FOOD AND DRUG ADMINISTRATION (FDA)
Center for Drug Evaluation and Research (CDER)

Oncologic Drugs Advisory Committee (ODAC) Meeting
Tommy Douglas Conference Center
10000 New Hampshire Avenue, Silver Spring, Maryland
September 14, 2016

DRAFT QUESTIONS

NDA 208714

Apaziquone for intravesical instillation

APPLICANT: Spectrum Pharmaceuticals, Inc.

PROPOSED INDICATION: For immediate intravesical instillation post-transurethral resection of bladder tumors in patients with non-muscle invasive bladder cancer

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The Applicant has conducted 2 randomized trials of a single instillation of apaziquone versus placebo following resection of nonmuscle invasive bladder cancer. One of the 2 very similar trials was conducted under a Special Protocol Assessment. The primary endpoint of both trials 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 nonmuscle invasive bladder cancer by central pathology review.

Both trials failed to demonstrate a reduction in disease recurrence with apaziquone at 2 years. The 2 year rate of recurrence was lower for apaziquone-treated than for placebo-treated patients in both trials. The magnitude of reduction (6.6% and 6.2%) was; however, lower than that seen with currently available therapy. The safety profile of apaziquone was similar to that of placebo.

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 (95% CI)	6.6% (-1.8%, 15.1%)		6.2% (-2.2%, 14.6%)	
Odds Ratio	0.76		0.78	
p-value	0.11		0.13	

The Applicant has conducted unplanned pooling of the results of the two studies. They have 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.

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The Agency's primary concern is whether the Applicant has demonstrated substantial evidence of efficacy. Substantial evidence ensures, through well controlled and well-conducted clinical trial(s), that a treatment effect has been identified and is not due to variability in the underlying disease, bias, or chance alone.

1. **VOTE**: Has substantial evidence of a treatment effect for apaziquone over placebo been demonstrated?

2. **DISCUSSION**: For those who voted "yes" to question 1 that an effect has been demonstrated, please discuss the clinical meaning of the results of studies 611 and 612.