2.2 STUDY DESIGN.

The studies were open -label, multicenter studies in adult patients with CIS who had failed or recurred on two or more prior intravesical regimens for the treatment of CIS. At least one of the prior regimens must have been BCG. Each patient was to receive six weekly treatments of 800mg of AD-32. Urine samples in participating patients were collected during the 24 hours post dose administration.

2.2.1 Inclusion criteria

1) Pathologically proven CIS with no evidence of muscle invasion
2) Papillary tumors were to be resected in patients with concurrent Ta orT1 papillary tumors
3) Prior treatment with at least two prior failed courses of intravesical therapy for CIS , one of which must have been BCG. The standard course of intravesical therapy must have included six weekly treatments. It was not necessary that BCG be the most immediate prior therapy
4) Bladder mapping with transurethral biopsies of suspicious as well as normal-appearing areas was to be done within 28 days of study treatment. Mapping should include the dome(D),posterior wall(PW) right and left lateral walls(LW) trigone(T), and if clinically indicated , prostatic urethra (PU).
5) Positive urine cytology, at baseline (≤28 days prior to the first AD-32 treatment).

2.2.2 Exclusion Criteria

1) Patients with non TCC urogenital tumors
2) Patients with residual papillary disease only at the time of treatment
3) Patients with other primary malignancy within 5years prior to treatment (excluding squamous cell or basal cell carcinoma of the skin)
4) Patients with evidence of muscle-invasive disease. (Stage >T1)
5) Prior systemic or radiation therapy for bladder cancer.
6) Prior intravesical therapy with AD-32, or any other intravesical therapy within 28 days prior to the first dose of AD-32.
7) Other concurrent therapy for treatment of primary bladder cancer during the course of study participation.
8) Pregnant or lactating women. Individuals of child bearing potential must agree to use of an effective contraception for themselves and their partners.
9) Patients who in the investigator's opinion are non-compliant or unable to understand the nature of the study.

2.2.3 Removal of Patients from Therapy or Assessment

Patients were to be withdrawn from study, if prior to completion of the six doses of therapy any of the following circumstances occurred:

1) Patients receive other therapy for primary bladder cancer.
2) Patients experience SWOG Grade 4 toxicity or other toxicity which at the discretion of the investigator or sponsor was judged to be unacceptable. This was to include: delay of scheduled instillation by more than 21 days due to adverse experiences or intercurrent illnesses which in the judgment of the investigator would have significantly affected clinical assessment, required discontinuation of study agent or both.
3) Noncompliance or refusal to continue participation on study.

2.2.4 Treatment

2.2.4.1 Dose Selection:
Each patient enrolled in the study was to receive instillation of 800mg dose of AD-32 per week for six consecutive weeks. This dose was selected based on results obtained from a phase I/II ascending dose study of intravesical administration of AD-32

2.2.4.2 Criteria for Dose adjustment or withdrawal:

Treatment was to be delayed for an additional week for the following reasons:

1)Grade 3 dysuria, frequency, or urgency lasting more than 24 hours or occurring on the day of treatment.
2)Grade 2 or 3 hematuria lasting more than 48 hours or occurring on the day of treatment.

2.2.5 Evaluation for efficacy and Safety.

Table 1 represents the Sponsor's outline of study parameters performed as well as the required schedule for performing those evaluations before, during and after treatment with AD-32.

2.2.6 Efficacy considerations

Urine Cytology:

- Positive Urine Cytology was defined as cytologic examination that was diagnostic (positive) or suspicious ("doubtful positive") for TCC.
- Terms such as "atypia", "dysphasia", "compatible with "did not constitute positive urine cytology.

Criteria for Primary Efficacy Determination

Complete Response:

No evidence of disease (NED) at primary disease evaluation (PDE i.e. approximately 6 weeks after administration of the last dose of AD-32.), and at the next follow up evaluation. NED is defined as

- complete resolution of all CIS,
- no recurrence of papillary disease,
- no new CIS or papillary lesions ,
- all biopsies and cytology specimen are negative for tumor
- patients with positive urine cytology only at any disease evaluation are considered NED if urine cytology is negative at next disease evaluation.

No Response or Recurrent Disease:

- Failure to meet the criteria for NED at a follow up evaluation as determined by positive biopsy at TUR and positive urine cytology
- positive urine cytology on two consecutive visits in patients with negative biopsies.

Reviewer's Comment: When a patient recurred by cytology alone, the FDA interpretation of the recurrence date was the date of the first of 2 consecutively positive cytologies. The applicant's recurrence date was the date of the second positive cytology. This difference accounts for 4 of the disparities in patients designated as complete responders.

2.2.7 Safety considerations

Toxicity Evaluation:

Table 2 is the checklist from the CRF for indicating the toxicity and other adverse experiences encountered by the patient and the timing of those adverse experience (AE) experiences in the course of the study. **An adverse experience (AE)** was defined as any untoward observation that occurred in the course of the study. **A serious adverse experience (SAE)** was defined as a life-threatening, permanently disabling event, requiring in-patient hospitalization or death. It also includes congenital anomaly, cancer(other than superficial bladder cancer) or overdose. **An unexpected adverse experience (UAE)** was one that was not identified in nature, severity or frequency in the Clinical Investigator's Brochure.

2.2.8 Statistics

The study was a non-randomized study involving a single dose level of AD-32. The trial was designed for two stages of accrual. The protocols were to enroll 45 patients each for

a total of 90 patients The sponsor's statistical section proposed this sample size in order to demonstrate that AD-32 is efficacious, defining efficacy as a "response rate of 30% or better".

Reviewer comment:
The FDA did not explicitly agree that a response rate of 30% would be sufficient. The FDA has never dogmatically stated what the CR rate and duration must be for approval in this indication. During the ODAC deliberations on the Bropirimine NDA in 1996, Dr. Temple of the FDA asked the committee what rate would be needed. The committee felt that the issue was too complex to answer since the prognosis of study populations varied so greatly from one study to the next. On several occasions in the past the FDA has noted that a 50% CR rate with CRs lasting up to a year would likely support approval.

The Sponsor used the Kaplan-Meier analyses to generate survival estimates for two efficacy variables defined as:

- Disease-free probability = time from first dose of AD32 to failure or recurrence of disease
- Probability of cystectomy = time from first dose of AD32 to cystectomy.

3.0 FDA APPROACH TO REVIEW OF THE DATA

The information submitted by the Sponsor was reviewed based on the following guidelines:

- Regulatory history (see introduction)
- Protocol: The protocol submitted by the sponsor with follow-up amendments, in terms of adherence to the protocol and with agreements reached with the Agency.
- Literature: Articles submitted by the sponsor as well as by a broader literature search.

The following represent important issues gleaned from these sources for evaluating efficacy as well as safety of any product proposed for use in CIS of the bladder.

History of prior intravesical therapy:

- Types of treatment and number of treatment courses.
- Evidence of failure on these therapies prior to embarking on an investigational therapy
- In the case of BCG there is a need for consistency in administered dose, type BCG administered (i.e. Tice, Canaught), and ascertain that a patient was a true BCG failure.

Surgical Issues:

Standard therapy is cystoscopy with transurethral resection (TUR) and fulguration of all visible lesions as well as associated papillary tumors constitute the primary therapy of CIS.

It is rarely definitive therapy in diffuse CIS. It is important that a defined schedule of baseline and follow up cystoscopy with biopsy be utilized. These should as a minimum include:

- Bladder mapping with adequate number (at least six) of samples taken from different segments of the bladder.
- Samples taken should include some muscle layer to assure that the disease is not invasive(T_2).
- At follow-up evaluation, there should be sampling of areas of previous pathology. (This is in an attempt to ensure that the diseased site has been truly impacted by the therapy administered).

Pathology Issues: The following are important pathology issues:

Multifocality

Approximately 10% of cases of CIS occur as an isolated unifocal pathologic finding, while the majority of cases present in a diffuse pattern ,with or without adjacent papillary lesions. The risk of muscle invasion is 8% versus 78% between the two patterns of presentation (Riddle et. al Brit. J. Urology,47:829,1976). Furthermore, an isolated lesion is more readily amenable to total surgical extirpation creating difficulties of differentiation between effect of drug treatment versus effect of TUR with biopsy preceding the drug therapy.

Consistency in pathology specimen review

CIS presents in a variety of patterns and with varied outcomes which require that standards be established to assure reasonable accuracy in reading both the baseline and follow-up biopsy specimens presented. There is also need for concordance among pathologists reading the same specimens. While a central pathology review would be ideal, there should at least be outside review or a secondary review for concurrence. Blinding the pathologist would add further credibility to the report generated.

Urine Cytology

Method of collection and analysis:
The result of cytology reported is strongly influenced by the methods for collection as by the techniques utilized for cytological analysis. Microscopic evaluation of the cytospin on a voided specimen provides a lower yield than from a catheterized or bladder wash specimen. Similarly, flow cytometry and biomarkers of nuclear proliferation provide higher rates of positivity than microscopic cytospin techniques. There is a need for consistency among Investigators in methods utilized.

Timing of collection post TUR

A post-TUR baseline urine collection at least 24 hours after the procedure should verify that cytology is still positive after the procedure, especially in patients who have only unifocal disease at baseline. This will assure that any reversal of cytologic findings is truly due to the experimental drug instillation and is not from surgical removal of the diseased focus.

4.0 FDA FINDINGS

4.1 Trial Conduct

Demographics
A total of 90 (ninety) patients were enrolled in these studies, while 88 (eighty-eight) completed treatment. These patients were treated in 41 centers by 43 investigators .
Mean age was 68.4 (range 31-85)
Gender: Males 79(87.8%) Females 11(12.2%)
Race : Caucasians 88(97.8%) African American 1(1.1%) Oriental 1 (1.1%)
Duration of disease(yrs)prior to study entry: Mean 4.8 Range (1-27)
Table 3 represents demographic and other baseline information on all 90 patients enrolled in the studies.

Number of patients listed by Sponsor as Complete responders to AD-32 treatment: 20 for a CR rate of 22.2%.
The following information relates to the 20 patients listed by the Sponsor as complete responders.

-Number of patients with prior intavesical therapy as per protocol: 20. One patient however appeared to have had inadequate BCG treatment. He subsequently received additional BCG therapy after failure of AD-32.

-Urine cytology: Method of collection was variable as was method of testing.

-Multifocality: Evidence of multifocal disease at baseline which supports the presence of a more aggressive form of CIS was variable and truly ascertainable at baseline in six patients.

AD-32 Administration: The was administered to all 20 patients as per protocol. The drug volume as well as retention time was consistent with protocol requirements.

4.2 Efficacy

4.2.1 Complete response

The following text and table represent FDA assessment of efficacy of the 20 patients treated on the study and reported by the applicant as complete responders (out of a total of 90 treated) Summary data tables from the NDA, prepared by the applicant, can be found in an Appendix to this review. The reader is encouraged to study these summary tables of data from individual patients while evaluating the FDA interpretation of these data. The pages of the individual patient tables in the Appendix are numbered 1-20 to correspond to the patient numbers in the FDA reviewer tables.

The assessment of complete response was a difficult undertaking. These tables have been constructed to help the viewer make an assessment of clinical benefit without strictly adhering to a particular definition of complete response. There are several key issues to ascertain:

1. How likely is it that the patient had poor prognosis, i.e. had the entity "diffuse disease." One can consider whether the patient presented at baseline with multiple lesions (strongest evidence), had a documented history of disease at multiple sites, or neither. As shown in the attached table, only 7 of the 20 CRs claimed by the applicant had multiple sites of disease documented at baseline.

2. Did the patient have baseline cytology that was positive? 8 of 20 did not have a positive baseline cytology. An additional 9 had a positive cytology that was collected only on the day of or before baseline biopsy. Only 3 had baseline cytology collected at least 24 hours after the baseline biopsy. (During the review of the Bropirimine NDA, this was a pre-requisite used by the FDA medical officer in determining response rate.) A positive baseline cytology would seem to be even more relevant in a patient with only a single site of disease documented. This issue relates to the possibility of a "false-positive" complete response either because the focus of disease might have been surgically extirpated at baseline or because follow-up cytologies might be less likely to detect the presence of residual or recurrent disease. 11 such patients had unifocal disease at baseline and negative or inadequate baseline urine cytology.

3. Was complete response adequately documented? This protocol was strict in requiring that follow-up examination document CR status at both 3-month and 6-month time points. 10 patients had the protocol-specified follow-up with documentation of CR status.

The FDA reviewer has grouped the Applicant's 20 claimed CRs into 4 groups according to these considerations.

- **Group A** (7 patients) had a protocol-specified CR with little chance of being false-positive CR.

- **Group B** (3 patients) had a protocol specified-CR but with some risk of being a false-positive CR because they had negative baseline cytology and had baseline unifocal disease.

SUMMARY OF FDA FINDINGS IN APPLICANT CR PATIENTS																				
Patient # (see key below)	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**20**
Site of baseline CIS not documented																		X		
Multifocality																				
-Single lesion and no Hx of multifocality																				X
-Single lesion with Hx of multifocality				X		X		X	X	X	X	X		X	X	X		X	X	
Positive baseline cytology																				
-None at baseline			X		X				X	X	X	X			X			X		
-Collected only on day of biopsies or before	X			X			X	X					X	X		X	X		X	
Documentation of disease clearance from all sites																				
-Not documented at PDE											X	X	X	X	X	X		X		
-Not documented at subsequent visits										X		X	X	X		X		X	X	X

Patient Key

# in table	Patient ID#	# in table	Patient ID#
1		11	
2		12	
3		13	
4		14	
5		15	
6		16	
7		17	
8		18	
9		19	
10		20	

- **Group C** (4 patients) did not have protocol-specified CR because of incomplete follow-up. However, slightly more liberal criteria would yield classification of CR in these patients. 3 of these cases would also qualify for group B.

- **Group D** (6 patients) Did not have a CR at 6 months even using liberal criteria.

The individual patients are discussed in the following section.

Group A

The following 7 patients had **complete responses** that seemed obvious on FDA review

Pt #	Patient ID

*Multifocality of baseline disease clarified by Applicant: 2 focal areas of disease were biopsied within same anatomical area of bladder.

Group B: Some risk of false positive CR based on single site, negative cytology

The following **3 CRs** might be considered borderline because they were from patients with single lesions with either negative baseline urine cytologies (1 patient) or positive cytologies collected either before or on the day when bladder biopsies were performed. Such CRs were disallowed during the FDA review of Bropirimine because it was felt that biopsy alone might have eradicated the disease.

Pt #	Patient ID

Group C : No CR according to strict protocol follow-up criteria; classification could be considered using more liberal criteria

The following **4 cases** were initially considered as having no CR by the FDA. The Applicant has provided additional information. Arguments can be constructed for classifying them as CRs despite not strictly meeting protocol criteria. However, 3 of these could also be eligible for Group B.

Pt Single lesion at baseline, with negative cytology at baseline, and with no follow-up biopsies of the original site documented in the Applicant's summary table. Originally this was listed by FDA as no CR, however additional information reveals that at 18 months there was a follow-up negative biopsy of the initial Tis site, the bladder neck. Given the long follow-up, it may be reasonable to consider this a CR despite only one negative follow-up biopsy of initial site.

Pt Two lesions at baseline, with follow-up biopsies of only one site. Positive cytology at baseline became negative at the PDE , 6 month, and 12 month visits, but was positive at 9 month and 15 month visits. One of the 2 lesions had adequate documentation of CR. If one assumed that specific follow-up of only one of the positive sites was adequate, one could call this a CR .

Pt Single lesion with baseline negative cytology and no follow-up biopsies of site according to summary table. However, the additional information from the applicant states that at month 15 there were 5 negative biopsies including one from the site which was positive at baseline, the anterior wall. Given the long follow-up it may be reasonable to consider this a CR despite only one negative follow-up biopsy of initial site.

Pt Baseline bladder biopsy sample submitted for pathology which was positive was not labeled according to site. Follow-up biopsies were done at 5-6 sites at PDE and 6 months visits. If one were being generous, one could assume that the baseline site was one of the sites biopsied at follow-up and specify this case as a CR of 6-months duration.

Group D: No CR

No CR; Inadequate biopsy documentation of CR:

The following **patient** was considered to have inadequate biopsy follow-up.

Pt Single lesion at baseline, with negative cytology at baseline, had no follow-up biopsies of the original baseline site (dome). The applicant notes that there were 5 biopsies at 3 months, and multiple cystoscopies with bladder normal by visual inspection at 3 month intervals up to 18 months.

No CR; Cytology relapses:

The following **4 patients** were considered to have cytologic evidence of persistent disease, and hence no CR. During FDA review, a positive cytology was considered evidence of progression unless a subsequent cytology was done and was negative. The date of progression is specified as the date the first cytology collection was positive. The applicant used a different approach: "If there were two positive cytology findings at consecutive disease evaluations with pathologic proof of disease recurrence at the second evaluation, the date of failure was the date of positive pathology because pathology took precedence over cytology."

Reviewer comment: I cannot understand the logic of this approach. The second test, whether a second cytology or pathology, is verifying that the initial cytology was an accurate indicator of the existence of disease; the time of recurrence of disease should be when disease was first detected by the initial test.

Pt Single baseline TIS site was negative at PDE and at 6 months. However, cytology was positive at 6 months and was never rechecked and therefore is assumed to be positive. This CR is not considered confirmed at 6 months. The patient recurred by biopsy at 8 months.

Pt Single lesion at baseline was not evaluated until 6 months; cytology was positive at 6 months and 9 months. Biopsy was positive at 9 months.

Pt Single baseline TIS site was negative at PDE. Multiple biopsies including the baseline site were negative at PDE and at 6 months but the original site was positive at 9 months. Cytology was positive at baseline and at PDE and was not subsequently rechecked; therefore is assumed to have remained positive and CR was not established.

Pt Single baseline TIS site was negative at PDE and at 6 months but positive at 9 months. Cytology was positive at baseline, negative at PDE but positive again at 6 months and 9 months. Therefore the CR at PDE was not verified at 6 months.

FDA and Applicant Agreed No CR

The Applicant agreed on re-examination that **one patient** did not achieve CR:

Pt Single baseline TIS site was negative at PDE, 6 months, and 9 months, but initially negative cytologies were positive at 6 months and 9 months. Therefore the CR at PDE was not verified.

4.2.1 Duration of complete response

Historically the Agency has expressed an interest in the number of patients with BCG-refractory diffuse CIS with complete responses lasting for at least 12 months. Just as definition of CR depends upon one's thoroughness of evaluation, duration of documented CR depends upon how stringent an evaluation is required for the last visit at which a patient is designated as being free of disease. The issue of baseline cytology seems particularly relevant in attempting to specify duration of complete response: it seems likely that follow-up cytology might not be a reliable indicator of recurrence in patients who had

negative cytology at baseline. In the attached table, the reviewer has attempted to present the data on duration of CR in a manner which allows the reader to look at the 3 groups (A, B, and C) and make a judgment regarding clinical benefit according to a variety of requirements one might enumerate for the last visit at which the patient is designated to be free of disease. The following categories of follow-up are designated:

1. Negative biopsy (initial site) and negative cytology
2. Negative biopsies (any sites) and negative cytology
3. Negative cystoscopy and negative cytology
4. Documented recurrence.

These categories are listed along the left column of the table. Patients are listed at the top of the table according to group (A,B, or C). The duration of CR (or potential CR for groups B and C) is listed for each patient according to each set of criteria. One must consider these results in relation to the Bropirimine submission. While the AD-32 protocol required 2 consecutive positive cytologies for recurrence, the protocol for the Bropirimine NDA required only one positive cytology. For this reason, recurrence times for single cytology values are also listed in this table (see footnotes). If cytology was verified by positive cytology or positive pathology on the next visit, time of recurrence was dated to the first of the consecutive visits.

If one looks at the entire group of 14 patients with CR or potential CR, the median duration of CR, measured from day of treatment, varies from 13.5 months if one requires biopsy proof of no recurrence, to 18 months if one requires negative cystoscopy and cytology, and finally to a median of 21 months for time to recurrence regardless of methodology. The latter corresponds to the usual method of expressing time to progression in oncology trials.

4.3 Safety

Toxicity: The drug was reasonably well-tolerated by most patients at the dose administered (800mg), the volume (75ml) and dwell time (2.0hours) Table 4 lists the types and grade of toxicities, and the number of patients experiencing these toxicities. Toxicities were limited to the bladder and consisted of mild to moderate cystitis, bladder pain, and dysuria. An occasional patient experienced urinary tract infection that did not delay drug therapy. There was no evidence of systemic effect of the drug as determined by hemogram and chemistry laboratory data There was no suggestion of cardiotoxicity attributable to the drug. This validates the pre-clinical studies implying no systemic absorption of AD-32 through an intact non-perforated bladder. One patient had a perforation of the bladder which resulted in hematologic cytopenias from which the patient fully recovered. Prior studies of intravenous administration of AD-32 had revealed the MTD in humans to be 600mg/m^2. Another patient experienced ureteric reflux of AD-32 with resulting nephrotocicity. This patient had an uneventful recovery as well.

COMPLETE RESPONSE DURATION IN PATIENTS WITH DEFINITE CR (GROUP A) OR POTENTIAL CR (B&C)

	GROUP A (Definite CR)							GROUP B (single lesions & negative or inadequate baseline cytology)			GROUP C (marginally adequate pathology follow-up)				MEDIAN (A,B,&C)
Patient #:															
Time (months) from initial treatment to last visit with the following findings:															
Negative biopsies of all sites which were positive at baseline and Negative cytology	6	12	6/12 [1]	24	15	6/12 [2]	27	12	9 or 33 [3]	15	18	0	21	0	13.5
Negative biopsies (of any site) and Negative cytology	6	12	6/12 [1]	24	15	6/12 [2]	27	12	27 or 33 [3]	15	18	12	15	6	13.5
Negative cystoscopy and Negative cytology (with or without biopsies)	9	18	9/15 [1]	24	18	6/12 [2]	27	15	27 or 33 [3]	24	18	12	21	6	18
Time of recurrence	12	21	12 or 15+ [1]	24+	21	9 or 12+ [2]	27+	18	30 or 36+ [3]	24+	21+	9/15 [4]	21+	9	21

[1] positive cytology at 12 months, negative cytology at 15 months.

[2] positive cytology at 9 months negative at 12; suspicious cystoscopy at 9 and 12 mos. Biopsies negative at 9 and 12 months.

[3] Biopsy negative at 30 months, but cytology positive. Next visit cytology negative but cystoscopy was suspicious.

[4] Cytology was positive at 9, 15, and 18 months but negative at 12 months.

"+" indicates that recurrence had not been documented at the time of last visit.

Clinical Laboratory Evaluation : Review of serum chemistry and hematologic data obtained at baseline and in the course of therapy reveal no changes in any of the patients that are attributable to drug therapy.

Serious Adverse events: One patient died of acute myocardial infarction. The event did not appear attributable to AD-32 treatment.

Clinical Stage at Treatment Failure and Pathologic Stage at Cystectomy

37 patients underwent cystectomy. 3 patients had deeply invasive bladder cancer (T3) at cystectomy.

Patient #	Stage at Baseline	Stage at Clinical Failure	Stage at Cystectomy
	Tis	TaG3	T3aN2M0
	Tis/T1G2	T1G2	T3bG3
	Tis	T1G3	TIS/T3bG3 squamous

3 other patients had T2 disease.

Deaths due to Bladder Cancer:

The following 4 patients, who did not have cystectomy, were reported to have died with bladder cancer:

Reviewer comment: It is disconcerting that 4 patients died of bladder cancer but might have been missed if one had relied on the recurrence data from cystectomy. It is uncertain how many of the remaining 50 patients are at risk of developing metastatic bladder cancer.

4.4 Summary

AD-32 is reasonably well-tolerated as intravesical therapy for patients with carcinoma-in-situ of the bladder who have failed prior intravesical therapy. In the NDA, the applicant found that 20 of 90 patients (22%) obtained a CR. The FDA found unquestionable CRs in 7 of 90 (8%) an additional 7 patients can be considered potential CRs (8%) using some non-protocol criteria discussed in section 4.1 of this review. These issues which are considered important in determining response rate involve baseline cytology (whether documented to be positive and whether that documentation is done after biopsy) and follow-up biopsy (whether the initial site was biopsied in follow-up and whether a subsequent biopsy verified CR). The issue of benefit imparted to patients is a complex one, and the reader is encouraged to carefully examine section 4.2 of this review. Only 7

of the CRs had documentation of multifocal disease at baseline. Most, however, had historical evidence that disease had occurred in multiple bladder foci in the past. Whether this group of patients as a whole represents the high-risk group in whom cystectomy is indicated once treatment has failed, is an important consideration. Duration of potential benefit is also an important consideration. If one looks at the entire group of 14 patients with CR or potential CR, the median duration of CR, measured from day of treatment, varies from 13.5 months if one requires biopsy proof of no recurrence, to 18 months if one requires negative cystoscopy and cytology, and finally to a median of 21 months for time to recurrence regardless of methodology.

Additionally, one should consider the number of patients who were subjected to a somewhat invasive procedure from which they derived no benefit. Even if one were to accept the Applicant's CR rate of 20 of 90(22%), 78% of patients had a delay in obtaining more definitive therapy. Ultimately 3 were found to have developed deeply invasive bladder cancer at cystectomy and at least four patients died from bladder cancer. Unlike many neoplasms for which there are few alternatives to an early death, patients with CIS of the bladder have other choices. Some of these choices currently include newer bladder preserving techniques such as the ileal neobladder.

4.5 Results of the of the ODAC Meeting , June 1st. 1998

The following is a summary of the votes of committee members taken at the meeting.

1) Did the 90 patients who received intravesical treatment with AD-32 in studies 9301 and 9302 have CIS of the urinary bladder that required consideration of immediate cystectomy because of the risk that they would develop invasive or metastatic bladder cancer?

YES - 0 NO - 10 Abstain - 1

2) Are studies 9301 and 9302 adequate and well controlled studies, providing substantial evidence of the safety and efficacy of AD-32 (Valrubicin) in the treatment of BCG - refractory carcinoma in situ of the urinary bladder? Specifically, do the studies show that in patients with CIS of the urinary bladder who are candidates for immediate cystectomy, the findings described represent sufficient benefit to support approval, considering the potential risk of invasive or metastatic disease when cystectomy is delayed, the observed toxicities of AD-32, and the morbidity of cystectomy?

YES - 0 NO - 10 Abstain -

4.6 RECOMMENDATION

There is insufficient evidence to show that many of the patients studied were in imminent need of cystectomy. Furthermore, in those patients in whom immediate cystectomy was indicated, it is difficult to estimate the ultimate risk of stage progression (to deeply invasive or metastatic bladder cancer) associated with delaying cystectomy in order to receive treatment with AD-32. The proven benefit from AD-32 therapy was small. Given the small evidence of benefit and the poorly-documented and uncertain risk associated with the delay in cystectomy, one cannot make an adequate risk-benefit assessment in the population studied without a randomized, concurrently-controlled study.

The FDA met with the applicant on 6/19,98 at which time the applicant suggested that a major amendment would be filed to demonstrate that AD-32 is safe and effective for patients with BCG-refractory CIS for whom cystectomy is contraindicated. Unless a satisfactory major amendment is filed, I recommend that a Non-Approvable letter be issued.

/S/ 6/24/98

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/S/ 6/24/98

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Table 1. Study Calendar

Evaluation →	Pre-Study[a]	Pre-Study[b]	Prior to Each Dose	After Each Dose	Primary Disease Evaluation[c]	Follow-up Disease Evaluation[d]
Visit Number →	1	2	3-8	3-8	12[e]	13-25
Demographics/History	X					
Physical Examination	X		X		X	X
Bladder Symptoms/ Toxicity Evaluation	X		X		X	X
Cystoscopy	X				X	X
Biopsies[f]	X				X[g]	X[g]
Urine Cytology[h]	X				X	X
Chest X-ray	X					
Blood Chemistry		X			X	
CBC, Differential, Platelet Count		X			X	
Urinalysis With Microscopic Evaluation		X	X		X	X
ECG	X				X	
Upper Tract Study	X					
Urine Anthracyclines				X[i]		

[a] Within 28 days prior to first AD 32 instillation, except that chest X-ray and upper tract study could have been performed within 6 months prior to first instillation.
[b] Within 14 days prior to first AD 32 instillation.
[c] Six weeks after last treatment.
[d] Every 3 months after primary disease evaluation for patients with no evidence of disease. Patients were contacted approximately every 6 months after disease recurrence, and subsequent therapies for bladder cancer were recorded (Visits ≥26).
[e] Visits 9 to 11 were used if any patient received additional doses of AD 32 after Visit 8. Those numbers were used in a similar study (Protocol A9303) in which patients could have been randomly assigned to receive nine doses. The sponsor wished to retain the same visit number (12) to identify the primary disease evaluation in both studies.
[f] Biopsies taken at baseline and subsequently at recurrence were sent for review to a central histopathology laboratory.
[g] In the absence of visual evidence of disease upon cystoscopic evaluation, preselected biopsies were required at months 3, 6, and 12, and annually thereafter.
[h] Baseline cytology specimens and all specimens with negative cytology from patients who showed no evidence of disease were sent for review to a central cytopathology laboratory.
[i] Urine was collected for up to 24 hours after dose administration from patients who chose to participate in the urinary recovery study; all urine samples from a single patient after a given dose were pooled for anthracycline assay.

TABLE 3

	All (N=90)	CRs (N=19)	Nonresponders (N=71)
Male	88%	89%	87%
White	98%	100%	97%
60-79 yr	79%	95%	75%
Median duration of transitional cell carcinoma[a]	3.3 yr	3.3 yr	3.4 yr
Median duration of Tis[a]	25 mo	28 mo	24 mo
Baseline local bladder symptoms	50%	68%	45%
≥2 Prior BCG	70%	68%	70%
Last BCG ≤3 mo before study entry	2%	5%	1%
Last BCG >3–24 mo before study entry	73%	68%	75%
Cytology (+) at baseline	63%	58%	65%
≥2 (+) biopsy sites at baseline	53%	47%	55%
History of ≥2 (+) biopsy sites	Not done	89%	Not done
Two sites (+) for Tis at baseline and (+) cytology	38%	32%	39%
Received intravesical tx after failure/recurrence	37%	37%	37%

[a] Time from initial diagnosis to study entry.

Table 4 Toxicities Encountered with AD-32 Treatment

Symptom	During Treatment (N=80)
Any Local Bladder Symptoms	69(86.3%)
Urinary frequency	45(56.3%)
Dysuria	41(51.3%)
Bladder spasm	26(32.5%)
Bladder pain	21(26.3%)
Hematuria(microscopic)	21(26.3%)
Hematuria(gross)	0 (0%)
Urinary incontinence	16(20.0%)
Non-Bladder Symptoms	
Abdominal Pain	7(8.8%)
Asthenia	4(5.0%)
Chest pain	3
Flank pain	3
Diarrhea	2
Nausea	3

7.0 Appendix: Patient Summary Tables from NDA for 20 Claimed Complete Responders.

Note: Pt # in lower right hand corner corresponds to Patient Numbers in Reviewer tables of response and response duration.

Summary Table 3: Patient Efficacy Profile - A9301

Patient:

Evaluation	*Visit*	*Biopsy Date*	*Biopsy Site & Tumor Stage*												*Un-specified**	*Cystoscopy*		*Cytology*	
			PW	*RW*	*LW*	*RU*	*LU*	*N*	*PU*	*U*	*AW*	*TR*	*D*	*PS*		*Date*	*Result*	*Date*	*Result*
Historical	0.01																	04/01/92	+
Historical	0.02																	06/15/92	-
Historical	0.03	07/00/92													Tis			09/11/92	-
Historical	0.04																	03/01/93	-
Historical	0.05																	05/19/93	+
Historical	0.06																	06/10/93	-
Historical	0.07																	08/19/93	-
Historical	0.08																	11/17/93	-
Historical	0.09																	02/09/94	+
Historical	0.1																	03/23/94	-
Historical	0.11																	04/07/94	-
Historical	0.12																	07/13/94	-
Historical	0.13																	10/14/94	+
Historical	0.14																	12/22/94	+
Historical	0.15																	01/18/95	+
Baseline	1	03/16/95	NED	Tis	NED							NED	Tis	NED		03/16/95	Susp	03/16/95	+
PDE	12	06/13/95	NED	NED	NED				NED			NED	NED			06/13/95	Neg	06/12/95	-
6 Months	13	09/12/95	NED	NED	NED							NED	NED			09/12/95	Neg	09/12/95	-
9 Months	14	NAP														12/08/95	Neg	12/07/95	-
12 Months	15	03/07/96	NED	NED	NED							NED	NED	NED		03/07/96	Susp	03/07/96	+
15 Months	16	06/11/96	NED	NED	NED							Ta	T1	NED		06/11/96	Neg	06/07/96	+

PDE=primary disease evaluation.

Biopsy Site: PW=posterior wall, RW=right wall, LW=left wall, RU=right ureteral orifice, LU=left ureteral orifice, N=neck, PU=prostatic urethra, U=urethra, AW=anterior wall, TR=trigone, D=dome, PS=prostatic substance.

Tumor Stage: NED=no evidence of disease, Tis=carcinoma in situ, TCC=transitional cell carcinoma, Ta=noninvasive papillary carcinoma, T1=tumor invades subepithelial connective tissue, T2=tumor invades subepithelial muscle, SevD=severe dysplasia.

Cystoscopy Result: Neg=appears negative for bladder cancer (BC), Pos=appears positive for BC; Susp=appears suspicious for BC, Unk=unknown; Other=in listing VII-11A.

Cytology Result: Class 0-3=Negative (-), Class 4-5=Positive (+).

AFIP=Armed Forces Institute of Pathology review of biopsy slides; NAP=not applicable (biopsies required at months 3, 6 and 12, and annually thereafter); NAV=not available.

* Unspecified indicates no bladder mapping locations were given on pathology report for biopsy samples.

** Only year is available (month and date not available).

*** Biopsy sample taken from left floor per pathology report.

Summary Table 3: Patient Efficacy Profile - A9302

Patient:

Evaluation	*Visit*	*Biopsy Date*	*Biopsy Site & Tumor Stage*													*Cystoscopy*		*Cytology*	
			PW	*RW*	*LW*	*RU*	*LU*	*N*	*PU*	*U*	*AW*	*TR*	*D*	*PS*	*Un-specified**	*Date*	*Result*	*Date*	*Result*
Historical	0.01	06/13/84													TCC			06/23/92	+
Historical	0.02	03/13/90													Ta/Tis			05/12/93	+
Historical	0.03	09/22/92													TCC			06/08/93	-
Historical	0.04	08/29/94		TCC	Tis						Tis							09/03/93	-
Historical	0.05																	06/30/94	-
Historical	0.06																	08/04/94	+
Historical	0.07																	03/22/95	+
Baseline	1	05/02/95	NED	NED	NED							Tis	Tis	NED		05/02/95	Susp	05/26/95	+
PDE	12	08/18/95	NED	NED	NED						NED	NED	NED	NED		08/18/95	Neg	08/18/95	-
6 Months	13	11/15/95	NED	NED	NED						NED	NED	NED	NED		11/15/95	Neg	11/15/95	-
9 Months	14	03/27/96	NED	NED	NED			NED			NED	NED		NED		03/27/96	Susp	03/27/96	-
12 Months	15	06/12/96	NED	NED	NED						NED	NED	NED	NED		06/12/96	Neg	06/12/96	-
15 Months	16	NAP														09/05/96	Neg	09/05/96	-
18 Months	17	NAP														11/25/96	Neg	11/25/96	-
21 Months	18	NAP														03/13/97	Neg	03/13/97	+

PDE=primary disease evaluation.

Biopsy Site: PW=posterior wall, RW=right wall, LW=left wall, RU=right ureteral orifice, LU=left ureteral orifice, N=neck, PU=prostatic urethra, U=urethra, AW=anterior wall, TR=trigone, D=dome, PS=prostatic substance.

Tumor Stage: NED=no evidence of disease, Tis=carcinoma in situ, TCC=transitional cell carcinoma, Ta=noninvasive papillary carcinoma, T1=tumor invades subepithelial connective tissue, T2=tumor invades subepithelial muscle, SevD=severe dysplasia.

Cystoscopy Result: Neg=appears negative for bladder cancer (BC), Pos=appears positive for BC; Susp=appears suspicious for BC, Unk=unknown; Other=in listing VII-11A.

Cytology Result: Class 0-3=Negative (-), Class 4-5=Positive (+).

AFIP=Armed Forces Institute of Pathology review of biopsy slides; NAP=not applicable (biopsies required at months 3, 6 and 12, and annually thereafter); NAV=not available.

* Unspecified indicates no bladder mapping locations were given on pathology report for biopsy samples.

** Only year is available (month and date not available).

*** Biopsy sample taken from left floor per pathology report.

Summary Table 3: Patient Efficacy Profile - A9302

Patient:

Evaluation	*Visit*	*Biopsy Date*	*Biopsy Site & Tumor Stage*													*Cystoscopy*		*Cytology*	
			PW	*RW*	*LW*	*RU*	*LU*	*N*	*PU*	*U*	*AW*	*TR*	*D*	*PS*	*Un-specified**	*Date*	*Result*	*Date*	*Result*
Historical	0.01	12/03/93			Tis													12/22/93	-
Historical	0.02	11/16/94			Tis													02/15/94	-
Historical	0.03																	04/14/94	-
Historical	0.04																	06/17/94	+
Historical	0.05																	11/15/94	-
Historical	0.06																	03/31/95	-
Baseline	1	08/17/95	NED	NED	Tis							Tis		NED		08/17/95	Pos	09/13/95	-
PDE	12	01/24/96	NED	NED	NED				NED			NED	NED			01/24/96	Neg	01/16/96	-
6 Months	13	05/01/96	NED	NED	NED				NED			NED	NED			05/01/96	Neg	05/01/96	-
9 Months	14	NAP														08/27/96	Neg	08/27/96	-
12 Months	15	12/05/96	NED	NED	NED				NED			NED	NED			12/05/96	Neg	12/05/96	+
15 Months	16	03/20/97	NED	NED	NED											03/20/97	Neg	03/20/97	-

PDE=primary disease evaluation.

Biopsy Site: PW=posterior wall, RW=right wall, LW=left wall, RU=right ureteral orifice, LU=left ureteral orifice, N=neck, PU=prostatic urethra, U=urethra, AW=anterior wall, TR=trigone, D=dome, PS=prostatic substance.

Tumor Stage: NED=no evidence of disease, Tis=carcinoma in situ, TCC=transitional cell carcinoma, Ta=noninvasive papillary carcinoma, T1=tumor invades subepithelial connective tissue, T2=tumor invades subepithelial muscle, SevD=severe dysplasia.

Cystoscopy Result: Neg=appears negative for bladder cancer (BC), Pos=appears positive for BC; Susp=appears suspicious for BC, Unk=unknown; Other=in listing VII-11A.

Cytology Result: Class 0-3=Negative (-), Class 4-5=Positive (+).

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* Unspecified indicates no bladder mapping locations were given on pathology report for biopsy samples.

** Only year is available (month and date not available).

*** Biopsy sample taken from left floor per pathology report.

Summary Table 3: Patient Efficacy Profile - A9302

Patient: Evaluation	Visit	Biopsy Date	Biopsy Site & Tumor Stage: PW	RW	LW	RU	LU	N	PU	U	AW	TR	D	PS	Un-specified*	Cystoscopy Date	Cystoscopy Result	Cytology Date	Cytology Result
Historical	0.01	05/20/92											Ta					NAV	
Historical	0.02	07/30/92			Tis														
Historical	0.03	06/23/93													TCC/Tis				
Historical	0.04	05/02/94													TCC/Tis				
Baseline	1	05/26/94	Tis	NED	NED				NED		NED	NED	NED			05/26/94	Other	05/26/94	+
PDE	12	08/30/94	NED													08/30/94	Neg	08/30/94	-
6 Months	13	01/10/95	NAV													12/05/94	Neg	12/05/94	-
9 Months	14	NAP														Not Done		Not Done	
12 Months	15	06/13/95	NED													06/13/95	Neg	06/08/95	-
15 Months	16	NAP														10/30/95	Neg	10/30/95	-
18 Months	17	03/14/96	SevD								Ta		NED			02/19/96	Susp	02/19/96	+

PDE=primary disease evaluation.

Biopsy Site: PW=posterior wall, RW=right wall, LW=left wall, RU=right ureteral orifice, LU=left ureteral orifice, N=neck, PU=prostatic urethra, U=urethra, AW=anterior wall, TR=trigone, D=dome, PS=prostatic substance.

Tumor Stage: NED=no evidence of disease, Tis=carcinoma in situ, TCC=transitional cell carcinoma, Ta=noninvasive papillary carcinoma, T1=tumor invades subepithelial connective tissue, T2=tumor invades subepithelial muscle, SevD=severe dysplasia.

Cystoscopy Result: Neg=appears negative for bladder cancer (BC), Pos=appears positive for BC; Susp=appears suspicious for BC, Unk=unknown; Other=in listing VII-11A.

Cytology Result: Class 0-3=Negative (-), Class 4-5=Positive (+).

AFIP=Armed Forces Institute of Pathology review of biopsy slides; NAP=not applicable (biopsies required at months 3, 6 and 12, and annually thereafter); NAV=not available.

* Unspecified indicates no bladder mapping locations were given on pathology report for biopsy samples.

** Only year is available (month and date not available).

*** Biopsy sample taken from left floor per pathology report.

Summary Table 3: Patient Efficacy Profile - A9302

Patient:

Evaluation	*Visit*	*Biopsy Date*	*Biopsy Site & Tumor Stage*												*Cystoscopy*		*Cytology*	
			PW	*RW*	*LW*	*RU*	*LU*	*N*	*PU*	*U*	*AW*	*TR*	*D*	*PS*	*Un-specified**	*Date*	*Result*	*Date*	*Result*
Historical	0.01	03/03/94		Tis									Tis		TCC			07/20/94	-
Historical	0.02	08/01/94		Tis														01/27/95	+
Baseline	1	02/02/95	NED	Tis	NED								NED			02/02/95	Susp	03/02/95	-
PDE	12	05/25/95	NED	NED	NED											05/25/95	Neg	05/24/95	-
6 Months	13	09/05/95	NED	NED	NED							NED	NED			09/05/95	Neg	08/23/95	-
9 Months	14	NAP														11/28/95	Neg	11/28/95	-
12 Months	15	03/04/96	NED	NED	NED							NED	NED			03/04/96	Neg	02/27/96	-
15 Months	16	NAP														06/14/96	Neg	06/14/96	-
18 Months	17	NAP														09/25/96	Neg	09/25/96	-
21 Months	18	12/03/96	NED	NED	NED				NED							12/03/96	Neg	Not Done	
24 Months	19	04/21/97	NED	NED	NED								NED			04/21/97	Neg	04/08/97	-

PDE=primary disease evaluation.

Biopsy Site: PW=posterior wall, RW=right wall, LW=left wall, RU=right ureteral orifice, LU=left ureteral orifice, N=neck, PU=prostatic urethra, U=urethra, AW=anterior wall, TR=trigone, D=dome, PS=prostatic substance.

Tumor Stage: NED=no evidence of disease, Tis=carcinoma in situ, TCC=transitional cell carcinoma, Ta=noninvasive papillary carcinoma, T1=tumor invades subepithelial connective tissue, T2=tumor invades subepithelial muscle, SevD=severe dysplasia.

Cystoscopy Result: Neg=appears negative for bladder cancer (BC), Pos=appears positive for BC; Susp=appears suspicious for BC, Unk=unknown; Other=in listing VII-11A.

Cytology Result: Class 0-3=Negative (-), Class 4-5=Positive (+).

AFIP=Armed Forces Institute of Pathology review of biopsy slides; NAP=not applicable (biopsies required at months 3, 6 and 12, and annually thereafter); NAV=not available.

* Unspecified indicates no bladder mapping locations were given on pathology report for biopsy samples.

** Only year is available (month and date not available).

*** Biopsy sample taken from left floor per pathology report.

Summary Table 3: Patient Efficacy Profile - A9301

Patient:		Biopsy	Biopsy Site & Tumor Stage													Cystoscopy		Cytology	
Evaluation	Visit	Date	PW	RW	LW	RU	LU	N	PU	U	AW	TR	D	PS	Un-specified*	Date	Result	Date	Result
Historical	0.01	03/26/93										T1/Tis						11/18/93	+
Historical	0.02	08/20/93													TCC				
Baseline	1	01/24/94	NED	NED	Tis				NED		NED	NED	NED			01/24/94	Susp	02/01/94	+
PDE	12	06/24/94	SevD	SevD	SevD				NED		SevD	SevD	SevD			06/24/94	Neg	Not Done	
6 Months	13	10/10/94	NED	NED	NED						NED	NED				10/10/94	Susp	10/10/94	-
9 Months	14	NAP														Not Done		Not Done	
12 Months	15	Not Done														02/13/95	Neg	02/13/95	-
15 Months	16	06/09/95	NED	NED	NED						NED	NED				06/09/95	Neg	06/09/95	-
18 Months	17	NAP														09/11/95	Neg	09/11/95	-
21 Months	18	NAP														01/15/96	Neg	01/15/96	+
24 Months	19	Not Done														04/08/96	Neg	04/08/96	+

PDE=primary disease evaluation.

Biopsy Site: PW=posterior wall, RW=right wall, LW=left wall, RU=right ureteral orifice, LU=left ureteral orifice, N=neck, PU=prostatic urethra, U=urethra, AW=anterior wall, TR=trigone, D=dome, PS=prostatic substance.

Tumor Stage: NED=no evidence of disease, Tis=carcinoma in situ, TCC=transitional cell carcinoma, Ta=noninvasive papillary carcinoma, T1=tumor invades subepithelial connective tissue, T2=tumor invades subepithelial muscle, SevD=severe dysplasia.

Cystoscopy Result: Neg=appears negative for bladder cancer (BC), Pos=appears positive for BC; Susp=appears suspicious for BC, Unk=unknown; Other=in listing VII-11A.

Cytology Result: Class 0-3=Negative (-), Class 4-5=Positive (+).

AFIP=Armed Forces Institute of Pathology review of biopsy slides; NAP=not applicable (biopsies required at months 3, 6 and 12, and annually thereafter); NAV=not available.

* Unspecified indicates no bladder mapping locations were given on pathology report for biopsy samples.

** Only year is available (month and date not available).

*** Biopsy sample taken from left floor per pathology report

Summary Table 3: Patient Efficacy Profile - A9302

Patient: Evaluation	Visit	Biopsy Date	Biopsy Site & Tumor Stage: PW	RW	LW	RU	LU	N	PU	U	AW	TR	D	PS	Un-specified*	Cystoscopy Date	Cystoscopy Result	Cytology Date	Cytology Result
Historical	0.01	01/24/91													TCC			12/27/91	-
AFIP	0.02	01/24/91							Tis						Tis			11/11/92	+
Historical	0.03	06/14/91	Tis								TCC	TCC							
Historical	0.04	06/16/94													Tis				
Baseline	1	06/30/94	NED	Tis	NED			NED				Tis	NED			06/30/94	Susp	06/16/94	+
PDE	12	10/11/94	NED	NED	NED			NED				NED	NED			10/11/94	Neg	10/26/94	-
6 Months	13	01/19/95	NED	NED	NED			NED				NED	NED			01/19/95	Neg	01/19/95	-
9 Months	14	05/11/95	NED	NED	NED			NED				NED	NED			05/11/95	Susp	04/19/95	+
12 Months	15	08/17/95	NED	NED	NED			NED				NED	NED			08/17/95	Susp	08/17/95	-

PDE=primary disease evaluation.

Biopsy Site: PW=posterior wall, RW=right wall, LW=left wall, RU=right ureteral orifice, LU=left ureteral orifice, N=neck, PU=prostatic urethra, U=urethra, AW=anterior wall, TR=trigone, D=dome, PS=prostatic substance.

Tumor Stage: NED=no evidence of disease, Tis=carcinoma in situ, TCC=transitional cell carcinoma, Ta=noninvasive papillary carcinoma, T1=tumor invades subepithelial connective tissue, T2=tumor invades subepithelial muscle, SevD=severe dysplasia.

Cystoscopy Result: Neg=appears negative for bladder cancer (BC), Pos=appears positive for BC; Susp=appears suspicious for BC, Unk=unknown; Other=in listing VII-11A.

Cytology Result: Class 0-3=Negative (-), Class 4-5=Positive (+).

AFIP=Armed Forces Institute of Pathology review of biopsy slides; NAP=not applicable (biopsies required at months 3, 6 and 12, and annually thereafter); NAV=not available.

* Unspecified indicates no bladder mapping locations were given on pathology report for biopsy samples.

** Only year is available (month and date not available).

*** Biopsy sample taken from left floor per pathology report.

Summary Table 3: Patient Efficacy Profile - A9301

Patient:

Evaluation	*Visit*	*Biopsy Date*	*Biopsy Site & Tumor Stage*													*Cystoscopy*		*Cytology*	
			PW	*RW*	*LW*	*RU*	*LU*	*N*	*PU*	*U*	*AW*	*TR*	*D*	*PS*	*Un-specified**	*Date*	*Result*	*Date*	*Result*
Historical	0.01	1970**													TCC			03/21/91	-
Historical	0.02	1984**													TCC			03/19/92	-
Historical	0.03	11/01/85													Tis			09/13/93	+
Historical	0.04																	11/19/93	+
Baseline	1	04/01/94	Ta	NED	NED				NED			Tis				04/01/94	Pos	04/01/94	+
PDE	12	07/18/94	NED	NED	NED				NED			NED				07/18/94	Neg	07/18/94	-
6 Months	13	10/19/94	NED	NED	NED				NED			NED	NED			10/19/94	Neg	10/19/94	-
9 Months	14	01/20/95	NED	NED	NED				NED			NED				01/20/95	Neg	01/23/95	-
12 Months	15	04/21/95	NED													04/21/95	Neg	04/21/95	-
15 Months	16	07/13/95						NED								07/13/95	Susp	07/13/95	-
18 Months	17	NAP														09/28/95	Neg	09/28/95	-
21 Months	18	NAP														01/17/96	Neg	01/17/96	-
24 Months	19	04/18/96						NED								04/18/96	Neg	04/18/96	-
27 Months	20	08/01/96		NED												08/01/96	Susp	08/01/96	-
30 Months	21	11/27/96	NED	NED	NED						NED	NED				11/27/96	Neg	11/27/96	+
33 Months	22	01/17/97	NED	NED	NED							NED	NED			01/17/97	Susp	01/21/97	-

PDE=primary disease evaluation.

Biopsy Site: PW=posterior wall, RW=right wall, LW=left wall, RU=right ureteral orifice, LU=left ureteral orifice, N=neck, PU=prostatic urethra, U=urethra, AW=anterior wall, TR=trigone, D=dome, PS=prostatic substance.

Tumor Stage: NED=no evidence of disease, Tis=carcinoma in situ, TCC=transitional cell carcinoma, Ta=noninvasive papillary carcinoma, T1=tumor invades subepithelial connective tissue, T2=tumor invades subepithelial muscle, SevD=severe dysplasia.

Cystoscopy Result: Neg=appears negative for bladder cancer (BC), Pos=appears positive for BC; Susp=appears suspicious for BC, Unk=unknown; Other=in listing VII-11A.

Cytology Result: Class 0-3=Negative (-), Class 4-5=Positive (+).

AFIP=Armed Forces Institute of Pathology review of biopsy slides; NAP=not applicable (biopsies required at months 3, 6 and 12, and annually thereafter); NAV=not available.

* Unspecified indicates no bladder mapping locations were given on pathology report for biopsy samples.

** Only year is available (month and date not available).

*** Biopsy sample taken from left floor per pathology report.

Summary Table 3: Patient Efficacy Profile - A9302

Patient: Evaluation	Visit	Biopsy Date	Biopsy Site & Tumor Stage: PW	RW	LW	RU	LU	N	PU	U	AW	TR	D	PS	Un-specified*	Cystoscopy Date	Cystoscopy Result	Cytology Date	Cytology Result
Historical	0.01	11/10/87													TCC			01/13/92	-
Historical	0.02	05/29/91				TCC													
Historical	0.03	06/01/93													Ta/Tis				
Historical	0.04	09/27/93													Tis				
Baseline	1	09/19/95	NED	NED	Tis							Ta	NED	NED		09/19/95	Pos	10/03/95	-
PDE	12	01/02/96	NED	NED	NED							NED	NED	NED		01/02/96	Other	01/17/96	-
6 Months	13	04/09/96	NED	NED	NED							NED	NED	NED		04/09/96	Neg	03/26/96	-
9 Months	14	NAP														08/02/96	Neg	Not Done	
12 Months	15	Not Done														Not Done		10/10/96	-
15 Months	16	01/31/97	NED	NED	NED							NED	NED	NED		01/31/97	Susp	01/20/97	-
18 Months	17	NAP														04/23/97	Neg	04/23/97	-

PDE=primary disease evaluation.

Biopsy Site: PW=posterior wall, RW=right wall, LW=left wall, RU=right ureteral orifice, LU=left ureteral orifice, N=neck, PU=prostatic urethra, U=urethra, AW=anterior wall, TR=trigone, D=dome, PS=prostatic substance.

Tumor Stage: NED=no evidence of disease, Tis=carcinoma in situ, TCC=transitional cell carcinoma, Ta=noninvasive papillary carcinoma, T1=tumor invades subepithelial connective tissue, T2=tumor invades subepithelial muscle, SevD=severe dysplasia.

Cystoscopy Result: Neg=appears negative for bladder cancer (BC), Pos=appears positive for BC; Susp=appears suspicious for BC, Unk=unknown; Other=in listing VII-11A.

Cytology Result: Class 0-3=Negative (-), Class 4-5=Positive (+).

AFIP=Armed Forces Institute of Pathology review of biopsy slides; NAP=not applicable (biopsies required at months 3, 6 and 12, and annually thereafter); NAV=not available.

* Unspecified indicates no bladder mapping locations were given on pathology report for biopsy samples.

** Only year is available (month and date not available).

*** Biopsy sample taken from left floor per pathology report.

Summary Table 3: Patient Efficacy Profile - A9301

Patient: Evaluation	Visit	Biopsy Date	Biopsy Site & Tumor Stage												Un-specified*	Cystoscopy		Cytology	
			PW	RW	LW	RU	LU	N	PU	U	AW	TR	D	PS		Date	Result	Date	Result
Historical	0.01	09/04/92													TI			NAV	
Historical	0.02	01/22/93													Ta				
Historical	0.03	07/02/93													Ta				
Historical	0.04	11/03/93													TI				
Historical	0.05	02/25/94										Ta	Tis/Ta						
Historical	0.06	05/03/94	Ta																
Historical	0.07	10/06/94						Tis					Ta						
Historical	0.08	07/11/95			Ta	Tis		Ta				Ta							
Historical	0.09	08/29/95						Ta											
Baseline	1	03/14/96	NED	NED	Tis		Ta		NED			Ta						04/16/96	-
PDE	12	07/25/96		NED	NED							NED	NED	NED		07/25/96	Neg	07/25/96	-
6 Months	13	10/25/96	NED	NED	NED				NED			NED	NED	NED		10/25/96	Unk	10/25/96	+
9 Months	14	11/25/96	Ta		Tis											11/25/96	Pos	Not Done	

PDE=primary disease evaluation.

Biopsy Site: PW=posterior wall, RW=right wall, LW=left wall, RU=right ureteral orifice, LU=left ureteral orifice, N=neck, PU=prostatic urethra, U=urethra, AW=anterior wall, TR=trigone, D=dome, PS=prostatic substance.

Tumor Stage: NED=no evidence of disease, Tis=carcinoma in situ, TCC=transitional cell carcinoma, Ta=noninvasive papillary carcinoma, T1=tumor invades subepithelial connective tissue, T2=tumor invades subepithelial muscle, SevD=severe dysplasia.

Cystoscopy Result: Neg=appears negative for bladder cancer (BC), Pos=appears positive for BC; Susp=appears suspicious for BC, Unk=unknown; Other=in listing VII-11A.

Cytology Result: Class 0-3=Negative (-), Class 4-5=Positive (+).

AFIP=Armed Forces Institute of Pathology review of biopsy slides; NAP=not applicable (biopsies required at months 3, 6 and 12, and annually thereafter); NAV=not available.

* Unspecified indicates no bladder mapping locations were given on pathology report for biopsy samples.

** Only year is available (month and date not available).

*** Biopsy sample taken from left floor per pathology report.

Summary Table 3: Patient Efficacy Profile - A9302

Patient: Evaluation	Visit	Biopsy Date	Biopsy Site & Tumor Stage: PW	RW	LW	RU	LU	N	PU	U	AW	TR	D	PS	Un-specified*	Cystoscopy Date	Cystoscopy Result	Cytology Date	Cytology Result
Historical	0.01	1989**													TCC			01/18/93	-
Historical	0.02	06/00/91					Tis												
Historical	0.03	03/02/93											Tis		Ta				
Historical	0.04	09/26/95									Ta/Tis				Ta/Tis				
Historical	0.05	01/30/96					Tis												
Baseline	1	06/06/96	NED	NED	NED			Tis						NED		06/06/96	Other	07/16/96	-
PDE	12	10/02/96	NED	NED	NED		NED					NED	NED	NED		10/02/96	Neg	10/01/96	-
6 Months	13	01/15/97	NED	NED	NED							NED	NED			01/15/97	Neg	01/14/97	-
9 Months	14	NAP														04/11/97	Neg	04/11/97	-

PDE=primary disease evaluation.

Biopsy Site: PW=posterior wall, RW=right wall, LW=left wall, RU=right ureteral orifice, LU=left ureteral orifice, N=neck, PU=prostatic urethra, U=urethra, AW=anterior wall, TR=trigone, D=dome, PS=prostatic substance.

Tumor Stage: NED=no evidence of disease, Tis=carcinoma in situ, TCC=transitional cell carcinoma, Ta=noninvasive papillary carcinoma, T1=tumor invades subepithelial connective tissue, T2=tumor invades subepithelial muscle, SevD=severe dysplasia.

Cystoscopy Result: Neg=appears negative for bladder cancer (BC), Pos=appears positive for BC; Susp=appears suspicious for BC, Unk=unknown; Other=in listing VII-11A.

Cytology Result: Class 0-3=Negative (-), Class 4-5=Positive (+).

AFIP=Armed Forces Institute of Pathology review of biopsy slides; NAP=not applicable (biopsies required at months 3, 6 and 12, and annually thereafter); NAV=not available.

* Unspecified indicates no bladder mapping locations were given on pathology report for biopsy samples.

** Only year is available (month and date not available).

*** Biopsy sample taken from left floor per pathology report.

Summary Table 3: Patient Efficacy Profile - A9301

Patient: Evaluation	Visit	Biopsy Date	Biopsy Site & Tumor Stage												Cystoscopy		Cytology	
			PW	RW	LW	RU	LU	N	PU	U	AW	TR	D	PS	Un-specified*	Date	Result	Date	Result
Historical	0.01	08/13/92													T1			NAV	
Historical	0.02	10/27/93													T1				
Historical	0.03	12/21/94													Tis				
Baseline	1	04/05/95	NED	NED	NED								Tis			04/05/95	Susp	05/30/95	-
PDE	12	10/11/95	NED	NED	NED				NED			NED				10/11/95	Neg	10/11/95	-
6 Months	13	Not Done														01/25/96	Neg	01/25/96	-
9 Months	14	NAP														04/18/96	Neg	04/18/96	-
12 Months	15	Not Done														07/08/96	Neg	07/08/96	-
15 Months	16	NAP														10/10/96	Neg	10/24/96	-
18 Months	17	NAP														02/04/97	Neg	02/06/97	-

PDE=primary disease evaluation.

Biopsy Site: PW=posterior wall, RW=right wall, LW=left wall, RU=right ureteral orifice, LU=left ureteral orifice, N=neck, PU=prostatic urethra, U=urethra, AW=anterior wall, TR=trigone, D=dome, PS=prostatic substance.

Tumor Stage: NED=no evidence of disease, Tis=carcinoma in situ, TCC=transitional cell carcinoma, Ta=noninvasive papillary carcinoma, T1=tumor invades subepithelial connective tissue, T2=tumor invades subepithelial muscle, SevD=severe dysplasia.

Cystoscopy Result: Neg=appears negative for bladder cancer (BC), Pos=appears positive for BC; Susp=appears suspicious for BC, Unk=unknown; Other=in listing VII-11A.

Cytology Result: Class 0-3=Negative (-), Class 4-5=Positive (+).

AFIP=Armed Forces Institute of Pathology review of biopsy slides; NAP=not applicable (biopsies required at months 3, 6 and 12, and annually thereafter); NAV=not available.

* Unspecified indicates no bladder mapping locations were given on pathology report for biopsy samples.

** Only year is available (month and date not available).

*** Biopsy sample taken from left floor per pathology report.

Summary Table 3: Patient Efficacy Profile - A9302

Patient: ____

Evaluation	*Visit*	*Biopsy Date*	*Biopsy Site & Tumor Stage*												*Un-specified**	*Cystoscopy*		*Cytology*	
			PW	*RW*	*LW*	*RU*	*LU*	*N*	*PU*	*U*	*AW*	*TR*	*D*	*PS*		*Date*	*Result*	*Date*	*Result*
Historical	0.01	10/05/87	Tis		Tis													05/04/88	-
Historical	0.02	01/26/88		Tis														09/28/90	+
Historical	0.03																	12/05/92	-
Historical	0.04																	07/01/93	-
Historical	0.05																	01/06/94	-
Historical	0.06																	07/07/94	-
Baseline	1	08/31/95	Tis	NED	NED				NED		NED	Tis	NED			08/31/95	Susp	08/29/95	+
PDE	12	12/12/95		NED	NED				NED		NED	NED	NED			12/12/95	Neg	12/12/95	-
6 Months	13	03/07/96		NED	NED				NED		NED	NED	NED			03/07/96	Neg	03/07/96	-
9 Months	14	NAP														07/01/96	Neg	07/01/96	+
12 Months	15	10/10/96		NED	NED				NED		NED	NED	NED			10/10/96	Susp	10/08/96	-
15 Months	16	NAP														12/19/96	Neg	01/21/97	+
18 Months	17	04/24/97	Tis	NED	NED				NED		NED	Tis	NED			04/24/97	Susp	04/24/97	+

PDE=primary disease evaluation.

Biopsy Site: PW=posterior wall, RW=right wall, LW=left wall, RU=right ureteral orifice, LU=left ureteral orifice, N=neck, PU=prostatic urethra, U=urethra, AW=anterior wall, TR=trigone, D=dome, PS=prostatic substance.

Tumor Stage: NED=no evidence of disease, Tis=carcinoma in situ, TCC=transitional cell carcinoma, Ta=noninvasive papillary carcinoma, T1=tumor invades subepithelial connective tissue, T2=tumor invades subepithelial muscle, SevD=severe dysplasia.

Cystoscopy Result: Neg=appears negative for bladder cancer (BC), Pos=appears positive for BC; Susp=appears suspicious for BC, Unk=unknown; Other=in listing VII-11A.

Cytology Result: Class 0-3=Negative (-), Class 4-5=Positive (+).

AFIP=Armed Forces Institute of Pathology review of biopsy slides; NAP=not applicable (biopsies required at months 3, 6 and 12, and annually thereafter); NAV=not available.

* Unspecified indicates no bladder mapping locations were given on pathology report for biopsy samples.

** Only year is available (month and date not available).

*** Biopsy sample taken from left floor per pathology report.

Summary Table 3: Patient Efficacy Profile - A9301

Patient: Evaluation	Visit	Biopsy Date	Biopsy Site & Tumor Stage: PW	RW	LW	RU	LU	N	PU	U	AW	TR	D	PS	Un-specified*	Cystoscopy Date	Cystoscopy Result	Cytology Date	Cytology Result
Historical	0.01	09/12/94													Tis			12/14/94	+
Historical	0.02	12/14/94						TCC	TCC										
AFIP	0.03	12/14/94						Tis	Tis										
Baseline	1	03/15/95	NED	NED	NED			NED	Tis							03/15/95	Susp	03/15/95	+
PDE	12	07/19/95	NED	NED	NED							NED				07/19/95	Neg	07/19/95	-
6 Months	13	11/01/95	NED	NED	NED				NED			NED	NED			11/01/95	Other	11/01/95	+
9 Months	14	03/13/96	Tis	Tis	Tis				SevD			Tis	Tis			03/13/96	Susp	03/13/96	+

PDE=primary disease evaluation.

Biopsy Site: PW=posterior wall, RW=right wall, LW=left wall, RU=right ureteral orifice, LU=left ureteral orifice, N=neck, PU=prostatic urethra, U=urethra, AW=anterior wall, TR=trigone, D=dome, PS=prostatic substance.

Tumor Stage: NED=no evidence of disease, Tis=carcinoma in situ, TCC=transitional cell carcinoma, Ta=noninvasive papillary carcinoma, T1=tumor invades subepithelial connective tissue, T2=tumor invades subepithelial muscle, SevD=severe dysplasia.

Cystoscopy Result: Neg=appears negative for bladder cancer (BC), Pos=appears positive for BC; Susp=appears suspicious for BC, Unk=unknown; Other=in listing VII-11A.

Cytology Result: Class 0-3=Negative (-), Class 4-5=Positive (+).

AFIP=Armed Forces Institute of Pathology review of biopsy slides; NAP=not applicable (biopsies required at months 3, 6 and 12, and annually thereafter); NAV=not available.

* Unspecified indicates no bladder mapping locations were given on pathology report for biopsy samples.

** Only year is available (month and date not available).

*** Biopsy sample taken from left floor per pathology report.

Summary Table 3: Patient Efficacy Profile - A9302

Patient:

Evaluation	Visit	Biopsy Date	Biopsy Site & Tumor Stage													Cystoscopy		Cytology	
			PW	RW	LW	RU	LU	N	PU	U	AW	TR	D	PS	Un-specified*	Date	Result	Date	Result
Historical	0.01	04/30/90													Ta			05/01/90	-
Historical	0.02	02/27/91													Ta			08/01/90	-
Historical	0.03	03/18/92											Ta					08/28/91	-
Historical	0.04	10/17/92													Ta			11/26/91	-
Historical	0.05	07/21/93	Ta		Tis													03/18/92	+
Historical	0.06	04/29/94	Ta															07/21/93	+
Baseline	1	09/19/95	Ta	NED	NED						Tis		Ta			09/19/95	Pos	11/20/95	-
PDE	12	Not Done														02/29/96	Neg	02/29/96	-
6 Months	13	06/07/96	NED													05/29/96	Susp	05/29/96	-
9 Months	14	NAP														09/04/96	Neg	09/04/96	-
12 Months	15	Not Done														12/04/96	Susp	12/04/96	-
15 Months	16	NAP														03/05/97	Other	03/05/97	-

PDE=primary disease evaluation.

Biopsy Site: PW=posterior wall, RW=right wall, LW=left wall, RU=right ureteral orifice, LU=left ureteral orifice, N=neck, PU=prostatic urethra, U=urethra, AW=anterior wall, TR=trigone, D=dome, PS=prostatic substance.

Tumor Stage: NED=no evidence of disease, Tis=carcinoma in situ, TCC=transitional cell carcinoma, Ta=noninvasive papillary carcinoma, T1=tumor invades subepithelial connective tissue, T2=tumor invades subepithelial muscle, SevD=severe dysplasia.

Cystoscopy Result: Neg=appears negative for bladder cancer (BC), Pos=appears positive for BC; Susp=appears suspicious for BC, Unk=unknown; Other=in listing VII-11A.

Cytology Result: Class 0-3=Negative (-), Class 4-5=Positive (+).

AFIP=Armed Forces Institute of Pathology review of biopsy slides; NAP=not applicable (biopsies required at months 3, 6 and 12, and annually thereafter); NAV=not available.

* Unspecified indicates no bladder mapping locations were given on pathology report for biopsy samples.

** Only year is available (month and date not available).

*** Biopsy sample taken from left floor per pathology report.

Summary Table 3: Patient Efficacy Profile - A9302

Patient:

Evaluation	*Visit*	*Biopsy Date*	*Biopsy Site & Tumor Stage*													*Cystoscopy*		*Cytology*	
			PW	*RW*	*LW*	*RU*	*LU*	*N*	*PU*	*U*	*AW*	*TR*	*D*	*PS*	*Un-specified**	*Date*	*Result*	*Date*	*Result*
Historical	0.01	07/00/91													Ta			02/00/92	-
Historical	0.02	02/00/92			Tis													11/01/92	+
Historical	0.03	02/00/94			Tis										Tis***			03/00/93	-
Historical	0.04	06/06/94			Tis													06/06/94	-
Historical	0.05																	07/06/94	-
Baseline	1	10/03/94	NED	NED	Tis						ScvD	NED				10/03/94	Susp	10/03/94	+
PDE	12	02/01/95	NED	NED	NED				NED				NED			02/01/95	Neg	02/01/95	+
6 Months	13	04/26/95	NED	NED	NED				NED		NED					04/26/95	Unk	Not Done	
9 Months	14	08/14/95			Tis											08/14/95	Unk	Not Done	

PDE=primary disease evaluation.

Biopsy Site: PW=posterior wall, RW=right wall, LW=left wall, RU=right ureteral orifice, LU=left ureteral orifice, N=neck, PU=prostatic urethra, U=urethra, AW=anterior wall, TR=trigone, D=dome, PS=prostatic substance.

Tumor Stage: NED=no evidence of disease, Tis=carcinoma in situ, TCC=transitional cell carcinoma, Ta=noninvasive papillary carcinoma, T1=tumor invades subepithelial connective tissue, T2=tumor invades subepithelial muscle, ScvD=severe dysplasia.

Cystoscopy Result: Neg=appears negative for bladder cancer (BC), Pos=appears positive for BC; Susp=appears suspicious for BC, Unk=unknown; Other=in listing VII-11A.

Cytology Result: Class 0-3=Negative (-), Class 4-5=Positive (+).

AFIP=Armed Forces Institute of Pathology review of biopsy slides; NAP=not applicable (biopsies required at months 3, 6 and 12, and annually thereafter); NAV=not available.

* Unspecified indicates no bladder mapping locations were given on pathology report for biopsy samples.

** Only year is available (month and date not available).

*** Biopsy sample taken from left floor per pathology report.

Summary Table 3: Patient Efficacy Profile - A9301

Patient:

Evaluation	*Visit*	*Biopsy Date*	*Biopsy Site & Tumor Stage*													*Cystoscopy*		*Cytology*	
			PW	*RW*	*LW*	*RU*	*LU*	*N*	*PU*	*U*	*AW*	*TR*	*D*	*PS*	*Un-specified**	*Date*	*Result*	*Date*	*Result*
Historical	0.01	11/17/92													Ta/Tis			05/04/94	+
Historical	0.02	02/24/93													Ta/Tis			12/05/94	+
Historical	0.03	06/23/93													Tis			12/06/94	+
Historical	0.04	07/07/94					Tis											12/07/94	+
Historical	0.05	12/14/94													Tis				
Baseline	1	01/19/95		NED	NED						Tis	Tis				01/19/95	Susp	01/19/95	+
PDE	12	04/18/95	NED	NED	NED			NED				NED	NED			04/18/95	Neg	04/18/95	-
6 Months	13	07/28/95	NED	NED	NED							NED	NED			07/28/95	Neg	07/28/95	+
9 Months	14	10/17/95	NED	NED	NED						NED	NED	NED			10/17/95	Neg	10/16/95	-
12 Months	15	01/23/96	NED	NED	NED							NED	NED			01/23/96	Neg	01/22/96	-
15 Months	16	Not Done														Not Done		Not Done	
18 Months	17	Not Done														06/13/96	Neg	06/13/96	-
21 Months	18	10/21/96										NED				10/21/96	Susp	10/21/96	-
24 Months	19	Not Done														Not Done		Not Done	
27 Months	20	04/29/97	NED	NED	NED						NED	NED				04/29/97	Susp	04/28/97	-

PDE=primary disease evaluation.

Biopsy Site: PW=posterior wall, RW=right wall, LW=left wall, RU=right ureteral orifice, LU=left ureteral orifice, N=neck, PU=prostatic urethra, U=urethra, AW=anterior wall, TR=trigone, D=dome, PS=prostatic substance.

Tumor Stage: NED=no evidence of disease, Tis=carcinoma in situ, TCC=transitional cell carcinoma, Ta=noninvasive papillary carcinoma, T1=tumor invades subepithelial connective tissue, T2=tumor invades subepithelial muscle, SevD=severe dysplasia.

Cystoscopy Result: Neg=appears negative for bladder cancer (BC), Pos=appears positive for BC; Susp=appears suspicious for BC, Unk=unknown; Other=in listing VII-11A.

Cytology Result: Class 0-3=Negative (-), Class 4-5=Positive (+).

AFIP=Armed Forces Institute of Pathology review of biopsy slides; NAP=not applicable (biopsies required at months 3, 6 and 12, and annually thereafter); NAV=not available.

* Unspecified indicates no bladder mapping locations were given on pathology report for biopsy samples.

** Only year is available (month and date not available).

*** Biopsy sample taken from left floor per pathology report.

Summary Table 3: Patient Efficacy Profile - A9302

Patient: Evaluation	Visit	Biopsy Date	Biopsy Site & Tumor Stage: PW	RW	LW	RU	LU	N	PU	U	AW	TR	D	PS	Un-specified*	Cystoscopy Date	Cystoscopy Result	Cytology Date	Cytology Result
Historical	0.01	10/14/91		Ta														01/16/92	-
Historical	0.02	04/22/92											TCC						
Historical	0.03	07/17/92													Tis				
Historical	0.04	07/12/93						TCC							Tis				
Baseline	1	10/11/94	Ta													10/11/94	Pos	11/02/94	-
PDE	12	03/08/95	NED	NED	NED							NED	NED			03/08/95	Pos	03/08/95	-
6 Months	13	06/07/95	NED	NED	NED						NED	NED	NED			06/07/95	Unk	06/06/95	-
9 Months	14	09/20/95	NED	NED	NED						NED	NED	NED			09/20/95	Other	09/20/95	+
12 Months	15	01/03/96	NED	SevD	NED						SevD	Ta	NED			12/13/95	Pos	Not Done	

PDE=primary disease evaluation.

Biopsy Site: PW=posterior wall, RW=right wall, LW=left wall, RU=right ureteral orifice, LU=left ureteral orifice, N=neck, PU=prostatic urethra, U=urethra, AW=anterior wall, TR=trigone, D=dome, PS=prostatic substance.

Tumor Stage: NED=no evidence of disease, Tis=carcinoma in situ, TCC=transitional cell carcinoma, Ta=noninvasive papillary carcinoma, T1=tumor invades subepithelial connective tissue, T2=tumor invades subepithelial muscle, SevD=severe dysplasia.

Cystoscopy Result: Neg=appears negative for bladder cancer (BC), Pos=appears positive for BC; Susp=appears suspicious for BC, Unk=unknown; Other=in listing VII-11A.

Cytology Result: Class 0-3=Negative (-), Class 4-5=Positive (+).

AFIP=Armed Forces Institute of Pathology review of biopsy slides; NAP=not applicable (biopsies required at months 3, 6 and 12, and annually thereafter); NAV=not available.

* Unspecified indicates no bladder mapping locations were given on pathology report for biopsy samples.

** Only year is available (month and date not available).

*** Biopsy sample taken from left floor per pathology report.

Summary Table 3: Patient Efficacy Profile - A9302

Patient:

Evaluation	*Visit*	*Biopsy Date*	*Biopsy Site & Tumor Stage*												*Cystoscopy*		*Cytology*	
			PW	*RW*	*LW*	*RU*	*LU*	*N*	*PU*	*U*	*AW*	*TR*	*D*	*PS*	*Un-specified**	*Date*	*Result*	*Date*	*Result*
Historical	0.01	09/14/88													TCC			01/08/89	-
Historical	0.02	09/26/88													TCC			04/10/89	+
Historical	0.03	11/29/89	Tis															08/23/89	-
Historical	0.04	02/06/90	Tis		Tis				Tis				Tis		TCC			11/29/89	+
Historical	0.05	03/06/90							Tis									03/06/90	+
Historical	0.06																	07/03/90	-
Historical	0.07																	02/18/91	-
Baseline	1	10/20/94	NED	NED	NED						NED	Tis				10/20/94	Other	10/20/94	+
PDE	12	02/06/95	NED	NED	NED				NED		NED	NED				02/06/95	Neg	02/06/95	-
6 Months	13	06/14/95	NED	NED	NED				SevD		NED	NED				05/17/95	Neg	05/17/95	+
9 Months	14	09/20/95	NED	NED	NED				NED		NED	NED				09/20/95	Other	10/02/95	+

PDE=primary disease evaluation.

Biopsy Site: PW=posterior wall, RW=right wall, LW=left wall, RU=right ureteral orifice, LU=left ureteral orifice, N=neck, PU=prostatic urethra, U=urethra, AW=anterior wall, TR=trigone, D=dome, PS=prostatic substance.

Tumor Stage: NED=no evidence of disease, Tis=carcinoma in situ, TCC=transitional cell carcinoma, Ta=noninvasive papillary carcinoma, T1=tumor invades subepithelial connective tissue, T2=tumor invades subepithelial muscle, SevD=severe dysplasia.

Cystoscopy Result: Neg=appears negative for bladder cancer (BC), Pos=appears positive for BC; Susp=appears suspicious for BC, Unk=unknown; Other=in listing VII-11A.

Cytology Result: Class 0-3=Negative (-), Class 4-5=Positive (+).

AFIP=Armed Forces Institute of Pathology review of biopsy slides; NAP=not applicable (biopsies required at months 3, 6 and 12, and annually thereafter); NAV=not available.

* Unspecified indicates no bladder mapping locations were given on pathology report for biopsy samples.

** Only year is available (month and date not available).

*** Biopsy sample taken from left floor per pathology report.

Summary Table 3: Patient Efficacy Profile - A9302

Patient:			*Biopsy Site & Tumor Stage*													*Cystoscopy*		*Cytology*	
Evaluation	*Visit*	*Biopsy Date*	*PW*	*RW*	*LW*	*RU*	*LU*	*N*	*PU*	*U*	*AW*	*TR*	*D*	*PS*	*Un-specified**	*Date*	*Result*	*Date*	*Result*
Historical	0.01	10/15/92													Ta			07/20/95	+
Historical	0.02	02/24/93													Ta			11/13/95	+
Historical	0.03	04/11/94													Ta				
Historical	0.04	03/09/95			Ta							Tis							
Historical	0.05	07/20/95										Tis							
Baseline	1	12/07/95			Ta							Tis				12/07/95	Pos	01/11/96	+
PDE	12	04/11/96		NED	NED				NED			NED	NED			04/11/96	Neg	04/19/96	-
6 Months	13	07/18/96	NED	NED	NED				NED			NED	NED			07/18/96	Susp	07/18/96	+
9 Months	14	11/04/96	Tis	NED	Tis				Tis		Tis	NED				11/04/96	Susp	11/04/96	+

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