NDA 208714

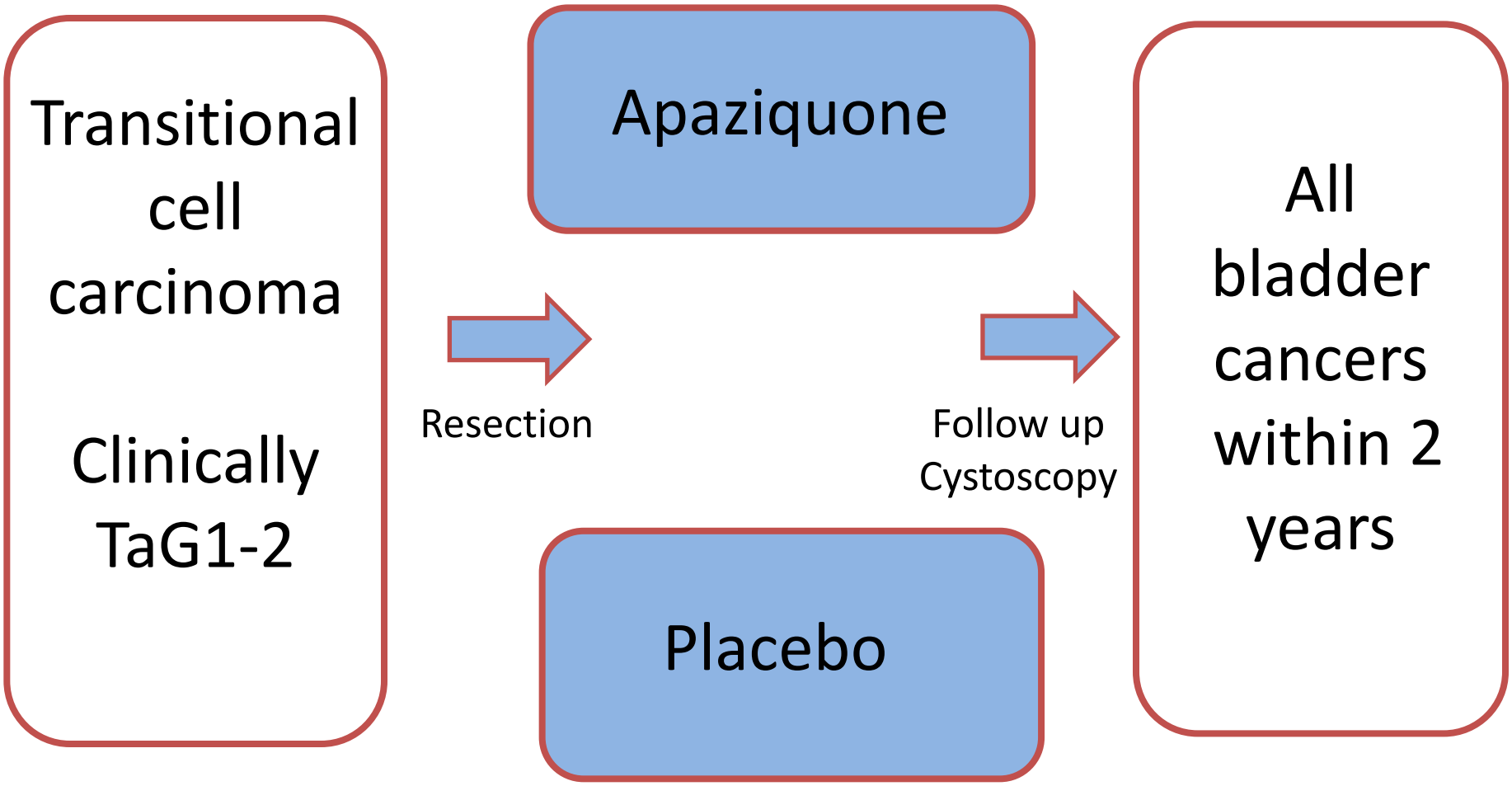
ODAC Meeting

September 14, 2016

Apaziquone

Spectrum Pharmaceuticals, Inc.

611 and 612 Study Design



Regulatory Background

- Special Protocol Assessment-February 2007
- Pre-NDA meeting December 2012
  - Each study failed to meet its primary endpoint.
  - FDA advised the Applicant NOT to submit the NDA based on this data.
- NDA submitted December 2015

Substantial Evidence

- Ensures that a treatment effect has been identified and is not due to variability in the underlying disease, bias, or chance alone.
- Treatment effect demonstrated through well-controlled and well-conducted investigation(s)
- Sound evidence of effectiveness is a crucial component of the benefit-risk assessment of a new product.

Issues for Discussion

Is there substantial evidence of a treatment effect?

- Both trials- not statistically different than placebo
- Post-hoc pooling strategy
- Post-hoc subgroup analysis
- Missing data

Issues for Discussion

Is this effect clinically meaningful?

~ 6% difference in 2-year recurrence between arms = smaller than expected

Type of recurrence decreased = primarily low grade, non-muscle invasive disease

Issues

Is there substantial evidence of a treatment effect?

Is this effect clinically meaningful?

NDA 208714
Apaziquone

FDA Presentation

ODAC Meeting

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Apaziquone Review Team

	Reviewers	Team Leaders
Clinical	Gwynn Ison (efficacy)	Ellen Maher
	Chana Weinstock (safety)	
Statistics	Erik Bloomquist	Shenghui Tang
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CMC/ Microbiology	David Bateman	Stephen Langille
OSI	Lauren Iacono-Connor	Susan D. Thompson
RBPM	Kristine Leahy	Luz Rivera
Administrative	Charlene Wheeler	Christy Cottrell

Proposed Indication

Apaziquone is a bioreductive alkylating indoloquinone indicated for immediate intravesical instillation post-transurethral resection of bladder tumors in patients with non-muscle invasive bladder cancer (NMIBC).

Issues

1. Has the Applicant demonstrated substantial evidence of the efficacy of apaziquone?

2. If an effect for apaziquone has been demonstrated, is it clinically meaningful?

Natural History of NMIBC

- Low risk bladder cancers
  - Recurrent disease
    - Recurrence is any new bladder cancer, regardless of the site within the bladder
  - Rarely progress to muscle invasive cancer
    - 0.2% risk at 1 year
    - 0.8% risk at 5 years
  - Regular surveillance by cystoscopy

Management of Low Risk NMIBC

- **TURBT → +/- single dose of intravesical chemotherapy**

- NCCN[1] and American Urological Association
  - Consider administration of a single postoperative instillation of intravesical chemotherapy

- European Association of Urology
  - Recommend immediate single postoperative instillation of intravesical chemotherapy

[1]National Comprehensive Cancer Network

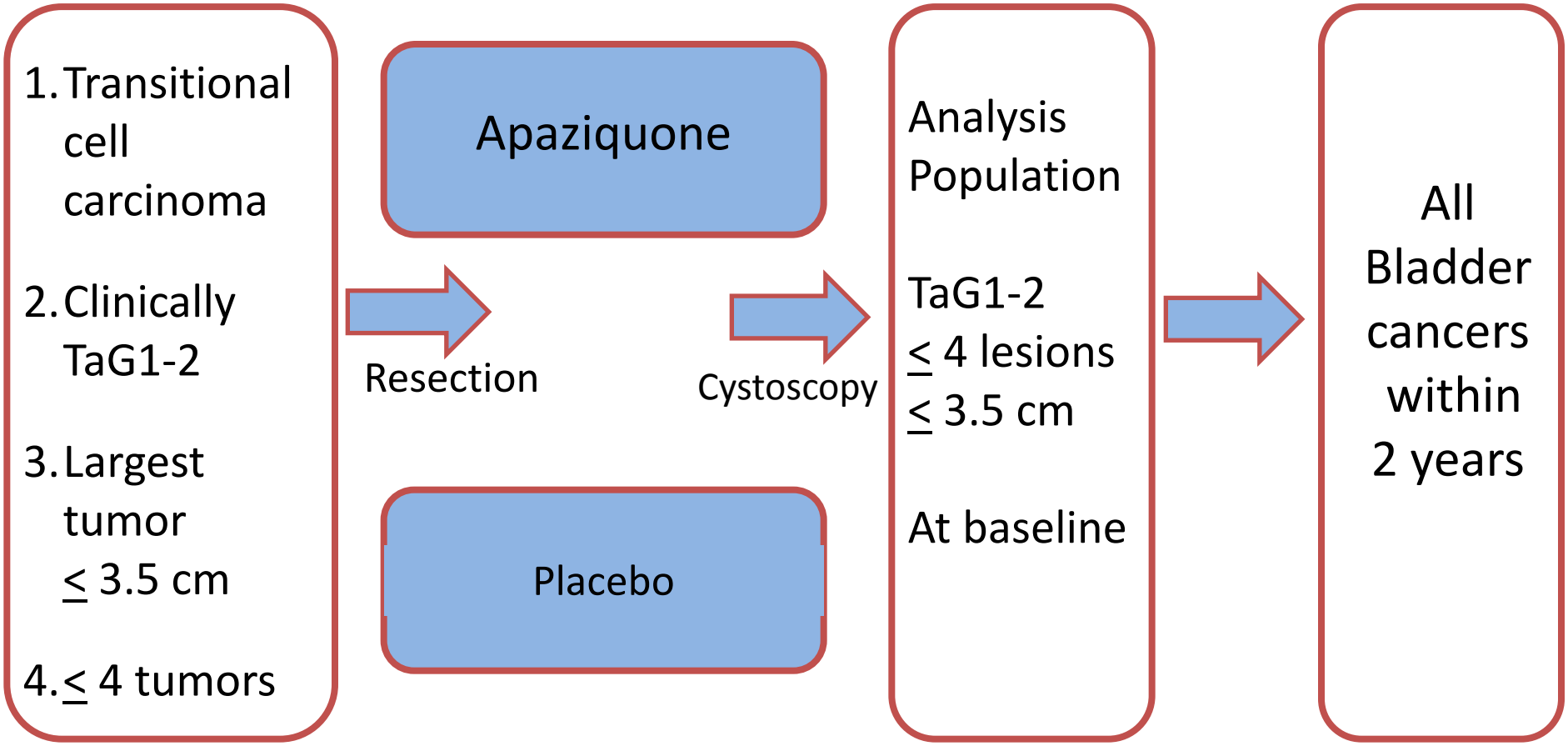
Therapies Included in Meta-analysis

Agent/Comparator*	# studies	# patients receiving agent	Treatment effect (Abs diff 5-y in recurrence)	HR (95% CI)
All (Single instillation/ TURBT)	11	1117	**14.0%** (44.8% v. 58.8%)	**0.65** (0.58-0.74)
Mitomycin/ TURBT	4	324	**18.5%** (34.9% v. 53.4%)	**0.58** (0.46-0.72)
Epirubicin/ TURBT	5	586	**14.9%** (46.2% v. 61.1%)	**0.63** (0.54-0.74)
Thiotepa/ TURBT	1	126	**-6.4%** (55.6% v. 49.2%)	**1.17** (0.83-1.64)
Pirarubicin/ TURBT	1	81	**17.1%** (25.9%v. 43%)	**0.44** (0.26-0.75)

*Comparators included: TURBT + No instillation, sterile water, or saline

Eur Urol 2016 69:231

611 and 612 Study Design



Study Endpoints

- **Primary endpoint:** 2-year recurrence rate

- **Secondary endpoints:**
  - Time to recurrence (any new cancer)
  - Time to progression to higher grade or stage
    - CIS<Ta<T1<T2 and G1<G2<G3
  - Progression rate at 2 years

Statistical Analysis Plan

- Designed to detect 12% decrease in 2-year recurrence with apaziquone, a = 0.05.

- Testing to include 95% CI for odds ratio and CMH chi-squared test.

Regulatory History

- Special Protocol Assessment agreement given to study SPI-611 in February 2007.
  - Studies 611 and 612 form the basis of the NDA and are very similar.

- Pre-NDA meeting December 2012
  - Topline results: Each study failed to meet the primary endpoint.
  - We advised NOT to submit the NDA based on this data.

- NDA Submitted December 2015

Efficacy Results

Baseline Central Pathology

	611		612	
	Apaziquone N=406 (%)	Placebo N=396 (%)	Apaziquone N=402 (%)	Placebo N=411 (%)
TaG1-2	295 (72)	272 (69)	288 (72)	304 (74)
Other	109 (27)	124 (31)	114 (28)	107 (26)
No tumor	35	31	43	34

Baseline Demographics

Primary Analysis Population				
	611 TaG1-2		612 TaG1-2	
	Apaziquone N=295 (%)	Placebo N=271 (%)	Apaziquone N=282 (%)	Placebo N=298 (%)
Median Age (Range)	68 (29-90)	68 (32-94)	67 (24-94)	67 (22-89)
Gender				
Male	210 (71)	199 (73)	203 (72)	208 (70)
Female	85 (29)	72 (27)	79 (28)	90 (30)
Race				
White	287 (97)	263 (97)	275 (98)	289 (97)
Country				
United States	276 (94)	261 (96)	59 (21)	57 (19)

Disease Characteristics

	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 < 3 cm	233 (79%)	218 (80%)	245 (87%)	256 (86%)
History of NMIBC				
Any	103 (35%)	105 (39%)	108 (38%)	109 (37%)
≤ 1 year	34 (12%)	29 (11%)	34 (12%)	42 (14%)
CIS present	0	1 (0.4%)	1 (0.4%)	1 (0.3%)

Missing Bladder Assessment in Patients “At Risk”

TaG1-2 Population	Apaziquone (%)	Placebo (%)
611		
Month 24 Visit	38/186 **(20%)**	37/153 **(24%)**
612		
Month 24 Visit	36/175 **(21%)**	13/162 **(8%)**

The missing data rate was greater than the difference in 2-year recurrence rate between arms (~6%).

Erik Bloomquist, PhD

FDA STATISTICAL ANALYSIS

Major Statistical Issues

- Primary endpoint analysis failed to demonstrate treatment effect
- Uncontrolled false-positive rate for secondary analysis, > 5%
- Exploratory post-hoc pooled analysis
- Exploratory post-hoc subgroup analysis

Primary Analysis Results

Study 611

	2-year Recurrence	
	Apaziquone (N=295)	Placebo (N=271)
2-Year Recurrence (%) (95% CI)	112 (38.0%) (32.4%, 43.8%)	121 (44.6%) (38.6%, 50.8%)
Odds Ratio (CI)	0.76 (0.54, 1.06)	
p-value	0.11	

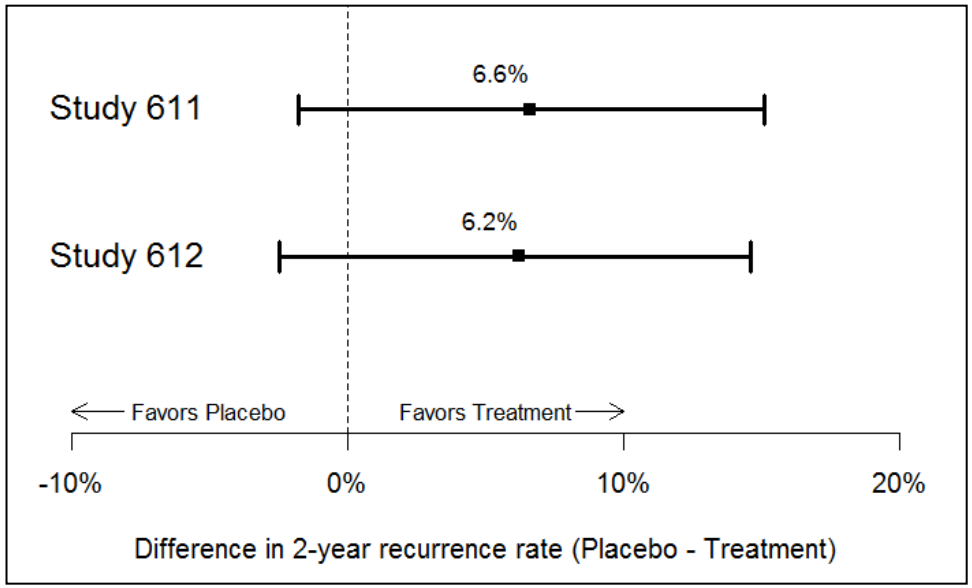
Study 612

	2-year Recurrence	
	Apaziquone (N=282)	Placebo (N=298)
2-Year Recurrence(%) (95% CI)	114 (40.4%) (33.1%, 44.5%)	139 (46.6%) (45.2%, 57.4%)
Odds Ratio (CI)	0.78 (0.56, 1.08)	
p-value	0.13	

*Both 611 and 612 used the Ta, G1-G2 population as the primary analysis population

Primary Analysis Results

- Difference in 2-year recurrence
  - 611: 6.6% (95% CI: -1.8%, 15.1%)
  - 612: 6.2% (95% CI: -2.2%,14.6%)
- Studies powered to detect 12% difference
- 14% estimated 5-year difference (Eur Urol 2016 69:231)



Primary Analysis Results

- Most recurrences were Ta, G1-G2
- In study 612, 2 patients recurred with T2 tumors (muscle-invasive)

Stage and Grade of First Recurrence in Primary Analysis Population				
	611		612	
	Apaziquone N = 112 (%)	Placebo N = 121 (%)	Apaziquone N = 114 (%)	Placebo N = 139 (%)
Ta, G1-G2	107 (95.5)	106 (87.6)	104 (91.2)	131 (94.2)
T2	0 (0)	0 (0)	2 (1.8)	0
Other	5 (4.5)	15 (12.4)	8 (7.0)	8 (5.8)

Other includes CIS, TaG3, and T1.

Primary Analysis Results

- The primary efficacy results do not provide adequate evidence that apaziquone has an effect on 2-year recurrence
- Confidence intervals for difference contain 0%, so neither study demonstrates apaziquone is different than placebo
- ~ 6% difference-less than 12% difference used at design stage
- ~ 6% difference-less than 14% estimated difference in recent meta-analysis (Sylvester, Eur Urology 2016)
- Missed cystoscopies can account for difference in 2-year recurrence

Secondary Endpoint Results

Study 611

	Time to Recurrence	
	Apaziquone N = 295	Placebo N = 271
Events	112	121
Median	NR	24.2 mos
Hazard Ratio	0.77 (0.59, 0.99)	
Nominal p-value	0.04	

Study 612

	Time to Recurrence	
	Apaziquone N = 282	Placebo N = 298
Events	114	139
Median	NR	NR
Hazard Ratio	0.81 (0.64, 1.04)	
Nominal p-value	0.10	

*Both 611 and 612 used the Ta, G1-G2 population as the primary analysis population

Secondary Endpoint Results

- Uncontrolled false-positive rate for endpoint > 0.05

- Neither study designed for time-to-event endpoint
  - Follow-up truncated at 24 months
  - Pre-specified information fraction to test

- Secondary analysis results do not provide evidence that apaziquone has an effect on 2-year recurrence.

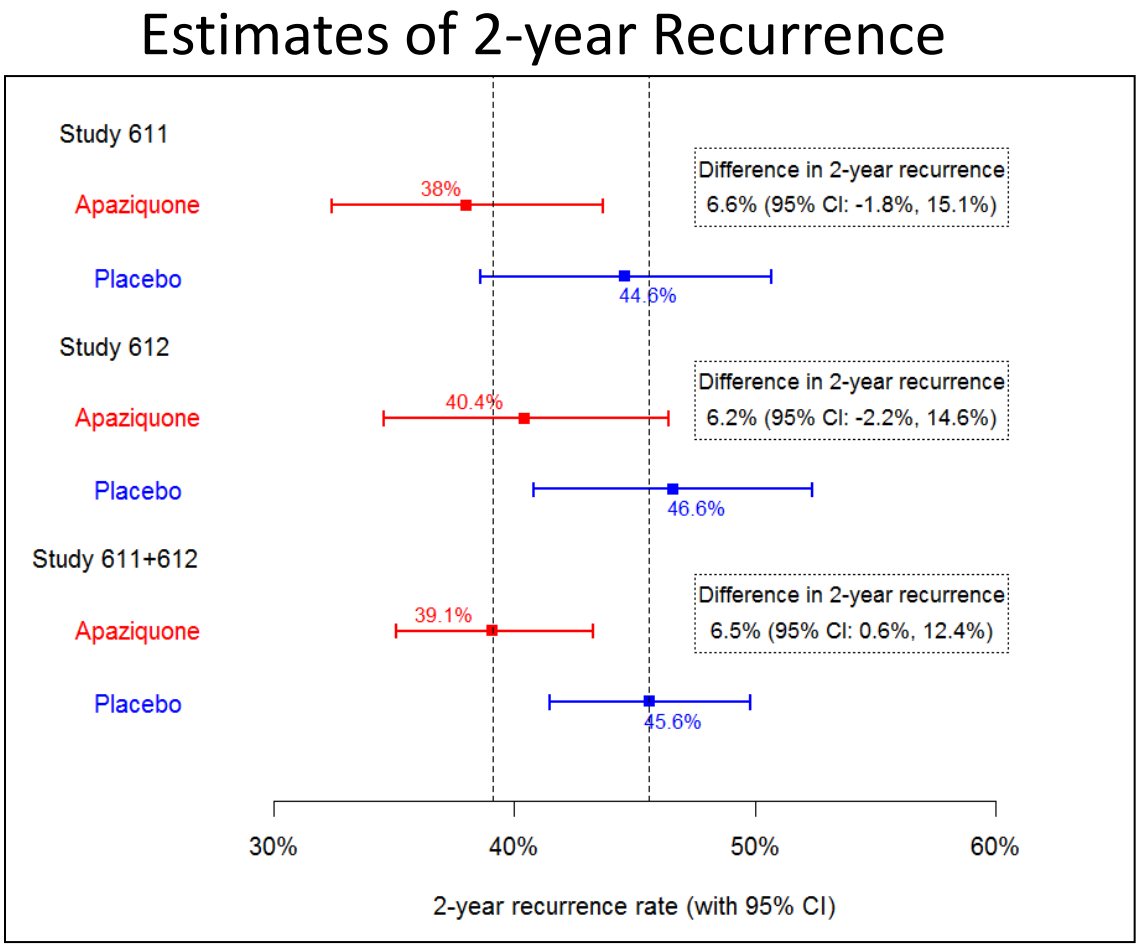
Additional Analyses

- Applicant has proposed additional analyses to support product
  - Pooling study results
  - Exploratory subgroup analyses

- FDA does not agree with these additional analyses

Pooling Analysis

- Primary purpose of pooling two studies is to narrow confidence intervals
- Has little effect on estimate of 2-year recurrence difference.
- Confidence intervals overlap



Regulatory Guidance

- ICH E9 is an internationally recognized guidance document for statistical practice in clinical trials
- Per ICH E9:
  - Individual clinical trials should always be large enough to satisfy their objectives.
  - 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.**

Subgroup Analysis

- Applicant has stated that time to instillation is an important efficacy subgroup
- Time to instillation is time from surgery to administration of agent
- Applicant has data showing that blood inactivates active drug, so instillation immediately after surgery could possibly decrease efficacy of drug
- Applicant focuses on administration of apaziquone > 30 minutes after surgery

Subgroup Analysis Results

Pooled TaG1-2 Population				
	0-30 Minutes		>30 Minutes	
	Apaz N=233	Placebo N = 223	Apaz N = 344	Placebo N = 346
2 Year Recurrence	44.6%	43.5%	35.6%	47.1%
Observed Difference	-1.1%		11.5%	

- Subgroup analysis is post-hoc, using trial data.
- 30 minute is **optimal cutpoint** between 0 and 2 hours (5 minute intervals)
- Results are hypothesis generating only
- Results to be verified in ongoing trial

Regulatory Guidance

- From ICH E9: “In most cases, however, subgroup or interaction analyses are exploratory and should be clearly identified as such…when exploratory, these analyses should be interpreted cautiously. **Any conclusion of treatment efficacy (or lack thereof) or safety based solely on exploratory subgroup analyses is unlikely to be accepted.”**

Regulatory Guidance

- ICH E3 is a international guidance document on clinical study reports

- From ICH E3: ‘[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 labelling information, patient selection, dose selection etc.’

Conclusions

- Study 611 and 612 failed to meet their primary endpoints
- ~ 6% difference difficult to interpret in light of missing data and meta-analysis by Sylvester et al. (Eu Urology 2016)
- Uncontrolled false-positive rate for secondary endpoint
- Post-hoc pooling analysis is exploratory
- Post-hoc subgroup analysis is exploratory
- Analysis and results have not demonstrated a significant effect of apaziquone over placebo

Safety

Safety Overview

Overall, Apaziquone and placebo arms had **similar adverse event profiles**

	All Treated 611		**All Treated 612**	
	Apaziquone N = 406	Placebo N = 396	Apaziquone N = 402	Placebo N = 411
Deaths				
Within 30 Days of Study Drug	0	0	0	0
All	3%	3%	3%	3%
Discontinuation	1%	0.8%	1%	0.7%
Grade 1-4 Serious Adverse Events	23%	24%	14%	15%
Grade 3-4 Adverse Events	19%	21%	17%	20%
Grade 1-4 Adverse Events	80%	75%	80%	81%

[1] No deaths within 30 days of instillation; no deaths considered related to study treatment

[2] No discontinuations within 30 days of instillation

Grade 1-4 Adverse Events Days 1-7

	611		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)

Summary

- Two trials failed to meet primary endpoint establishing the efficacy.
- 20% missing data more than treatment effect, making estimate less reliable.
- The pooled 6.5% (95% CI -1.8%, 15.1%) difference in 2-year recurrence between arms is smaller than expected and its clinical meaning is uncertain.
- Post-hoc pooling of the two trials to achieve statistical significance insufficient to establish efficacy.
- Subgroup analyses are hypothesis-generating and are insufficient to establish efficacy. Applicant has ongoing trial to test the impact of timing of instillation on efficacy.

Question for ODAC

The Applicant has conducted 2 randomized trials of a single instillation of apaziquone versus placebo following resection of non-muscle invasive bladder cancers.

The efficacy results are shown below. The safety profile was similar to placebo.

	611 TaG1-2		**612 TaG1-2**	
	Apaziquone N = 295	Placebo N = 271	Apaziquone N = 282	Placebo N = 298
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 (95% CI)	0.76		0.78	
p-value	0.11		0.13	

Questions for ODAC

VOTE:

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

Questions for ODAC

DISCUSS:

Question 2: 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.

NDA208714 - Apaziquone
FDA BACK-UP SLIDE SHOWN

Meta-Analysis