pennsylvania, United States, 17604
Contact: Dorie Rodriguez 717-431-2285
Principal Investigator: Paul Seiber, MD

Fox Chase Cancer Center
Philadelphia, Pennsylvania, United States, 19111-2497
Contact: Trish O'Brien 215-214-3993

Principal Investigator: Richard Greenberg, MD

Triangle Urology Group
Pittsburgh, Pennsylvania, United States, 15212
Contact: Chantal Mitchell 412-246-2458
Principal Investigator: John Lyne, MD

Susquehenna Urology
Williamsport, Pennsylvania, United States, 17701
Contact: Debrah Scott 570-326-8040
Principal Investigator: Steven Rockoff, MD

United States, South Carolina
Carolina Urologic Research Center
Myrtle Beach, South Carolina, United States, 29572
Contact: Jennifer Baiden 843-449-1010 Ext. 237
Principal Investigator: Neil Shore, MD

United States, Tennessee
The Conrad Pearson Clinic
Germantown, Tennessee, United States, 38138
Contact: Sonia Orask 901-481-9593
Principal Investigator: Lynn Conrad, MD

United States, Texas
Corpus Christi Urology Group LLC
Corpus Christi, Texas, United States, 78404
Contact: Anastasia Bartosh 361-884-6381 Ext. 175
Contact: Veronica Bazaldua
Principal Investigator: Robert Naismith, MD

Urology Clinics of North Texas
Dallas, Texas, United States, 75231
Contact: Jessica Gillespie 214-580-1482
Contact: Christi Grunberg
Principal Investigator: James Cochran, MD

Urologic Consultants of Houston, PA
Houston, Texas, United States, 77074
Contact: Julia Powers 713-456-4011
Principal Investigator: Samuel Axelrad, MD

Urology San Antonio Research
San Antonio, Texas, United States, 78229
Contact: Joe Perez 210-617-4116
Contact: Jerry Ramoz 210 617-4116

Principal Investigator: Daniel Saltzstein, MD

United States, Virginia
Mary Washington Hospital and Urology Associates of Fredericksburg
Fredericksburg, Virginia, United States, 22401
Contact: Christie Rickard 540-374-3131
Principal Investigator: Daniel Hoffman, MD

Urology of Virginia, PC
Norfolk, Virginia, United States, 23502
Contact: Jennifer Kucenski 757-457-5123
Contact: Laurie Jackson
Principal Investigator: Robert Given, MD

Urology of Virginia, PC
Virginia Beach, Virginia, United States, 23454
Contact: Michele Schindler 757-457-5462
Principal Investigator: Gregg Eure, MD

United States, Washington
Integrity Medical Research, LLC
Mountlake Terrace, Washington, United States, 98043
Contact: Somer Macek 425-275-0680
Principal Investigator: Karny Jacoby, MD

Seattle Urological Associates
Seattle, Washington, United States, 98104
Contact: Angie Sievers 206-838-1638
Principal Investigator: John S. Mullen, MD

United States, Arizona
Sun Health Research Institute
Sun City, Arizona, United States, 85032
Contact: Carolyn Liebsack 623-875-6514
Principal Investigator: Jeffery Stern, MD, MPF

IPDSharing

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References

Citations:

Links:

Available IPD/Information:

Delayed Results

Delay Type	Certify New Use
Intervention Name(s)	Intravesical EOquin® as a Surgical Adjuvant Instilled in the Early Postoperative Period in Patients

Study Results

Participant Flow

Reporting Groups

	Description
Apaziquone	Apaziquone: TURBT + a single intravesical dose of Apaziquone 4mg in 40ml instilled into the bladder post-TURBT
Placebo	Placebo: TURBT + a single intravesical dose of placebo instilled into the bladder post-TURBT

Overall Study

	Apaziquone	Placebo
Started	406	396
Completed	317	311
Not Completed	89	85

Baseline Characteristics

Baseline Analysis Population Description

Safety/ITT Population

Reporting Groups

	Description
Apaziquone	Apaziquone: TURBT + a single intravesical dose of Apaziquone 4mg in 40ml instilled into the bladder post-TURBT
Placebo	Placebo: TURBT + a single intravesical dose of placebo instilled into the bladder post-TURBT

Baseline Measures

		Apaziquone	Placebo	Total
Overall Number of Participants		406	396	802
Age, Continuous Mean (Standard Deviation) Unit of measure: years	Number Analyzed	406 participants	396 participants	802 participants
		67.5 (10.92)	68.2 (10.72)	67.8 (10.82)
Age, Customized Measure Type: Count of Participants Unit of measure: participants	Number Analyzed	406 participants	396 participants	802 participants
Age	<65	159 39.16%	146 36.87%	305 38.03%
	65-75	140 34.48%	139 35.1%	279 34.79%
	>75	107 26.35%	111 28.03%	218 27.18%
Sex: Female, Male Measure Type: Count of Participants Unit of measure: participants	Number Analyzed	406 participants	396 participants	802 participants
	Female	108 26.6%	102 25.76%	210 26.18%
	Male	298 73.4%	294 74.24%	592 73.82%
Ethnicity (NIH/ OMB) Measure Type: Count of Participants Unit of measure: participants	Number Analyzed	406 participants	396 participants	802 participants
	Hispanic or Latino	13 3.2%	17 4.29%	30 3.74%

		Apaziquone	Placebo	Total
	Not Hispanic or Latino	393 96.8%	379 95.71%	772 96.26%
	Unknown or Not Reported	0 0%	0 0%	0 0%
Race (NIH/OMB) Measure Type: Count of Participants Unit of measure: participants	Number Analyzed	406 participants	396 participants	802 participants
	American Indian or Alaska Native	0 0%	0 0%	0 0%
	Asian	1 0.25%	3 0.76%	4 0.5%
	Native Hawaiian or Other Pacific Islander	0 0%	0 0%	0 0%
	Black or African American	11 2.71%	9 2.27%	20 2.49%
	White	392 96.55%	383 96.72%	775 96.63%
	More than one race	2 0.49%	1 0.25%	3 0.37%
	Unknown or Not Reported	0 0%	0 0%	0 0%
Region of Enrollment Measure Type: Number Unit of measure: participants	Number Analyzed	406 participants	396 participants	802 participants
United States		381	375	756
Poland		25	21	46

Outcome Measures

1. Primary Outcome Measure:

Measure Title	Recurrence Rate at 2 Years
Measure Description	The percentage of participants with histologically confirmed recurrence of the bladder tumor at any time after randomization and on or before year 2.
Time Frame	2 years

Analysis Population Description

Target Ta, G1-G2 Population: 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.

Reporting Groups

	Description
Apaziquone	Apaziquone: TURBT + a single intravesical dose of Apaziquone 4mg in 40ml instilled into the bladder post-TURBT
Placebo	Placebo: TURBT + a single intravesical dose of placebo instilled into the bladder post-TURBT

Measured Values

		Apaziquone	Placebo
Overall Number of Participants Analyzed		295	271
Recurrence Rate at 2 Years Measure Type: Count of Participants Unit of measure: participants	Recurrence	112 37.97%	121 44.65%
	Non-Recurrence	183 62.03%	150 55.35%

Statistical Analysis 1 for Recurrence Rate at 2 Years

Statistical Analysis Overview	Comparison Group Selection	Apaziquone, Placebo
	Comments	[Not specified]
	Type of Statistical Test	Superiority
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	0.1068
	Comments	[Not specified]
	Method	Cochran-Mantel-Haenszel
	Comments	[Not specified]

Method of Estimation	Estimation Parameter	Odds Ratio (OR)
	Estimated Value	0.76
	Confidence Interval	(2-Sided) 95% 0.54 to 1.06
	Estimation Comments	[Not specified]

2. Secondary Outcome Measure:

Measure Title	Time to Recurrence
Measure Description	The number of months from randomization to histologically confirmed recurrence of the patient's bladder tumor.
Time Frame	2 years

Analysis Population Description

Target Ta, G1-G2 Population: 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.

Reporting Groups

	Description
Apaziquone	Apaziquone: TURBT + a single intravesical dose of Apaziquone 4mg in 40ml instilled into the bladder post-TURBT
Placebo	Placebo: TURBT + a single intravesical dose of placebo instilled into the bladder post-TURBT

Measured Values

	Apaziquone	Placebo
Overall Number of Participants Analyzed	295	271
Time to Recurrence Mean (Standard Error) Unit of measure: months	18.3 (0.47)	16.7 (0.55)

Statistical Analysis 1 for Time to Recurrence

Statistical Analysis Overview	Comparison Group Selection	Apaziquone, Placebo
	Comments	[Not specified]
	Type of Statistical Test	Superiority
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	0.0412
	Comments	[Not specified]
	Method	Log Rank
	Comments	[Not specified]

Method of Estimation	Estimation Parameter	Hazard Ratio (HR)
	Estimated Value	0.77
	Confidence Interval	(2-Sided) 95% 0.59 to 0.99
	Estimation Comments	[Not specified]

3. Secondary Outcome Measure:

Measure Title	Progression Rate at 2 Years
Measure Description	The percentage of participants that progress to either a higher stage or grade from the histologically confirmed stage and grade at time of randomization.
Time Frame	2 years

Analysis Population Description

Target Ta, G1-G2 Population: 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.

Reporting Groups

	Description
Apaziquone	Apaziquone: TURBT + a single intravesical dose of Apaziquone 4mg in 40ml instilled into the bladder post-TURBT
Placebo	Placebo: TURBT + a single intravesical dose of placebo instilled into the bladder post-TURBT

Measured Values

		Apaziquone	Placebo
Overall Number of Participants Analyzed		295	271
Progression Rate at 2 Years Measure Type: Count of Participants Unit of measure: participants	Progression	30 10.17%	39 14.39%
	Non-Progression	265 89.83%	232 85.61%

4. Secondary Outcome Measure:

Measure Title	Time to Progression
Measure Description	The number of months from randomization to progression to either a higher stage or grade of the patient's bladder tumor.
Time Frame	2 years

Analysis Population Description

Target Ta, G1-G2 Population: 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.

Reporting Groups

	Description
Apaziquone	Apaziquone: TURBT + a single intravesical dose of Apaziquone 4mg in 40ml instilled into the bladder post-TURBT
Placebo	Placebo: TURBT + a single intravesical dose of placebo instilled into the bladder post-TURBT

Measured Values

	Apaziquone	Placebo
Overall Number of Participants Analyzed	295	271
Time to Progression Mean (Standard Error) Unit of measure: months	22.9 (0.26)	22.0 (0.34)

5. Secondary Outcome Measure:

Measure Title	Number of Recurrences Per Patient
Measure Description	The number of histologically confirmed recurrences during the course of the study.
Time Frame	2 years

Analysis Population Description

Target Ta, G1-G2 Population: 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.

Reporting Groups

	Description
Apaziquone	Apaziquone: TURBT + a single intravesical dose of Apaziquone 4mg in 40ml instilled into the bladder post-TURBT
Placebo	Placebo: TURBT + a single intravesical dose of placebo instilled into the bladder post-TURBT

Measured Values

	Apaziquone	Placebo
Overall Number of Participants Analyzed	295	271
Number of Recurrences Per Patient Mean (Standard Deviation) Unit of measure: times	0.6 (1.03)	0.9 (1.21)

6. Secondary Outcome Measure:

Measure Title	Disease Free Interval
Measure Description	The number of months from randomization to histologically confirmed progression of the patient's bladder tumor or death from any cause
Time Frame	2 years

Analysis Population Description

Target Ta, G1-G2 Population: 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.

Reporting Groups

	Description
Apaziquone	Apaziquone: TURBT + a single intravesical dose of Apaziquone 4mg in 40ml instilled into the bladder post-TURBT
Placebo	Placebo: TURBT + a single intravesical dose of placebo instilled into the bladder post-TURBT

Measured Values

	Apaziquone	Placebo
Overall Number of Participants Analyzed	295	271
Disease Free Interval Mean (Standard Error) Unit of measure: months	22.9 (0.26)	22.0 (0.34)

7. Secondary Outcome Measure:

Measure Title	Disease Free Survival
Measure Description	The number of months from randomization to histologically confirmed recurrence of the patient's bladder tumor or death from any cause
Time Frame	2 years

Analysis Population Description

Target Ta, G1-G2 Population: 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.

Reporting Groups

	Description
Apaziquone	Apaziquone: TURBT + a single intravesical dose of Apaziquone 4mg in 40ml instilled into the bladder post-TURBT
Placebo	Placebo: TURBT + a single intravesical dose of placebo instilled into the bladder post-TURBT

Measured Values

	Apaziquone	Placebo
Overall Number of Participants Analyzed	295	271

	Apaziquone	Placebo
Disease Free Survival Mean (Standard Error) Unit of measure: months	18.0 (0.48)	16.4 (0.55)

8. Secondary Outcome Measure:

Measure Title	Overall Survival
Measure Description	The number of months from randomization to death from any cause.
Time Frame	2 years

Analysis Population Description

Target Ta, G1-G2 Population: 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.

Reporting Groups

	Description
Apaziquone	Apaziquone: TURBT + a single intravesical dose of Apaziquone 4mg in 40ml instilled into the bladder post-TURBT
Placebo	Placebo: TURBT + a single intravesical dose of placebo instilled into the bladder post-TURBT

Measured Values

	Apaziquone	Placebo
Overall Number of Participants Analyzed	295	271
Overall Survival Mean (Standard Error) Unit of measure: months	20.3 (0.13)	23.7 (0.14)

Reported Adverse Events

Time Frame	Treatment-emergent Adverse Events (ie, AEs that occurred or worsened following the TURBT procedure) were recorded from the time of randomization to Month 6; after Month 6 until Month 24 (end of study), only genitourinary AEs and Serious AEs (SAEs) were recorded.

Adverse Event Reporting Description	[Not specified]

Reporting Groups

	Description
Apaziquone	Apaziquone: TURBT + a single intravesical dose of Apaziquone 4mg in 40ml instilled into the bladder post-TURBT
Placebo	Placebo: TURBT + a single intravesical dose of placebo instilled into the bladder post-TURBT

All-Cause Mortality

	Apaziquone	Placebo
	Affected/At Risk (%)	Affected/At Risk (%)
Total All-Cause Mortality	11/406 (2.71%)	13/396 (3.28%)

Serious Adverse Events

	Apaziquone	Placebo
	Affected/At Risk (%)	Affected/At Risk (%)
Total	93/406 (22.91%)	98/396 (24.75%)
Blood and lymphatic system disorders		
Anemia [A] *	0/406 (0%)	1/396 (0.25%)
Anemia of chronic disease [A] *	1/406 (0.25%)	0/396 (0%)
Iron deficiency anemia [A] *	1/406 (0.25%)	1/396 (0.25%)
Cardiac disorders		
Acute Coronary Syndrome [A] *	2/406 (0.49%)	0/396 (0%)
Acute Myocardial Infarction [A] *	2/406 (0.49%)	1/396 (0.25%)
Arteriosclerosis coronary artery [A] *	0/406 (0%)	1/396 (0.25%)
Atrial Fibrillation [A] *	6/406 (1.48%)	0/396 (0%)
Atrial tachycardia [A] *	0/406 (0%)	1/396 (0.25%)
Atrioventricular block complete [A] *	1/406 (0.25%)	1/396 (0.25%)
Bradycardia [A] *	1/406 (0.25%)	0/396 (0%)

	Apaziquone	Placebo
	Affected/At Risk (%)	Affected/At Risk (%)
Cardiac Failure Congestive [A] *	5/406 (1.23%)	6/396 (1.52%)
Cardiac arrest [A] *	1/406 (0.25%)	0/396 (0%)
Cardiac perforation [A] *	0/406 (0%)	1/396 (0.25%)
Cardiac tamponade [A] *	1/406 (0.25%)	0/396 (0%)
Cardiopulmonary failure [A] *	0/406 (0%)	1/396 (0.25%)
Coronary Artery Disease [A] *	3/406 (0.74%)	6/396 (1.52%)
Coronary artery stenosis [A] *	1/406 (0.25%)	0/396 (0%)
Myocardial Infarction [A] *	3/406 (0.74%)	3/396 (0.76%)
Palpitations [A] *	0/406 (0%)	1/396 (0.25%)
Sinus bradycardia [A] *	1/406 (0.25%)	0/396 (0%)
Ventricular fibrillation [A] *	1/406 (0.25%)	0/396 (0%)
Ventricular tachycardia [A] *	0/406 (0%)	1/396 (0.25%)
Eye disorders		
Cataract [A] *	0/406 (0%)	1/396 (0.25%)
Gastrointestinal disorders		
Abdominal pain [A] *	1/406 (0.25%)	0/396 (0%)
Colitis ischemic [A] *	0/406 (0%)	1/396 (0.25%)
Colitis ulcerative [A] *	0/406 (0%)	1/396 (0.25%)
Diarrhea [A] *	1/406 (0.25%)	0/396 (0%)
Duodenal ulcer [A] *	1/406 (0.25%)	0/396 (0%)
Duodenal ulcer hemorrhage [A] *	0/406 (0%)	1/396 (0.25%)
Gallstone ileus [A] *	0/406 (0%)	1/396 (0.25%)
Gastrointestinal hemorrhage [A] *	0/406 (0%)	1/396 (0.25%)

	Apaziquone	Placebo
	Affected/At Risk (%)	Affected/At Risk (%)
Ileus [A] *	1/406 (0.25%)	0/396 (0%)
Inguinal hernia, obstructive [A] *	0/406 (0%)	1/396 (0.25%)
Intestinal perforation [A] *	1/406 (0.25%)	0/396 (0%)
Intra-abdominal hemorrhage [A] *	1/406 (0.25%)	0/396 (0%)
Large intestine polyp [A] *	1/406 (0.25%)	0/396 (0%)
Nausea [A] *	1/406 (0.25%)	0/396 (0%)
Pancreatic mass [A] *	0/406 (0%)	1/396 (0.25%)
Pancreatitis acute [A] *	0/406 (0%)	2/396 (0.51%)
Rectal prolapse [A] *	0/406 (0%)	1/396 (0.25%)
Retroperitoneal hemorrhage [A] *	0/406 (0%)	1/396 (0.25%)
Small Intestinal Obstruction [A] *	1/406 (0.25%)	2/396 (0.51%)
Upper gastrointestinal hemorrhage [A] *	1/406 (0.25%)	0/396 (0%)
Vomiting [A] *	1/406 (0.25%)	0/396 (0%)
General disorders		
Asthenia [A] *	1/406 (0.25%)	0/396 (0%)
Chest Pain [A] *	5/406 (1.23%)	4/396 (1.01%)
Death [A] *	2/406 (0.49%)	0/396 (0%)
Generalised oedema [A] *	0/406 (0%)	1/396 (0.25%)
Ischemic ulcer [A] *	1/406 (0.25%)	0/396 (0%)
Hepatobiliary disorders		
Cholecystitis [A] *	1/406 (0.25%)	0/396 (0%)
Cholecystitis Acute [A] *	2/406 (0.49%)	0/396 (0%)
Immune system disorders		

	Apaziquone	Placebo
	Affected/At Risk (%)	Affected/At Risk (%)
Anaphylactic reaction [A] *	1/406 (0.25%)	0/396 (0%)
Infections and infestations		
Abdominal wall abscess [A] *	1/406 (0.25%)	0/396 (0%)
Appendicitis [A] *	1/406 (0.25%)	0/396 (0%)
Appendicitis perforated [A] *	0/406 (0%)	1/396 (0.25%)
Brain abscess [A] *	0/406 (0%)	1/396 (0.25%)
Bronchitis [A] *	1/406 (0.25%)	0/396 (0%)
Cellulitis [A] *	5/406 (1.23%)	3/396 (0.76%)
Cystitis [A] *	0/406 (0%)	1/396 (0.25%)
Gastroenteritis viral [A] *	1/406 (0.25%)	0/396 (0%)
Herpes zoster [A] *	0/406 (0%)	1/396 (0.25%)
Influenza [A] *	1/406 (0.25%)	0/396 (0%)
Osteomyelitis [A] *	0/406 (0%)	1/396 (0.25%)
Peritonitis [A] *	0/406 (0%)	1/396 (0.25%)
Pneumonia [A] *	5/406 (1.23%)	7/396 (1.77%)
Sepsis [A] *	2/406 (0.49%)	3/396 (0.76%)
Urinary Tract Infection [A] *	2/406 (0.49%)	5/396 (1.26%)
Urinary tract infection enterococcal [A] *	0/406 (0%)	1/396 (0.25%)
Injury, poisoning and procedural complications		
Ankle fracture [A] *	1/406 (0.25%)	0/396 (0%)
Cervical vertebral fracture [A] *	0/406 (0%)	1/396 (0.25%)
Fall [A] *	0/406 (0%)	1/396 (0.25%)
Femur fracture [A] *	0/406 (0%)	1/396 (0.25%)

	Apaziquone	Placebo
	Affected/At Risk (%)	Affected/At Risk (%)
Hip fracture [A] *	0/406 (0%)	2/396 (0.51%)
Incisional hernia [A] *	1/406 (0.25%)	0/396 (0%)
Multiple injuries [A] *	0/406 (0%)	1/396 (0.25%)
Pneumothorax traumatic [A] *	0/406 (0%)	1/396 (0.25%)
Post procedural hematuria [A] *	1/406 (0.25%)	0/396 (0%)
Post procedural hemorrhage [A] *	0/406 (0%)	1/396 (0.25%)
Procedural nausea [A] *	1/406 (0.25%)	0/396 (0%)
Procedural pain [A] *	1/406 (0.25%)	0/396 (0%)
Seroma [A] *	0/406 (0%)	1/396 (0.25%)
Spinal compression fracture [A] *	1/406 (0.25%)	0/396 (0%)
Subdural hematoma [A] *	1/406 (0.25%)	1/396 (0.25%)
Toxicity to various agents [A] *	1/406 (0.25%)	1/396 (0.25%)
Investigations		
Anticoagulation drug level above therapeutic [A] *	0/406 (0%)	1/396 (0.25%)
Metabolism and nutrition disorders		
Cachexia [A] *	0/406 (0%)	1/396 (0.25%)
Dehydration [A] *	2/406 (0.49%)	1/396 (0.25%)
Diabetes mellitus [A] *	0/406 (0%)	1/396 (0.25%)
Diabetes mellitus inadequate control [A] *	0/406 (0%)	1/396 (0.25%)
Electrolyte imbalance [A] *	1/406 (0.25%)	0/396 (0%)
Hyponatremia [A] *	0/406 (0%)	1/396 (0.25%)
Metabolic acidosis [A] *	0/406 (0%)	1/396 (0.25%)

	Apaziquone	Placebo
	Affected/At Risk (%)	Affected/At Risk (%)
Type 2 diabetes mellitus [A] *	1/406 (0.25%)	0/396 (0%)
Musculoskeletal and connective tissue disorders		
Back Pain [A] *	2/406 (0.49%)	1/396 (0.25%)
Flank pain [A] *	0/406 (0%)	1/396 (0.25%)
Intervertebral Disc Degeneration [A] *	2/406 (0.49%)	0/396 (0%)
Intervertebral disc protrusion [A] *	0/406 (0%)	1/396 (0.25%)
Lumbar spinal stenosis [A] *	1/406 (0.25%)	1/396 (0.25%)
Muscular weakness [A] *	1/406 (0.25%)	0/396 (0%)
Osteoarthritis [A] *	1/406 (0.25%)	1/396 (0.25%)
Osteonecrosis [A] *	0/406 (0%)	1/396 (0.25%)
Spinal osteoarthritis [A] *	1/406 (0.25%)	0/396 (0%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)		
Adenocarcinoma of colon [A] *	1/406 (0.25%)	0/396 (0%)
Bladder cancer recurrent [A] *	1/406 (0.25%)	0/396 (0%)
Brain cancer metastatic [A] *	0/406 (0%)	1/396 (0.25%)
Cholesteatoma [A] *	0/406 (0%)	1/396 (0.25%)
Colon cancer [A] *	1/406 (0.25%)	0/396 (0%)
Gastrointestinal stromal tumor [A] *	1/406 (0.25%)	1/396 (0.25%)
Lung adenocarcinoma stage I [A] *	1/406 (0.25%)	0/396 (0%)
Lung neoplasm [A] *	0/406 (0%)	1/396 (0.25%)
Lung neoplasm malignant [A] *	1/406 (0.25%)	0/396 (0%)
Metastases to lung [A] *	0/406 (0%)	1/396 (0.25%)
Metastases to spine [A] *	0/406 (0%)	1/396 (0.25%)

	Apaziquone	Placebo
	Affected/At Risk (%)	Affected/At Risk (%)
Metastatic bronchial carcinoma [A] *	0/406 (0%)	1/396 (0.25%)
Neoplasm malignant [A] *	0/406 (0%)	1/396 (0.25%)
Non-small cell lung cancer metastatic [A] *	0/406 (0%)	1/396 (0.25%)
Prostate cancer [A] *	0/406 (0%)	1/396 (0.25%)
Prostate cancer metastatic [A] *	0/406 (0%)	1/396 (0.25%)
Renal cell carcinoma [A] *	1/406 (0.25%)	1/396 (0.25%)
Renal cell carcinoma [A] *	1/406 (0.25%)	1/396 (0.25%)
Ureteric cancer [A] *	1/406 (0.25%)	0/396 (0%)
Urinary tract neoplasm [A] *	0/406 (0%)	1/396 (0.25%)
Nervous system disorders		
Carotid artery disease [A] *	1/406 (0.25%)	0/396 (0%)
Cerebral hemorrhage [A] *	0/406 (0%)	1/396 (0.25%)
Cerebrospinal fluid retention [A] *	1/406 (0.25%)	0/396 (0%)
Cerebrovascular Accident [A] *	1/406 (0.25%)	2/396 (0.51%)
Dementia Alzheimer's type [A] *	1/406 (0.25%)	0/396 (0%)
Dizziness [A] *	1/406 (0.25%)	0/396 (0%)
Encephalopathy [A] *	1/406 (0.25%)	0/396 (0%)
Hepatic encephalopathy [A] *	1/406 (0.25%)	0/396 (0%)
Nerve compression [A] *	0/406 (0%)	1/396 (0.25%)
Partial seizures [A] *	1/406 (0.25%)	0/396 (0%)
Status epilepticus [A] *	1/406 (0.25%)	0/396 (0%)
Subarachnoid hemorrhage [A] *	1/406 (0.25%)	0/396 (0%)

	Apaziquone	Placebo
	Affected/At Risk (%)	Affected/At Risk (%)
Syncope [A] *	3/406 (0.74%)	2/396 (0.51%)
Transient Ischemic Attack [A] *	2/406 (0.49%)	1/396 (0.25%)
Psychiatric disorders		
Agitation [A] *	0/406 (0%)	1/396 (0.25%)
Anxiety [A] *	0/406 (0%)	1/396 (0.25%)
Bipolar disorder [A] *	1/406 (0.25%)	0/396 (0%)
Completed suicide [A] *	1/406 (0.25%)	0/396 (0%)
Suicide attempt [A] *	0/406 (0%)	1/396 (0.25%)
Renal and urinary disorders		
Acute prerenal failure [A] *	0/406 (0%)	1/396 (0.25%)
Bladder perforation [A] *	0/406 (0%)	1/396 (0.25%)
Calculus ureteric [A] *	0/406 (0%)	2/396 (0.51%)
Hematuria [A] *	6/406 (1.48%)	8/396 (2.02%)
Nephrolithiasis [A] *	1/406 (0.25%)	0/396 (0%)
Renal Failure Acute [A] *	2/406 (0.49%)	2/396 (0.51%)
Renal colic [A] *	1/406 (0.25%)	0/396 (0%)
Renal failure chronic [A] *	0/406 (0%)	1/396 (0.25%)
Renal impairment [A] *	0/406 (0%)	1/396 (0.25%)
Ureteric obstruction [A] *	1/406 (0.25%)	0/396 (0%)
Urinary Bladder Hemorrhage [A] *	3/406 (0.74%)	0/396 (0%)
Urinary retention [A] *	1/406 (0.25%)	1/396 (0.25%)
Respiratory, thoracic and mediastinal disorders		
Acute Respiratory Failure [A] *	1/406 (0.25%)	2/396 (0.51%)

	Apaziquone	Placebo
	Affected/At Risk (%)	Affected/At Risk (%)
Chronic Obstructive Pulmonary Disease [A] *	5/406 (1.23%)	4/396 (1.01%)
Pulmonary Embolism [A] *	1/406 (0.25%)	3/396 (0.76%)
Respiratory Failure [A] *	3/406 (0.74%)	3/396 (0.76%)
Status asthmaticus [A] *	0/406 (0%)	1/396 (0.25%)
Skin and subcutaneous tissue disorders		
Diabetic foot [A] *	1/406 (0.25%)	0/396 (0%)
Psoriasis [A] *	1/406 (0.25%)	0/396 (0%)
Surgical and medical procedures		
Abdominal hernia repair [A] *	1/406 (0.25%)	0/396 (0%)
Angioplasty [A] *	1/406 (0.25%)	0/396 (0%)
Aortic aneurysm repair [A] *	1/406 (0.25%)	0/396 (0%)
Aortic valve replacement [A] *	1/406 (0.25%)	0/396 (0%)
Bladder neoplasm surgery [A] *	0/406 (0%)	1/396 (0.25%)
Cardiac rehabilitation therapy [A] *	1/406 (0.25%)	1/396 (0.25%)
Carotid endarterectomy [A] *	1/406 (0.25%)	0/396 (0%)
Coronary arterial stent insertion [A] *	1/406 (0.25%)	0/396 (0%)
Hip Arthroplasty [A] *	4/406 (0.99%)	2/396 (0.51%)
Implantable defibrillator insertion [A] *	0/406 (0%)	1/396 (0.25%)
Knee Arthroplasty [A] *	3/406 (0.74%)	4/396 (1.01%)
Mitral valve replacement [A] *	1/406 (0.25%)	0/396 (0%)
Penile prosthesis insertion [A] *	1/406 (0.25%)	0/396 (0%)
Radical prostatectomy [A] *	0/406 (0%)	1/396 (0.25%)
Salpingo-oophorectomy [A] *	1/406 (0.25%)	0/396 (0%)

	Apaziquone	Placebo
	Affected/At Risk (%)	Affected/At Risk (%)
Spinal fusion surgery [A] *	1/406 (0.25%)	0/396 (0%)
Ventriculo-peritoneal shunt [A] *	0/406 (0%)	1/396 (0.25%)
Vascular disorders		
Aortic aneurysm [A] *	1/406 (0.25%)	1/396 (0.25%)
Hypertension [A] *	0/406 (0%)	1/396 (0.25%)
Hypotension [A] *	0/406 (0%)	2/396 (0.51%)
Labile hypertension [A] *	1/406 (0.25%)	0/396 (0%)
Peripheral artery aneurysm [A] *	1/406 (0.25%)	0/396 (0%)
Thrombophlebitis [A] *	1/406 (0.25%)	0/396 (0%)

* Indicates events were collected by non-systematic methods.
A Term from vocabulary, MedDRA (17.0)

Other Adverse Events

Frequency Threshold Above Which Other Adverse Events are Reported: 5%

	Apaziquone	Placebo
	Affected/At Risk (%)	Affected/At Risk (%)
Total	312/406 (76.85%)	285/396 (71.97%)
Gastrointestinal disorders		
Nausea [A] *	16/406 (3.94%)	19/396 (4.8%)
Infections and infestations		
Urinary tract infection [A] *	70/406 (17.24%)	58/396 (14.65%)
Injury, poisoning and procedural complications		
Procedural pain [A] *	31/406 (7.64%)	27/396 (6.82%)
Renal and urinary disorders		
Bladder pain [A] *	22/406 (5.42%)	18/396 (4.55%)

	Apaziquone	Placebo
	Affected/At Risk (%)	Affected/At Risk (%)
Bladder spasm [A] *	29/406 (7.14%)	23/396 (5.81%)
Dysuria [A] *	74/406 (18.23%)	67/396 (16.92%)
Haematuria [A] *	38/406 (9.36%)	57/396 (14.39%)
Micturition urgency [A] *	31/406 (7.64%)	37/396 (9.34%)
Pollakiuria [A] *	39/406 (9.61%)	46/396 (11.62%)
Urinary retention [A] *	17/406 (4.19%)	30/396 (7.58%)

***** Indicates events were collected by non-systematic methods.
A Term from vocabulary, MedDRA (17.0)

Limitations and Caveats

[Not specified]

More Information

Certain Agreements:

Principal Investigators are NOT employed by the organization sponsoring the study.

There IS an agreement between the Principal Investigator and the Sponsor (or its agents) that restricts the PI's rights to discuss or publish trial results after the trial is completed.

First publication is the multi-center publication of Study results from all study sites. Other than the multi-center publication, site may publish an independent publication of data generated by site subject to Sponsor review rights (e.g., review for intellectual property, confidentiality).

Results Point of Contact:

Name/Official Title: Gajanan Bhat, PhD
Organization: Spectrum Pharmaceuticals
Phone: 949-743-9219
Email: Gajanan.Bhat@sppirx.com