ODAC Briefing Document

NDA 208714/S000
Qapzola (apaziquone)

FDA Briefing Document
Oncologic Drugs Advisory Committee Meeting
September 14, 2016

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Qapzola (apaziquone)
Applicant: Spectrum Pharmaceuticals, Inc.

The attached package contains background information prepared by the Food and Drug Administration (FDA) for the panel members of the advisory committee. The FDA background package often contains assessments and/or conclusions and recommendations written by individual FDA reviewers. Such conclusions and recommendations do not necessarily represent the final position of the individual reviewers, nor do they necessarily represent the final position of the Review Division or Office. We have brought apaziquone to this Advisory Committee in order to gain the Committee's insights and opinions, and the background package may not include all issues relevant to the final regulatory recommendation and instead is intended to focus on issues identified by the Agency for discussion by the advisory committee. The FDA will not issue a final determination on the issues at hand until input from the advisory committee process has been considered and all reviews have been finalized. The final determination may be affected by issues not discussed at the advisory committee meeting.

1. Introduction

In December 2015, Spectrum Pharmaceuticals submitted a new drug application (NDA) for the following indication:

- Immediate intravesical instillation post-transurethral resection of bladder tumors in patients with non-muscle invasive bladder cancer (NMIBC).

The submission included two randomized controlled trials of a single dose of apaziquone or placebo immediately after transurethral resection of the bladder tumor. One of the trials was conducted under a Special Protocol Assessment. The primary endpoint was disease recurrence, defined as any histologically-confirmed bladder cancer, within the 2 year study period. The primary analysis population included patients with Ta grade 1 or 2 NMIBC at baseline. A 12% decrease in the proportion of patients with recurrent disease in the apaziquone arm at 2 years was used to estimate the sample size and was postulated, by the Applicant, to be clinically significant.

Both trials failed to demonstrate a reduction in disease recurrence with apaziquone at 2 years (J Urol 2016 195(4s): e290; Abstract PD11-07). In both trials, the 2 year rate of recurrence was lower for apaziquone-treated than for placebo-treated patients. The magnitude of reduction (6.6% and 6.2%) was; however, lower than that seen with current therapy, thus precluding the consideration of accelerated approval for this application.

The Applicant has identified, in post-hoc analyses, that the timing of intravesical therapy relative to resection could enhance the effect of apaziquone. The Applicant is currently testing this hypothesis (and the administration of a 2nd dose of apaziquone) in a large, randomized trial in the same patient population under another Special Protocol Assessment.

The FDA acknowledges the need for agents that can effectively reduce the rate of recurrence and prolong the time to recurrence of NMIBC. It is important, however, to consider that few patients with TaG1-2 disease will progress to muscle invasive disease. Thus, the numerical decrease in bladder cancers that was observed with apaziquone should be considered in the context of prevention of non-muscle invasive disease.

The significant review issues identified with this application include:

- The failure to demonstrate a reduction in 2 year recurrence with apaziquone when compared to placebo in each study;
- The clinical relevance of the magnitude of reduction in 2 year recurrence associated with apaziquone; and
- Post-hoc, hypothesis-generating analyses that are currently being tested in an ongoing clinical trial that is conducted under a Special Protocol Agreement.

Draft Issue for the Oncologic Drugs Advisory Committee

The Agency seeks the advice of the Oncologic Drugs Advisory Committee regarding the apaziquone NDA on the:

- Relevance of the results of Studies 611 and 612 in the evaluation of the risk-benefit profile of apaziquone for the treatment of NIMBC.

2. Background

Non-muscle invasive bladder cancer includes the following.

- **CIS:** Carcinoma in situ
- **Ta:** tumor confined to the epithelial layer
- **T1:** tumor which invades the subepithelial connective tissue

Several grading systems are used in bladder cancer. The two applicable to this submission are listed below.

- **2004** WHO/1998 International Society of Urological Pathology
- **1973** WHO: This includes grade 1 (low), grade 2, and grade 3 (high) disease and is the system used in the central pathology review.

Based on the stage, grade, lesion size, previous history of NMIBC, and the presence of carcinoma in situ, these tumors are divided into low, intermediate and high-risk disease. Low-risk disease includes stage Ta, low grade lesions that are < 3 cm. Patients with multiple or recurrent lesions or who have carcinoma in situ are not considered to have low-risk disease. Low-risk disease may be treated with resection alone or resection plus a single post-operative dose of intravesical chemotherapy. Patients with intermediate or high-risk disease also undergo resection and may, but do not typically, receive a single post-operative dose of intravesical therapy. Instead most of these patients receive 6 weekly doses of intravesical therapy and may also receive periodic maintenance therapy. In the 2 studies included in this submission, the primary analysis population was limited to patients with Ta grade 1 and 2 (TaG1-2) disease, many of whom had low-risk disease. The rationale for this analysis population is that these patients are likely to receive no additional therapy, thus isolating the effect of apaziquone. Note that while the primary analysis populations were limited to patients with TaG1-2 disease many of those patients had tumors > 3 cm, multiple lesions, or recurrent disease.

Immediate intravesical chemotherapy is thought to prevent the deposition of free-floating tumor cells that are released during transurethral resection of the bladder tumor. It may also have an effect on tumor cells present at the base of a resected lesion. It is unclear whether it has any effect on lesions that were too small to be identified at initial cystoscopy. As the name implies, immediate intravesical chemotherapy is given prior to the availability of a tissue diagnosis of cancer and prior to information concerning the cancer stage. No drugs are

approved for this use, but mitomycin, epirubicin, and thiotepa are typically used. Apaziquone is chemically related to mitomycin.

The use of immediate intravesical chemotherapy is controversial and professional societies have the following recommendations.

- The American Urological Association states, "In a patient with suspected or known low- or intermediate-risk bladder cancer, a clinician should consider administration of a single postoperative instillation of intravesical chemotherapy (e.g., mitomycin C or epirubicin) within 24 hours of transurethral resection of the bladder tumor."
- The National Comprehensive Cancer Network states that practitioners should consider single-dose intravesical chemotherapy within 24 hours of transurethral resection of the bladder tumor.
- The European Association of Urology states, "Immediate single instillation has been shown to act by destroying circulating tumor cells after transurethral resection of the bladder tumor, and by an ablative effect (chemoresection) on residual tumor cells at the resection site and on small overlooked tumors."

The use of immediate intravesical chemotherapy is based on the results of several meta-analyses, shown in the table below. The first meta-analysis (J Urol 2004 171:2186) found an ~ 12% reduction in the number of patients with recurrent bladder cancer following immediate intravesical chemotherapy. Most of the benefit was seen with epirubicin and mitomycin. This study was published prior to the conduct of the submitted studies and it appears that the estimate of the treatment effect and the sample size was based on the 12% difference seen in this meta-analysis. Recent articles have suggested that a 15% reduction in recurrence (Urology 2014 83:262) or a 6% reduction in recurrence (Bladder Cancer 2016 2:165) may be clinically meaningful.

Table 1: Meta-analyses of Immediate Intravesical Chemotherapy

Citation	Study Population	Findings
J Urol 2004 171: 2186	7 trials, N = 1,476 Median follow up 3.4 yrs	36.7% vs. 48.4% recurrence Resection + immediate intravesical therapy vs. resection
Eur Urol 2013 64:421	4 trials, N = 429	7.8% vs. 21.1% 1 year recurrence Resection + immediate intravesical therapy vs. resection
J NCCN 2013 11:477[1]	18 trials, N = 3103	37% vs. 50% recurrence Resection + immediate intravesical therapy vs. resection
Eur Urol 2016 69:231[2]	11 trials, N = 2278	58.8% vs. 44.8% 5 year recurrence Resection + immediate intravesical therapy vs. resection

[1]Subgroup analyses suggested that most of the benefit was in patients with low grade, solitary lesions.
[2]Patients with EORTC Recurrence Score $\geq$ 5 did not seem to benefit.

Several large, randomized, placebo-controlled studies provide primary evidence for the use of immediate intravesical chemotherapy. Berrum-Svennung et al (J Urol 2008 179:101) randomized 404 patients to epirubicin or saline placebo. Among the 307 patients in the efficacy evaluable population (largely those with low-risk disease), 51% in the epirubicin and 62.5% in the placebo arm recurred at 2 years. Passive diffusion of mitomycin was examined in a randomized study of 248 patients with pTa/T1 disease (Lancet Oncol 2011 12:871). Most patients received additional intravesical therapy. Overall, 59% in the mitomycin and 64% in the resection alone group developed recurrent disease. There were no recurrences, in either arm, in patients with low-risk disease who received no additional intravesical therapy (N=19).

Articles discussing the actual use of immediate intravesical therapy in clinical practice are shown in the table below. Despite the studies listed above, routine use of immediate intravesical therapy is uncommon. Given the limited use of immediate intravesical therapy, a placebo control was thought to be acceptable in the submitted apaziquone studies.

Table 2: Use of Immediate Intravesical Chemotherapy in the US

Citation	Data Source	Findings
J Urol 2012 188:2108	5 USQC Practices pts[1] 2010-2012	27-50% of 696 Ta/T1 pts received immediate intravesical therapy
J Urol 2012 187:1571	259 US Urologists[2]	60% of 1,010 pts received immediate intravesical therapy
Cancer 2011 117:5392	SEER-Medicare Data 1992-2002	2.8 to 3.2% of 4,545 pts received immediate intravesical therapy
Cancer 2009 15:2660	MEDSTAT medical claims 1997-2004	0.33% of 14,677 pts received immediate intravesical therapy

[1]US Urological Surgery Quality Collaborative
[2]Urologists distributed throughout the US, no information on how they were chosen; authors disclosed relationship with Spectrum Pharmaceuticals

The first publication (J Urol 2012 188:2108) found that 26.6-50.3% of patients with 1-2 clinical stage Ta/T1 papillary tumors received immediate intravesical therapy. This study also provided insight into the reasons immediate intravesical therapy was not administered. These included: disease characteristics (54%), logistic factors (24%), uncertainty regarding the benefits of immediate chemotherapy (20%), technical factors (17%), and other (12%). Disease characteristics included the suspected presence of CIS, recurrent disease, etc. that would require a 6 week course of intravesical therapy. Nine percent (9%) of patients did not receive immediate intravesical therapy due to concern that the resection was too deep.

Timing of Instillation

After examining their data, the Applicant found that apaziquone instillation 31-90 minutes after resection appeared to be optimal and included this interval in their application. This is a post-hoc subgroup analysis and should be considered hypothesis generating. Apaziquone is metabolized rapidly in red blood cells (RBCs) (Br J Pharmacol 2002 137:701). The Applicant postulates that apaziquone is not effective prior to 30 minutes because of the large number of RBCs present immediately after resection. The Applicant also postulated that floating tumor cells have settled and are protected by the bladder mucosa after 90 minutes. Most studies of immediate intravesical chemotherapy require instillation within 6 hours of resection (some up

to 24 hours). No published articles provide detailed information on outcome relative to the timing of instillation. The Applicant is currently conducting a trial examining the value of administration of apaziquone 31-90 minutes after resection followed by an additional dose of apaziquone 1 week later.

Regulatory History
In February 2007, a Special Protocol Assessment agreement was reached concerning Study 611. As part of the special protocol assessment, FDA recommended 2 year recurrence as the primary endpoint. This was based on the extensive use of endpoints such as 18 month recurrence, 2 year recurrence, etc. in the urology literature. Study 612 was not conducted under a special protocol assessment, but is similar in design to 611. In December 2012, the Agency noted that both 611 and 612 did not meet the pre-specified criteria for superiority when compared to placebo and that the pooled analysis, using data from both studies, was done post-hoc and was not part of the statistical plan. The Agency discouraged the Applicant from submitting a NDA and questioned whether the effect size was clinically meaningful.

3. Study Design

This application is primarily supported by two Phase 3 studies.

1. **611:** A Multicenter, Randomized, Placebo-Controlled, Double-Blind, Phase 3 Trial of Single-Dose Intravesical Apaziquone as a Surgical Adjuvant Instilled in the Early Postoperative Period in Patients Undergoing Transurethral Resection for Noninvasive Bladder Cancer
2. **612:** A Multicenter, Randomized, Placebo-Controlled, Double-Blind, Phase 3 Trial of Single-Dose Intravesical Apaziquone as a Surgical Adjuvant Instilled in the Early Postoperative Period in Patients Undergoing Transurethral Resection for Noninvasive Bladder Cancer

Apaziquone has been administered intravesically in 6 additional studies.

Eligibility in 611 and 612
1. Clinically apparent TaG1-2 transitional cell carcinoma of the bladder
2. Largest tumor $\leq$ 3.5 cm
3. 611: Patients with 1 lesion and no history of NMIBC, lesion must be $\geq$ 0.5 cm
4. 611: $\leq$ 4 tumors; 612: $\leq$ 5 tumors
5. No suspected CIS
6. Previous history of bladder cancer:
    a. Only transitional cell
    b. Only TaG1-2 disease
    c. No CIS
    d. No bladder cancer within 4 mos of entry
7. In patients with no history of bladder cancer, the smallest lesion must be $\geq$ 0.5 cm.
8. No active urine infection
9. Absolute neutrophil count (ANC) $\geq$ 1500/mm^3, Hemoglobin $\geq$ 10 g/dL, Creatinine $\leq$ 2 mg/dL

Treatment
Patients were randomized in blocks of 4 at each site and there were no stratification factors. The blind was maintained by Spectrum Quality Assurance.

1. Apaziquone 4 mg in 40 mL diluent
2. Placebo in 40 mL diluent (used FD&C # 40 to match the red of apaziquone)

- Administered within 6 hours of transurethral resection of the bladder tumor and retained in the bladder for 1 hour.
- Local pathology results were reviewed at Week 3.
  - If the lesion was TaG1-2, patients were to receive no further therapy.
  - Patients with other stages and grades could receive additional intravesical therapy. All therapy was to be recorded.

Safety Monitoring
- Routine Laboratories: Complete blood count (CBC) and chemistries at baseline, Week 3, and Month 3 Urinalysis at baseline, Week 3, Month 3, then every 3 months for 2 years
- Adverse Events: Recorded baseline to Month 6; Genitourinary adverse events (AEs) and serious adverse events (SAEs) collected for 2 years; Graded using CTCAE v 3
- Concomitant Medications: All medications were recorded from baseline to Month 6. All intravesical therapies and mediations to treat genitourinary AEs and SAEs were recorded for 2 years.

Tumor Monitoring
- Cystoscopy: Cystoscopy every 3 months for 2 years
- Urine Cytology: baseline then every 6 months for 2 years

Functional Bladder Capacity: Functional bladder capacity was assessed at baseline, Year 1, and Year 2 in ~ 150 patients at preselected US sites. This substudy collected urine frequency and volume with 3 day voiding diaries. In the office, voided volume (patients were to have a full bladder) and post-void residual by ultrasound were assessed. In the office, the bladder was not filled prior to testing.

Central Pathology: Central pathology review was conducted by Bostwick Laboratories using the 1973 WHO/ISUP grading system. Bostwick Laboratories also provided local pathology readings for many of the sites. At other sites which did not use Bostwick Laboratories for local pathology review, reports of the central pathology review were not provided to the site. At these sites, it is unknown whether the same slides were used in the central and local review. Urine cytology was not used in the assessment of recurrence or progression. Urine cytology was read by either Mayo Laboratories or Bostwick Laboratories.

Statistical Analysis Plan (SAP)

SAP Development

- Study 611 was conducted April 2007-January 2012. Study 612 was conducted August 2007-January 2012. Both databases were locked in April 2012. The original SAP was finalized in April 2009 for 611 and November 2008 for 612.
- Changes in October 2011 (prior to study completion): Defined the primary analysis population for 612 as patients with ≤ 4 lesions.
- Changes in the June 2015 Versions (after study completion): Added analyses of the timing of the instillation of study drug (0-30, 31-90, > 90 minutes).
- The SAPs did not contain a plan for pooling the data of 611 and 612.

Primary Endpoint

1. The primary endpoint of both trials was the proportion of patients with a new, histologically confirmed bladder cancer (by central pathology) on or before Year 2.
2. Urine cytology was not used in the assessment of the primary endpoint.
3. The primary analysis population of both trials included patients with: TaG1-2 pathology by central review, ≤ 4 lesions, and all lesions ≤ 3.5 cm at baseline.
4. Differences between arms were tested using the odds ratio and its 95% CI.

Sample Size: The original SAPs required 562 patients with TaG1-2 disease to have 80% power to detect a 12% decrease in 2 year recurrence with apaziquone using an alpha of 0.05. The number of patients with TaG1-2 disease by central pathology review was examined (without knowledge of the study arm) and found to be lower than expected. A protocol amendment increased the sample size to ~ 800 patients.

Secondary Endpoints

- Time to Recurrence
  - For both trials, this was defined as the time from randomization to the date of the first histologically confirmed bladder cancer by central pathology review. The date of recurrence was the earliest bladder imaging study. For example, if a lesion was seen on cystoscopy, resected by transurethral resection of bladder tumor (TURBT), and the TURBT specimen contained cancer, the date of cystoscopy was used.
  - Patients who did not recur were censored at their last negative cystoscopy. Patients who died during the treatment period were considered to have recurred or progressed at their date of death. If possible, patients who discontinued were followed for the date of recurrence. If the date of recurrence could not be obtained in patients who discontinued, these patients were censored at their last assessment.
  - A Cox proportional hazard model, using treatment as a covariate, was used to determine the hazard ratio and a log-rank test to determine the p value. Kaplan-Meier curves were generated and the median time to recurrence was estimated.

- Time to Progression and Progression Rate at 2 Years

- In both studies, progression was defined as a histologically confirmed bladder cancer (central pathology review) with either a higher grade or stage when compared to baseline. The Applicant used the follow sequence for progression: CIS < Ta < T1 < T2 and G1 < G2 < G3.
- The date of progression was the time from randomization to the date of histologically confirmed bladder cancer (central pathology review) with either a higher grade or stage when compared to baseline.
- Censoring rules and testing were identical to those of time to recurrence.

- Additional secondary endpoints include number of recurrences within 2 years, disease-free survival, disease-free interval, and overall survival.

4. Efficacy

Patient Disposition
611: 79 sites enrolling 1-62 pts with 6 enrolling > 20 patients included in the primary analysis
612: 73 sites enrolling 1-35 pts with 8 enrolling > 20 patients included in the primary analysis

The reasons for patient discontinuation are shown in the table below. In both studies, most discontinuations were characterized as Withdrew Consent, Lost-to-Follow Up, or Investigator Decision. The majority of adverse events leading to discontinuation were related to comorbid disease. On 612, 12/35 patients who discontinued due to an adverse event withdrew due to cancer, usually a 2nd primary malignancy. Among the patients who discontinued due to "Other", the majority underwent cystectomy. This includes 16 patients on 611 (8 apaziquone, 8 placebo) and 22 on 612 (8 apaziquone, 14 placebo).

Table 3: Patient Disposition of All Randomized Patients

	611		612	
	Apaziquone	Placebo	Apaziquone	Placebo
Treated	406	396	402	411
Completed 2 years	317	311	329	347
Discontinued	89	85	73	64
Withdrew Consent	25	29	19	14
Lost-to-follow Up	23	13	12	11
Death/Adverse Event	14	17	18	17
Investigator Decision	7	5	4	2
Patient Refused Cystoscopy	6	5	9	2
Sponsor Decision	0	1[1]	0	1[2]
Other	14	15	11	17

[1]Investigator moved from the site [2]During follow up, the patient chose to enroll on another study

Central and Local Pathology Review
Patients with clinically apparent TaG1-2 disease were eligible for study entry while the primary analysis population included only patients with TaG1-2 disease by central pathology review. The table below provides a breakdown of stage and grade, by central review, in all randomized patients.

- Note that 78 patients with no evidence of tumor by central review received apaziquone.

Table 4: Baseline Central Pathology Review in All Randomized Patients				
	611		612	
	Apaziquone N = 406	Placebo N = 396	Apaziquone N = 402	Placebo N = 411
TaG1-2[1]	297 (73%)	272 (69%)	288 (72%)	304 (74%)
Other	109 (27%)	124 (31%)	114 (28%)	107 (26%)
No Tumor	35	31	43	34
CIS	20	27	25	17
TaG3	15	20	15	22
T1G1	1	1	0	0
T1G2	11	10	5	5
T1G3	22	25	24	20
T2-T3	5	7	2	9

[1]The number of patients is larger than the primary analysis population since it includes patients with > 4 lesions and those whose largest lesion is > 3.5 cm.

The datasets provided a composite result of pathology review in patients with > 1 lesion and did not distinguish between benign and malignant lesions in recording the number of lesions. For example, a patient with 3 lesions may have had a T1G2, TaG3, and T0G0 (benign) lesion. This would be recorded as 3 lesions with a composite stage and grade of T1G3. The Applicant was unable to provide the pathology results for each lesion. On reviewing their data to address this question, the Applicant found that ~1% of the data was entered incorrectly.

Given these constraints, the correlation between central and local pathology was examined in 581 patients (330 from 611, 251 from 612). These patients had 1 baseline lesion that was graded (locally and centrally) using the 1973 grading system. Central review used only the 1973 grading system while local pathology review used either the 1973 or 2004 system. Central and local pathology agreed in 64% of patients on 611 and 56% of patients on 612 and was similar between arms. In examining the percentage of agreement, note that Bostwick Laboratories provided both central and local pathology review (with 100% agreement) in 20% of evaluable patients on 611 and 7% on 612. Nevertheless, these results appear to be consistent with the published literature which shows a substantial variability between pathologists (Eur Urol 2010 57:850, Clin Genitourin Cancer 2016 14:e307).

Demographics

In the primary analysis populations of 611 and 612, demographic characteristics were well balanced between arms and were similar to those of all randomized patients. The median age was 68 years on both arms of 611 and 67 years on both arms of 612. On both studies, ~ 70% of patients were male and over 95% White. Study 611 was conducted largely in the US (>90%) with approximately 20% of participants on 612 from the US.

Baseline Characteristics

The table below provides information on baseline disease characteristics and the European Organisation for Research and Treatment of Cancer (EORTC) recurrence score in the primary analysis population. Throughout the rest of this document, TaG1-2 will refer to the primary analysis population. The date of the last occurrence of bladder cancer prior to entry was not well collected and patients with a history NMIBC > 90 to 365 days prior to the treatment start date are included in the table below as recurrence within 1 year. This may have underestimated number of patients with NMIBC within 1 year of entry. Among those with a history of NMIBC, slightly less than half received prior intravesical therapy, most commonly Bacillus Calmette-Guerin vaccine (BCG).

The EORTC recurrence score is based on a weighted average of prognostic factors including: number of lesions, lesion size, history of NMIBC, presence of CIS, and grade. These appear to be balanced between arms. Note that many of the patients had a recurrence score $\geq$ 5. One study reported that the benefit of immediate intravesical therapy in patients with a recurrence score < 5 (Eur Urol 2016 69:231).

Table 5: Baseline Disease Characteristics in the Primary Analysis Population

	611 TaG1-2		612 TaG1-2	
	Apaziquone N = 295	Placebo N = 271	Apaziquone N = 282	Placebo N = 298
Number of Lesions				
1	191 (65%)	181 (67%)	167 (59%)	181 (61%)
2-4	104 (35%)	90 (33%)	115 (41%)	117 (39%)
Lesion Size				
All Lesions < 3 cm	233 (79%)	218 (80%)	245 (87%)	256 (86%)
Any Lesion 3-3.5 cm	62 (21%)	53 (20%)	37 (13%)	42 (14%)
History of NMIBC				
Any	103 (35%)	105 (39%)	108 (38%)	109 (37%)
$\leq$ 1 year	34 (12%)	29 (11%)	34 (12%)	42 (14%)
CIS	0	1 (0.4%)	1 (0.4%)	1 (0.3%)
EORTC Recurrence Score				
0	81 (27%)	58 (21%)	69 (24%)	88 (30%)
1-4	139 (47%)	146 (54%)	141 (50%)	128 (43%)
5-9	74 (25%)	67 (25%)	71 (25%)	81 (27%)
10-17	1 (0.3%)	0	1 (0.4%)	1 (0.3%)

Assessments

The number of patients in the primary analysis population undergoing cystoscopy at various time points is shown in the table below. There is a substantial amount of missing data, particularly at later time points. While this appears to be balanced between arms, the amount of missing data should be viewed in the context of a less than 10% difference, between arms, in the percentage of patients with recurrent disease.

Table 6: Compliance with of Follow Up Cystoscopy in the Primary Analysis Population				
	611 TaG1-2		612 TaG1-2	
	Apaziquone N = 295	Placebo N = 271	Apaziquone N = 282	Placebo N = 298
Month 3	286 (97%)	256 (94%)	276 (98%)	293 (98%)
Month 6	271 (92%)	246 (91%)	264 (94%)	280 (94%)
Month 9	263 (89%)	237 (87%)	250 (89%)	278 (93%)
Month 12	259 (88%)	225 (83%)	251 (89%)	261 (88%)
Month 15	250 (85%)	225 (83%)	241 (85%)	255 (86%)
Month 18	244 (83%)	216 (80%)	233 (83%)	247 (83%)
Month 21	238 (81%)	212 (78%)	227 (80%)	246 (83%)
Month 24	243 (82%)	216 (80%)	239 (85%)	263 (88%)

Urine cytology is not part of the routine follow up for patients with TaG1-2 disease, but was obtained every 6 months in all patients. The primary endpoint included only histological findings and the results of urine cytology were not included.

Additional Therapy

Additional treatment, after study entry, could alter the development of recurrent NMIBC. Therefore, its use, prior to the Month 3 visit, was examined in the primary analysis population. The Month 3 time point was chosen because therapy prior to this date would be directed to the disease at study entry rather than recurrent disease. Few patients in the primary analysis population, even those with unfavorable prognostic features received additional intravesical therapy.

Table 7: Additional Therapy in the First 3 Months in the Primary Analysis Population				
	611		612	
	Apaziquone N = 295	Placebo N = 271	Apaziquone N = 282	Placebo N = 298
Any Intravesical Therapy	3 (1%)	14 (5%)	8 (3%)	5 (2%)

Use of additional therapy was also examined in patients with high-risk NMIBC. These patients were not included in the primary analysis population, but were randomized and did receive apaziquone/placebo. Among all randomized patients with T1 disease by local pathology review, 43% of patients on 611 and 32% on 612 received additional intravesical therapy. This suggests that additional intravesical therapy may have been poorly recorded and brings into question the results of the analysis shown in the table above.

Primary Analysis

The results of the primary analyses are shown in the table below. The values in the table differ slightly from those of the Applicant. Three patients had their Month 24 assessment after Day 765 (end of the Month 24 visit window) and were not included in the Applicant's analysis. They are included in the FDA analysis. Assessments outside the visit window are protocol

deviations and are typically included in the primary analysis, but not in the per protocol analysis. The addition of these 3 patients did not change the statistical significance of this analysis.

Table 8: FDA Primary Analyses				
	611 TaG1-2		612 TaG1-2	
	Apaziquone N = 295	Placebo N = 271	Apaziquone N = 282	Placebo N = 298
Number of Recurrences	112 (38.0%)	121 (44.6%)	114 (40.4%)	139 (46.6%)
Difference	6.6%		6.2%	
Odd Ratio (95% CI)	0.76 (0.54, 1.06)		0.78 (0.56, 1.08)	
p-value	0.11		0.13	

The observed decreases in recurrence in the apaziquone arm in both studies were less than anticipated in the trial design and neither study reached statistical significance. Note that when the primary analysis fails to reach statistical significance that further analyses are uninterpretable. Existing agents are thought to result in an approximately 12% decrease in recurrence and are seldom used. This suggests that a 12% decrease in recurrence may not be considered to be clinically meaningful by many physicians and brings into question the clinical relevance of the observed difference seen with apaziquone. The Applicant has noted that apaziquone can be used safely in patients with bladder perforation and believes this may result in increased use, despite the observed decrease in recurrence. However, in a single study that recorded the reason immediate intravesical chemotherapy was not given, a deep resection (and therefore possible perforation) was reported in 9% of patients (J Urol 2012 188:2108)

Characteristics of Patient Recurrence

The table below provides information, from central pathology review, on the stage and grade of all histologically documented bladder cancers (recurrence) during the 2 year study period. Most lesions were TaG1-2. With a decrease in TaG1-2 disease, patients would require fewer transurethral resections, but would still require extensive follow up cystoscopy.

A larger concern is a reduction in disease progression. Progression is typically considered the development of muscle invasive, T2 disease. T2 disease may require a cystectomy and urinary diversion. In both studies, few patients in the primary analysis population (4 apaziquone, 2 placebo) developed T2 disease.

Table 9: Recurrent Bladder Cancer in the Primary Analysis Population				
	611 TaG1-2		612 TaG1-2	
Number of Patients				
	Apaziquone N = 295	Placebo N = 271	Apaziquone N = 282	Placebo N = 298
Recurrence per Patient				
1	63 (21%)	56 (21%)	71 (25%)	62 (21%)
2	29	33	24	45
≥ 3	18	32	19	32
Number of Recurrences				
Stage and Grade of Recurrence	Apaziquone N = 193	Placebo N = 236	Apaziquone N = 185	Placebo N = 268
CIS	8	16	11	9
TaG1	142 (74%)	173 (73%)	134 (72%)	199 (75%)
TaG2	38 (20%)	38 (16%)	30 (16%)	53 (20%)
TaG3	1	3	0	2
T1G2	3	4	1	2
T1G3	1	1	5	2
T2G2	0	0	2	1
T2G3	0	1	2	0

Sensitivity Analyses

The table below provides sensitivity analyses in a variety of patient populations. First, is a post-hoc analysis of pooled data from 611 and 612. The use of a post-hoc pooled analysis violates several statistical principles. The International Conference on Harmonization (ICH) provides a series of guidelines for clinical trial design and review by regulatory agencies. Per ICH E9, Statistical Principles for Clinical Trials, "Individual clinical trials should always be large enough to satisfy their objectives." It is also stated that "Under exceptional circumstances a meta analytic approach may also be the most appropriate way, or the only way, of providing sufficient overall evidence of efficacy via an overall hypothesis test. When used for this purpose the meta-analysis should have its own prospectively written protocol." Note that with the use of a pooled analysis the difference between arms is approximately 7%.

The next analysis included in the table uses the results of local pathology review. Here, the analysis population included patients with TaG1-2 or Ta low grade disease by local pathology review as well as ≤ 4 lesions and all lesions ≤ 3.5 cm. Recurrence was based on the results of local pathology. In this analysis, the difference between arms in 612 was 3%. A sensitivity analysis (Additional Events) was also conducted in which: 1) patients in whom cystoscopy was recorded as tumor present and no pathology results were available for that time point and 2) patients with malignant urine cytology were considered to have had an event. This was conducted in the primary analysis population and used the results of central pathology review. Finally, an analysis was done in all randomized patients. It should be noted that all patients in

this analysis were not available for evaluation of recurrence due to cystectomy or patient drop out.

Table 10: Sensitivity Analyses					
		N	2 Year Recurrence	Difference	Odds Ratio (95% CI)
Pooled Analysis					
	Apaziquone	577	226 (39%)	7%	0.77 (0.61, 0.97)
	Placebo	569	260 (46%)		
Local Pathology					
611	Apaziquone	275	111 (40%)	6%	0.80 (0.56, 1.13)
	Placebo	244	112 (46%)		
612	Apaziquone	254	103 (41%)	3%	0.86 (0.61, 1.22)
	Placebo	260	115 (44%)		
Additional Events					
611	Apaziquone	295	122 (41%)	5%	0.82 (0.64, 1.05)
	Placebo	271	125 (46%)		
612	Apaziquone	282	121 (43%)	6%	0.77 (0.56, 1.07)
	Placebo	298	147 (49%)		
All Randomized Patients					
611	Apaziquone	406	150 (37%)	5%	0.80 (0.61, 1.07)
	Placebo	396	167 (42%)		
612	Apaziquone	402	161 (40%)	6%	0.78 (0.59, 1.03)
	Placebo	410	189 (46%)		

Subgroup Analyses

Among US patients in the primary analysis population, 2 year recurrence, in the apaziquone vs. the placebo arm, was 38% vs. 44% in 611 and 42% vs. 46% in 612. In patients in the primary analysis population with an EORTC Recurrence Score < 5, 2 year recurrence, in the apaziquone vs. the placebo arm, was 32% vs. 36% in 611 and 33% and 40% in 612. The differences between arms, 4% and 7%, were similar to or less than those seen in the primary analysis. Note that all of these subgroup analyses should be considered hypothesis-generating.

A post-hoc subgroup analysis emphasized by the Applicant in their submission is 2 year recurrence based on the timing of administration of study drug. The Applicant optimized these time intervals to $\leq$ 30, 31-90, and > 90 minutes between the completion of the procedure and the administration of study drug. It is unclear how accurately these times were recorded. As shown in the tables below, the interval suggesting the greatest benefit for apaziquone, 31-90 minutes has the smallest number of patients. The Applicant has speculated that when apaziquone is given at an early time point, it is inactivated by blood within the bladder and that when it is given at a late time point, the free floating malignant cells are protected by the bladder mucosa. Studies showing a benefit for immediate intravesical chemotherapy have typically required instillation within 6 hours (occasionally 24 hours) of resection. Finally, in the 0 to 30 minute subgroup in 612, the recurrence was increased with the administration of apaziquone. This seems unlikely and further calls into question the results of these subgroups

analyses. That is, the results of these analyses are just as likely to be due to chance alone. Again, post-hoc subgroup analysis should be considered hypothesis generating.

Table 11: 2 Year Recurrence by Time of Study Drug Administration in the Primary Analysis Population						
	0 to 30 Minutes		31 to 90 Minutes		> 90 Minutes	
611	Apaziquone N = 134	Placebo N = 145	Apaziquone N = 60	Placebo N = 39	Apaziquone N = 101	Placebo N = 87
Recurrence	62 (46%)	69 (48%)	14 (23%)	17 (44%)	36 (36%)	35 (40%)
Odds Ratio (95% CI)	0.95 (0.59, 1.52)		0.39 (0.16, 0.94)		0.82 (0.46, 1.49)	
612	Apaziquone N = 99	Placebo N = 78	Apaziquone N = 57	Placebo N = 61	Apaziquone N = 126	Placebo N = 159
Recurrence	42 (42%)	28 (36%)	19 (33%)	33 (54%)	53 (42%)	78 (49%)
Odds Ratio (95% CI)	1.32 (0.71, 2.42)		0.42 (0.20, 0.89)		0.75 (0.47, 1.21)	

Per ICH E3, Structure and Content of Clinical Study Reports, "These analyses (subgroup analyses) are not intended to "salvage" an otherwise non-supportive study but may suggest hypotheses worth examining in other studies or be helpful in refining labeling information, patient selection, dose selection, etc." The timing of the administration of study drug is being examined in an ongoing trial.

Secondary Endpoint-Time to Recurrence

Note that no alpha is available for testing of any secondary endpoints since the results of the primary analysis were not statistically significant.

Table 12: Time to Recurrence in the Primary Analysis Population				
	611 TaG1-2		612 TaG1-2	
	Apaziquone N = 295	Placebo N = 271	Apaziquone N = 282	Placebo N = 298
Events	112	121	114	139
Median	NR[1]	24.2 mos	NR	NR
Hazard Ratio (95% CI)	0.77 (0.59, 0.99)		0.81 (0.64, 1.04)	

[1]Not reached

Other Intravesical Studies

The Applicant has conducted 6 other studies of intravesical apaziquone.

- ND-019903: This Phase 1-2 study administered apaziquone weekly x 6 to patients with a low grade marker lesion. A complete response (CR) was seen in 4/6 Phase 2 patients.
- ND-03020: Apaziquone was administered weekly x 6 to patients with TaG1-2, T1G1-2 disease who had an unbiopsied marker lesion. A CR was achieved by 41/46 patients.
- SPI-515: Immediate intravesical apaziquone was administered to 20 patients with TaG1-2 or T1G1-2 tumors. Patients were followed for 3 months.
- SPI-05-003: Apaziquone weekly x 6 was administered to 53 patients with high-risk bladder cancer. Among 49 patients without CIS, 45% recurred within 18 months.

- 1011 and 1012: These studies administered immediate intravesical apaziquone to all patients and then randomized patients with ~ low to intermediate-risk disease to apaziquone or placebo weekly x 6. These studies were closed for business reasons after 59 patients were treated on the randomized portions of the studies.

The Applicant also has 1 ongoing study under a Special Protocol Agreement, SPI-EOQ-13-305: A Multicenter, Multi-arm, Randomized, Multi-Dose, Placebo-Controlled, Double-Blind, Phase 3 Study of Intravesical Apaziquone as a Surgical Adjuvant in the Immediate Postoperative Period in Patients Undergoing Transurethral Resection for Non-Muscle Invasive Bladder Cancer." Here, patients with TaG1-2 disease will receive apaziquone or placebo 31-120 minutes after resection followed by a 2nd dose 1 week later. The primary endpoint is time to recurrence.

5. Safety

Studies 611 and 612 administered apaziquone to 808 patients and are the primary focus of the safety analysis. Both studies administered 1 dose of apaziquone or placebo immediately after resection. Genitourinary adverse events and serious adverse events were collected for 2 years. Routine adverse events were collected for 6 months after administration of study drug.

Exposure
All randomized patients on 611 and 612 received study drug. Most received 40 mL and retained this for 1 hour. Less than 40 mL was administered to 3 patients on 611 and 2 on 612 (all 5 placebo). Study drug was retained for less than 1 hour in 19 patients on 611 (12 apaziquone, 7 placebo) and in 11 patients on 612 (5 apaziquone, 6 placebo).

The number of patients who remained on study and continued to undergo follow up cystoscopy in the primary analysis populations is shown in the table above, Compliance with Follow-up Cystoscopy. However, safety assessments are based on all randomized patients. Compliance with follow up cystoscopy was slightly lower in this group. At each time point, the percentage of the randomized population undergoing follow up cystoscopy ranged from 93-77% in 611 and 97-77% in 612.

Summary of Adverse Events
The table below provides a summary of adverse events in all treated patients. This is followed by additional information concerning deaths, discontinuations due to adverse events, serious adverse events, and grade 1-4 adverse events.

Table 13: Summary of Adverse Events in All Treated Patients				
	ITT 611		ITT 612	
	Apaziquone N = 406	Placebo N = 396	Apaziquone N = 402	Placebo N = 411
Deaths				
≤ 30 Days of Study Drug	0	0	0	0
All	11 (3%)	13 (3%)	14 (3%)	14 (3%)
Discontinuation due to Grade 1-4 AEs	4 (1%)	3 (0.8%)	4 (1%)	3 (0.7%)

Grade 1-4 Serious Adverse Events	92 (23%)	96 (24%)	58 (14%)	62 (15%)
Grade 3-4 Adverse Events	76 (19%)	85 (21%)	67 (17%)	81 (20%)
Grade 1-4 Adverse Events	326 (80%)	297 (75%)	320 (80%)	332 (81%)

Deaths: In both 611 and 612, none of the deaths occurred within 30 days of the single dose of study drug and none appeared to be related to study drug.

Discontinuations due to Grade 1-4 Adverse Events:

- Most of the discontinuations appeared to be unrelated to study drug and none occurred within 30 days of dosing. Two patients in the placebo arm (1 on each study) discontinued due to metastatic bladder cancer. One patient in the apaziquone arm of 611 discontinued due to grade 2 cystitis on Day 585 (last cystoscopy Day 543).

Serious Adverse Events: Grade 1-4 serious adverse events in > 1% of apaziquone patients and at a higher incidence than placebo are shown below with the incidence in the apaziquone arm shown in parentheses.

- 611- Atrial fibrillation (1.5%), Chest pain (1.2%), COPD (1.2%), and Cellulitis (1.2%)
- 612- Urinary retention (2.2%), Heart failure (2%)

Grade 1-4 Adverse Events: Grade 1-4 adverse events in > 5% of apaziquone patients and at a higher incidence than placebo are shown below with the incidence in the apaziquone arm shown in parentheses. Urinary tract infection (UTI) is a composite term that includes Escherichia UTI, UTI entercoccal, and urosepsis.

- 611-Dysuria (18%), Urinary tract infection (18%), Bladder pain/discomfort (9%), Procedural pain (8%), and Bladder spasm (7%)
- 612-Dysuria (21%), Pollakiuria (11%), Bladder pain/discomfort (8%)

Grade 1-4 Adverse Events on Days 1-7: Grade 1-4 adverse events during the first 7 days after the administration of study drug were examined in an effort to detect adverse events associated with apaziquone. Grade 1-4 adverse events in > 5% of patients receiving apaziquone and at a higher incidence than placebo are shown in the table below.

Table 13: Grade 1-4 Adverse Events on Days 1-7 in All Treated Patients				
	ITT 611		ITT 612	
	Apaziquone N = 406	Placebo N = 396	Apaziquone N = 402	Placebo N = 411
Dysuria	42 (10%)	38 (10%)	56 (14%)	48 (12%)
Bladder pain/discomfort	29 (7%)	22 (6%)	27 (7%)	24 (6%)
Procedural pain	29 (7%)	24 (6%)	11 (3%)	15 (4%)
Bladder spasm	23 (6%)	20 (5%)	10 (2%)	11 (3%)

Bladder Perforation

Bladder perforation occurred in 3 patients on 611 and 5 patients on 612 (0.5% overall). Among the 3 events on 611, all occurred with the initial TURBT and 1 grade 3 event resulted in

hospitalization. The 5 events on 612 occurred at various time points. Two events were grade 3. One event required surgical closure and a 2nd required a procedure to remove bladder clots. The incidence of bladder perforation on these studies is lower than the 1.3% incidence reported in the literature (J Urol 2000 164:1529).

Laboratories

CBC, chemistries, and urinalysis were collected at baseline, Week 3, and Month 3. Urinalysis was also collected prior to each cystoscopy. The focus of the laboratory analysis is on CBCs at baseline and Week 3.

On 611, 4 patients on apaziquone had a grade 3-4 ANC at Week 3. One of these patients had a grade 2 ANC at baseline. Apaziquone levels are not available. These 4 patients were examined for associated adverse events and none could be attributed to a low ANC. No patients on 611 had grade 3-4 thrombocytopenia. On 612, no patients had neutropenia, but 1 patient had a grade 4 platelet count at Week 3. This patient was diagnosed with idiopathic thrombocytopenic purpura and ultimately required a splenectomy.

6. Issues for ODAC

In Studies 611 and 612, the percentage of patients with recurrent disease in the apaziquone arm was numerically lower than that of placebo (difference 6.6% and 6.2%). Recurrent disease was most commonly TaG1-2, and while a decrease in the recurrence of TaG1-2 disease could potentially translate into a requirement of fewer transurethral resections, patients would still require extensive follow up cystoscopy. These individual studies did not meet statistical significance. The magnitude of the observed, numerical reduction of the rate of recurrence was less than that seen with current therapy, precluding accelerated approval. The multiple, post-hoc, hypothesis-generating analyses of Studies 611 and 612 have resulted in optimization efforts that are currently being tested in an ongoing clinical trial that is conducted under a Special Protocol Agreement.

The Draft Issue for ODAC:

- Discuss the relevance of the results of Studies 611 and 612 in the evaluation of the risk-benefit profile of apaziquone for the treatment of NIMBC.